Proposed Preferred Drug List

with

Clinical Criteria

Proposal for TennCare

February 23, 2012
Responsibilities of the TennCare Pharmacy Advisory Committee

Source: Tennessee Code/Title 71 Welfare/Chapter 5 Programs and Services for Poor Persons/Part 24 Tennessee TennCare Pharmacy Advisory Committee/71-5-2401 through 71-5-2404.

- Make recommendations regarding a preferred drug list (PDL) to govern all state expenditures for prescription drugs for the TennCare program.
  - The TennCare Pharmacy Advisory Committee shall submit to the bureau of TennCare both specific and general recommendations for drugs to be included on any state PDL adopted by the bureau. In making its recommendations, the committee shall consider factors including, but not limited to, efficacy, the use of generic drugs and therapeutic equivalent drugs, and cost information related to each drug. The committee shall also submit recommendations to the bureau regarding computerized, voice, and written prior authorization, including prior authorization criteria and step therapy.
  - The state TennCare pharmacy advisory committee shall include evidence-based research in making its recommendations for drugs to be included on the PDL.
  - The TennCare bureau shall consider the recommendations of the state TennCare pharmacy advisory committee in amending or revising any PDL adopted by the bureau to apply to pharmacy expenditures within the TennCare program. The recommendations of the committee are advisory only and the bureau may adopt or amend a PDL regardless of whether it has received any recommendations from the committee. It is the legislative intent that, insofar as practical, the TennCare bureau shall have the benefit of the committee’s recommendations prior to implementing a PDL or portions thereof.

- Keep minutes of all meetings including votes on all recommendations regarding drugs to be included on the state preferred drug list

- The chair may request that other physicians, pharmacists, faculty members of institutions of higher learning, or medical experts who participate in various subspecialties act as consultants to the committee as needed.
PDL Decision Process

- The primary clinical decision that needs to be made is determining if the drugs within the therapeutic class of interest can be considered therapeutic alternatives.

- A **The Therapeutic Alternative** is defined by the AMA as: “drug products with different chemical structures but which are of the same pharmacological and/or therapeutic class, and usually can be expected to have similar therapeutic effects and adverse reaction profiles when administered to patients in therapeutically equivalent doses”\(^1\).

- The Committee should not feel obligated to decide if every drug within the therapeutic class is exactly equal to all other drugs within the class, nor should they feel obligated to decide if every drug within the therapeutic class works equally well in every special patient population or in every disease.

- In special situations (e.g., presence of comorbid conditions) and in special populations (e.g., pediatrics) use of a non-preferred drug might be the most appropriate therapy. These cases can be handled through prior authorization (PA). PA serves as a “safety valve” in that it facilitates use of the most appropriate agent regardless of PDL status.

**LENGTH OF AUTHORIZATIONS:** Dependent upon diagnosis and length of therapy needed to treat. (Most medications are used chronically, and thus would be approved for 1 year.)

1. Is there any reason the patient cannot be changed to a medication not requiring prior approval within the same class?
   
   *Acceptable reasons include:*
   
   - **Allergy** to medications not requiring prior approval
   - **Contraindication** to or drug-to-drug interaction with medications not requiring prior approval
   - **History** of unacceptable/toxic side effects to medications not requiring prior approval

2. The requested medication may be approved if both of the following are true:
   
   - If there has been a therapeutic failure of at least two medications within the same class not requiring prior approval (unless otherwise specified)
   - The requested medication’s corresponding generic (if a generic is available and preferred by the State) has been attempted and failed or is contraindicated

3. The requested medication may be approved if the following is true:
   
   - An indication which is unique to a non-preferred agent and is supported by peer-reviewed literature or an FDA approved indication exists.

The information provided for each drug class is organized into the following sections, when applicable:

**BACKGROUND:**
- General overview
- Pharmacology
- Therapeutic effect(s)
- Adverse reactions
- Outcomes data
- Place in therapy according to current Treatment Guidelines

**RECOMMENDATION:**
- General recommendation regarding utility and therapeutic equivalence among the agents in the class, as well as requirements for product availability (PDL placement)

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\(^1\) AMA Policy H-125.991 Drug Formularies and Therapeutic Interchange
BACKGROUND

- The penicillin antibiotics are part of a larger group of agents known as the β-lactam antibiotics. The β-lactam antibiotics are typically considered bactericidal. Specifically, the penicillin agents inhibit the synthesis of the bacterial cell wall and are FDA approved for a variety of infections that are caused by susceptible organisms. For the purposes of this class review, the focus will be on oral penicillin agents.
- The American Hospital Formulary Service has classified the penicillin family into 4 major groups based on their spectrum of activity. These 4 groups include 1) natural penicillins, 2) penicillinase-resistant penicillins, 3) aminopenicillins, and 4) extended-spectrum penicillins.
- The natural penicillins include penicillin V which is active against many gram-positive cocci, including many strains of streptococci and staphylococci. The natural penicillins also have activity against most gram negative aerobic cocci, some gram-positive aerobic and anaerobic bacilli. However, the natural penicillins are ineffective against most strains of staphylococcus aureus as they are hydrolyzed by the penicillin-inactivating enzyme, penicillinase.
- Dicloxacillin is included in the penicillinase-resistant penicillin group. This agent is active against penicillinase-producing staphylococci and streptococci (excluding enterococci). The penicillinase-resistant penicillins have no activity against gram-negative bacteria.
- The aminopenicillins, which include amoxicillin and ampicillin, have extended activity compared to the previous groups mentioned. These agents are active against gram-negative bacilli (excluding penicillinase-producing staphylococci) and are inhibitors of β-lactamases of gram-negative bacilli. Their extended spectrum of activity is due to greater penetration of the outer membranes of gram-negative bacteria and a higher affinity for penicillin-binding proteins.
- The final group includes the extended-spectrum penicillins. This group includes the injectable agents ticarcillin, (also known as carboxypenicillin) and piperacillin. This group has the spectrum of activity similar to aminopenicillins along with additional activity against gram-negative organisms. However, ticarcillin and piperacillin are not specifically reviewed in this class review, as they are not absorbed orally and must be given IV or IM.
- The adverse reactions experienced with penicillins are similar to those of other antibiotics, for example superinfection, hypersensitivity reactions (i.e. angioedema), as well as hematological and neurological reactions. Specifically, the following adverse events could occur with the use of penicillin agents (See MedMetrics class review, Table 7, pg. 52):
  - **Gastrointestinal:** nausea, vomiting, diarrhea, pseudomembranous colitis
  - **Dermatological:** rash, maculopapular rash, urticaria, exfoliative dermatitis
  - **Hematological:** leukopenia, thrombocytopenia
- The penicillins are contraindicated in patients with a history of allergic reaction to any penicillin. Prior to initiating therapy with penicillins, a careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens as anaphylactic reactions are more likely to occur in individuals with a history of penicillin and/or multiple allergen hypersensitivity. Additionally, penicillins should be used with caution in patients with a history of asthma. Patients receiving prolonged ampicillin therapy should have a periodic assessment of renal, hepatic and hematopoietic status. On rare occasions, deaths have been reported (less than 1% per 4 million prescriptions) with most of the patients having a serious underlying disease or concomitant medication. Amoxicillin/clavulanate should be used cautiously in patients with hepatic dysfunction.
- Significant drug interactions of penicillins include concomitant use with methotrexate (increased methotrexate serum concentration and risk of toxicity), oral contraceptives (reduced effectiveness of oral contraceptives), and tetracyclines (impaired bacteriocidal effects of penicillins). Concomitant use of allopurinol with ampicillin may increase the risk of a skin rash. Also use of atenolol with ampicillin may impair gastrointestinal absorption.
of atenolol reducing the pharmacological effects of atenolol (i.e. decreased antihypertensive and antianginal effects).

**Clinical Trials** (see MedMetrics class review, Table 5, pg. 7):

- A clinical trial performed by Stenstrom, et al evaluated amoxicillin 20mg/kg/day for 10 days versus amoxicillin/clavulanate 20mg/kg/day for 7 days. This double-blind prospective randomized controlled trial included children 6 months of age to 10 years of age with recurrent acute otitis media or failure of penicillin therapy. The primary endpoint showed no significant difference between amoxicillin/clavulanate and amoxicillin groups in terms of clinical improvement rate (86.7% versus 86.1%). Also this trial demonstrated that both drugs were well tolerated (24% vs. 20% had adverse effects, one patient vs. 3 patients discontinued therapy, P value not reported).

- Feder et al, evaluated amoxicillin 750 mg orally daily for 10 days versus penicillin V 250 mg orally TID for 10 days versus penicillin V 250 mg orally TID for 10 days. This was a prospective, randomized controlled trial in children with group A ß-hemolytic streptococcal pharyngitis. The primary endpoints were clinical or bacterial eradication within 18-24 hours. The results showed no significant differences between clinical response (about 90% for both groups; P=NS) or bacteriologic response at 18 to 24 hour follow-up visit (P=NS). Treatment failure occurred in 5% of the patients in the amoxicillin group and 11% of the patients in the penicillin V group (P value not reported).

- The 2011 Institute for Clinical Systems Improvement guidelines for diagnosis and treatment of respiratory illness in children and adults recommend penicillin as the drug of choice with amoxicillin listed as an acceptable alternative due to poor palatability of penicillin suspension.

- The 2005 Infectious Diseases Society of America practice guidelines for the diagnosis and management of skin and soft-tissue infections state minor skin and soft-tissue infections may be empirically treated with semisynthetic penicillins, first or second generation oral cephalosporins, macrolides, or clindamycin. However, resistance to clindamycin has been found in almost 50% of methicillin-resistant staphylococcus aureus (MRSA) strains. For patients with severe infection or infection that has progressed while on empirical antibiotic treatment, the selection of therapeutic agents should be based on results of the gram stain, culture and drug susceptibility analysis.

- The 2009 American Heart Association guidelines for treatment of acute streptococcal pharyngitis recommends penicillin V and amoxicillin as the antibiotics of choice. In symptomatic patients who fail an initial course of penicillin, retreatment with a narrow spectrum cephalosporin, clindamycin, amoxicillin/clavulanate or a combination of penicillin plus rifampin is recommended. The guidelines mention that the once-daily amoxicillin formulation has shown to be effective for group A streptococcal pharyngitis in clinical trials and may enhance adherence. However, no specific recommendations are given regarding this agent.

**RECOMMENDATION**

The penicillin agents are indicated to treat a variety of infections. Clinical trials have generally demonstrated safety and efficacy of these agents based on their respective indications. Clinical guidelines recommend penicillins as first-line agents for certain strains of community acquired pneumonia, otitis media, group A ß-hemolytic streptococcal pharyngitis, bacterial sinusitis, and minor skin and soft tissue infections. An extended formulation of amoxicillin is available and clinical trials have shown its effectiveness in group A streptococcal pharyngitis. However, these trials have not shown that the extended release amoxicillin is superior to other agents in the class and safety and efficacy has not been established in pediatric patients less than 12 years of age. Additionally, given the differences in the subclasses of penicillins such as inactivation by beta-lactamase and spectrum of activity, at least one agent in each of the subclasses should be available. Therefore, it is recommended that at least 3 oral penicillin agents are available for use. Additionally, due to high utilization in the pediatric population, at least one liquid formulation should be available.
ANTHINFECTIVE AGENTS

COMMITTEE VOTE:

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RE-REVIEW: Penicillins

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References


RE-REVIEW: CEPHALOSPORINS 1ST GENERATION

BACKGROUND

- Cephalosporins are another antibiotic family that is part of a larger group of antibiotics known as β-lactam antibiotics. The penicillin and cephalosporin family make up the majority of the β-lactam antibiotics. In general, the β-lactam antibiotics are considered bactericidal and work by inactivating enzymes involved with bacterial cell wall synthesis.
In general, cephalosporins are grouped into generations based on their spectrum of activity.

- The first generation cephalosporins are active against gram-positive aerobes and typically have poor activity against gram-negative organisms. However, some strains of Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis and Shigella may be susceptible.
- Second generation cephalosporins have greater activity against Haemophilus influenza (H.flu) and enhanced activity against gram-negative organisms in vitro compared to first generation cephalosporins.
- The third generation cephalosporins are more active against gram-negative bacilli versus first or second generation cephalosporins. However, they are not as active against susceptible strains of staphylococci compared to first generation cephalosporins. With the exception of cefuroxime, the first and second generation cephalosporins are not able to effectively penetrate the cerebrospinal fluid and therefore should not be used to treat central nervous system infections. Conversely, the third generation cephalosporins do effectively penetrate the cerebrospinal fluid.
- The fourth generation cephalosporins have enhanced activity against gram-negative bacteria compared to the first and second generation cephalosporins and have activity in vitro against gram-negative bacteria that are typically resistant to the third generation cephalosporins, including Pseudomonas aeruginosa and Enterobacteriaceae. The fourth generation currently includes only 1 parenteral agent, cefepime.

- The cephalosporin class reviews will focus on the oral first through third generation agents. More specifically, this class review will discuss the oral first generation cephalosporins.
- The first generation cephalosporin agents include cefadroxil and cephalexin. Cefadroxil is FDA (Food and Drug Administration) indicated for the treatment of urinary tract infections, skin and skin structure infections, pharyngitis, and tonsillitis. Cephalexin is FDA approved to treat dermatological, genitourinary, respiratory, bone and joint infections.

**Common and Severe Adverse Reactions (See MedMetrics class review, Table 7, pg. 17):**

- **Cefadroxil**
  - Dermatologic- Erythema multiforme and Stevens-Johnson syndrome
  - Gastrointestinal- Clostridium difficile diarrhea
  - Hematologic- Thrombocytopenia
  - Hepatic- Liver failure
  - Immunologic- Anaphylaxis and hypersensitivity reaction

- **Cephalexin**
  - Dermatologic- Stevens-Johnson syndrome, Toxic epidermal necrolysis
  - Gastrointestinal- Diarrhea and pseudomembranous enterocolitis
  - Immunologic- Anaphylaxis
  - Renal- Interstitial nephritis and renal failure

- The first generation cephalosporins are contraindicated in patients with a known allergy to the cephalosporin group of antibiotics. Careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins or other drugs before therapy with a first generation cephalosporin is initiated, as caution should be exercised due to documented cross-sensitivity among β-lactam antibiotics which may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction occurs, discontinue the drug.
- *Clostridium difficile* associated diarrhea (CDAD) has been reported with the use of almost all antibacterial agents, ranging in severity from mild diarrhea to fatal colitis. Careful medical history is required as CDAD may occur over two months after administration of antibiotics. If CDAD is suspected or confirmed, ongoing
antibiotics not intended to treat CDAD may have to be discontinued. Cefadroxil and cephalexin should be used with caution in patients with markedly impaired renal function (creatinine clearance <50 mL/minute) and in patients with a history of gastrointestinal disease and/or colitis.

- **Clinical Trials** (See MedMetrics class review, Table 5, pg. 4):
  - A meta-analysis performed by Ballantyne et al compared cefadroxil (500mg BID, 1,000mg QD, and 1,000mg BID) and cephalexin 500 mg QID in 2 double-blind trials with various skin and soft tissue infections including furunculosis. These trials included a total of 224 patients with 10 day duration. In study A, participants received either cefadroxil 1,000 mg BID or cephalexin; in study B, participants received either cefadroxil 500 mg BID or 1,000 mg QD or cephalexin.
    - **Study A** - improvements in clinical and bacteriologic evaluations were reported in patients treated with cefadroxil and cephalexin (100 vs. 91%, respectively; no P value reported).
    - **Study B** - improvement in clinical and bacteriologic evaluations was reported in patients treated with both cefadroxil doses and cephalexin (98 vs. 97 vs. 98%, respectively; no P value reported).
  - A prospective randomized controlled trial performed by Blaser et al evaluated cefadroxil 500mg BID versus cephalexin 250 mg QID in patients 19 to 92 years of age with community-acquired pneumonia of mild to moderate severity. This trial included 34 participants with duration of 10 days. All 34 cases achieved clinical cure. No additional information was given in regards to differences in clinical cure rates were reported between cefadroxil and cephalexin (P values not reported).

- The 2011 Institute for Clinical Systems Improvement guidelines for treatment of pharyngitis recommend penicillin as the drug of choice. However, the guidelines identify first generation cephalosporins as acceptable alternatives along with macrolides, clindamycin, and amoxicillin/clavulanate.
- The Infectious Diseases Society of America 2005 guidelines recommend the first or second generation cephalosporin agents for empiric treatment of minor skin and soft tissue infections, cellulitis and impetigo.

**RECOMMENDATION**

Cephalosporins are grouped into generations based on their spectrum of activity. The first generation cephalosporins include cefadroxil and cephalexin. The first generation cephalosporins are active against gram-positive aerobes and typically have poor activity against gram-negative organisms. However, there is some susceptibility to some strains of *Escherichia coli* (*E.coli*), *Klebsiella pneumoniae*, *Proteus mirabilis* and *Shigella*. Overall, the first generation cephalosporins have demonstrated efficacy for their respective indications. Comparison within the class has failed to consistently demonstrate “superiority” of one agent over the other for the treatment of respiratory tract infections, skin and soft tissue infections or urinary tract infections; however, given that cephalexin is the only agent approved for bone and joint infections and cefadroxil is the only agent approved for pharyngitis and tonsillitis, it is recommended that both cefadroxil and cephalexin are available for use.

**COMMITTEE VOTE:**

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BACKGROUND

- Cephalosporins are another antibiotic family that is part of a larger group of antibiotics known as β-lactam antibiotics. The penicillin and cephalosporin family make up the majority of the β-lactam antibiotics. In general, the β-lactam antibiotics are considered bactericidal and work by inactivating enzymes involved with bacterial cell wall synthesis.

- In general, cephalosporins are grouped into generations based on their spectrum of activity.
  - The first generation cephalosporins are active against gram-positive aerobes and typically have poor activity against gram-negative organisms. However, some strains of Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis and Shigella may be susceptible.
  - Second generation cephalosporins have greater activity against Haemophilus influenza (H.flu) and enhanced activity against gram-negative organisms in vitro compared to first generation cephalosporins.
  - The third generation cephalosporins are more active against gram-negative bacilli versus first or second generation cephalosporins. However, they are not as active against susceptible strains of staphylococci compared to first generation cephalosporins. With the exception of cefuroxime, the first and second generation cephalosporins are not able to effectively penetrate the cerebrospinal fluid and therefore should not be used to treat central nervous system infections. Conversely, the third generation cephalosporins do effectively penetrate the cerebrospinal fluid.
  - The fourth generation cephalosporins have enhanced activity against gram-negative bacteria compared to the first and second generation cephalosporins and have activity in vitro against gram-negative bacteria that are typically resistant to the third generation cephalosporins, including Pseudomonas aeruginosa and Enterobacteriaceae. The fourth generation currently includes only 1 parenteral agent, cefepime.
  - The cephalosporin class reviews will focus on the oral first through third generation agents. More specifically, this class review will discuss the oral second generation cephalosporins.

- The second generation cephalosporin agents include cefaclor, cefprozil, and cefuroxime. Cefaclor is FDA (Food and Drug Administration) approved to treat respiratory (i.e. bronchitis, otitis media, pharyngitis, and tonsillitis), dermatological, and urinary tract infections. Cefprozil is FDA approved for treatment of respiratory (i.e. bronchitis, otitis...
media, pharyngitis, sinusitis and tonsillitis) and dermatological infections. Cefuroxime is approved to treat dermatological, genitourinary and respiratory infections and early Lyme disease. (See MedMetrics class Review, Table 3, pg. 2)

- **Common and Severe Adverse Reactions** (See MedMetrics class review, Table 7, pg. 23):
  - **Cefaclor**: diarrhea, Stevens-Johnson syndrome, toxic epidermal necrolysis, pseudomembranous enterocolitis, hemolytic anemia, and serum sickness like reaction.
  - **Cefprozil**: diapher, diarrhea, nausea, ALT/SGPT level raised, AST/SGOT level raised, superinfection, pruritus of genital organs, and vaginitis, Stevens-Johnson syndrome, pseudomembranous enterocolitis, and anaphylaxis
  - **Cefuroxime**: eosinophilia, erythema multiforme (rare), Stevens-Johnson syndrome (rare), toxic epidermal necrolysis (rare), thrombocytopenia, anaphylaxis (rare), hypersensitivity reaction (rare), and interstitial nephritis (rare).

  o The second generation cephalosporins are contraindicated in patients with a known allergy to the cephalosporin group of antibiotics. Careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins or other drugs before therapy with a second generation cephalosporin is initiated, as caution should be exercised due to documented cross-sensitivity among β-lactam antibiotics which may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction occurs, discontinue the drug.

  o *Clostridium difficile* associated diarrhea (CDAD) has been reported with the use of almost all antibacterial agents, ranging in severity from mild diarrhea to fatal colitis. Careful medical history is required as CDAD may occur over two months after administration of antibiotics. If CDAD is suspected or confirmed, ongoing antibiotics not intended to treat CDAD may have to be discontinued. The second generation cephalosporins should be used with caution in patients with a history of gastrointestinal disease and/or colitis.

  o Cephalosporins may be associated with a fall in prothrombin activity. Renal or hepatic impairment, poor nutritional state, patients receiving a protracted course of antibiotic therapy and patients previously stabilized on anticoagulant therapy are at an increased risk. Prothrombin time should be monitored. Also patients receiving cefaclor, cefprozil or cefuroxime may show false-positive reactions for glucose in the urine with tests that use Benedict’s and Fehling’s solutions and also with Clinitest® tablets.

  o **Drug-Drug Interactions**: Concomitant use of cefuroxime with aminoglycosides may increase the risk of nephrotoxicity. Aminoglycoside and renal levels should be monitored.

  - A clinical trial performed by Parish et al evaluated cefaclor 250 mg TID (or 20 mg/kg/day in 3 divided doses) vs. cefprozil 500 mg QD (or 20 mg/kg/day) in a multicenter, randomized controlled trial. Patients aged 2 to 99 years of age with skin or skin structure infections were studied. This trial included 422 participants and patients were given 5 to 10 days of treatment. Satisfactory clinical response was observed in 92% of patients in the cefaclor group and 93% of patients in the cefprozil group (P value not reported). Also, 89% of patients in the cefaclor group showed pathogen eradication with 91% of patients exhibiting pathogen eradication in the cefprozil group (P value not reported).

  - Another clinical trial by Schleupner et al, evaluated cefuroxime 250 mg BID vs. cefuroxime 500 mg BID vs. cefaclor 500 mg TID in a randomized controlled trial. This trial included patients 12 years of age and older with evidence of a lower respiratory tract infection. The trial duration was 10 days and included 69 participants. The results showed no significant difference was observed between groups in clinically cured and improved patients (P value not reported). Additionally, bacteriologic cure rates were 80%
for cefuroxime 250 mg, 93% for cefuroxime 500 mg and 60% for cefaclor patients, respectively (P values not reported).

- The American College of Chest Physicians 2005 guidelines for management of community-acquired pneumonia list amoxicillin/clavulanate and some 2nd generation cephalosporins (ie. cefuroxime, cefprozil) as alternatives for low risk patients.

- The American Academy of Pediatrics and American Academy of Family Physicians guidelines on the management of otitis media consider cefuroxime as an alternative to amoxicillin for patients with a history of non-type-1 penicillin allergy.

- The 2011 Institute for Clinical Systems Improvement guidelines for the treatment of respiratory illness in children and adults list 2nd generation cephalosporins among other agents as second-line agents for patients infected with penicillin and SMX/TMP (sulfamethoxazole/trimethoprim) resistant bacteria.

**RECOMMENDATION**

The second generation cephalosporins are used to treat a variety of infections including skin and skin structure, genitourinary tract and respiratory tract infections. Second generation cephalosporins have greater activity against *Haemophilus influenza* (H. flu) compared to the first generation cephalosporins and exhibit enhanced activity against gram-negative bacteria in vitro. Treatment guidelines identify second generation cephalosporins as treatment options for community acquired pneumonia and alternative agents for patients with a non-type 1 penicillin allergy for the treatment of pharyngitis. Clinical trials comparing the oral second generation cephalosporins to each other do not consistently favor one agent over another. However, clinical guidelines recommend cefuroxime as an alternative agent for otitis media in penicillin allergic patients. Also there are differences in spectrum of activity and FDA indications within the class. Therefore, it’s recommended that at least 2 second generation cephalosporins should be available, one of which should include cefuroxime. Additionally, a liquid formulation should be available for the pediatric population.

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**RE-REVIEW: 2ND GENERATION CEPHALOSPORINS**

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**References**

RE-REVIEW: 3rd GENERATION CEPHALOSPORINS

BACKGROUND

- Cephalosporins are another antibiotic family that is part of a larger group of antibiotics known as β-lactam antibiotics. The penicillin and cephalosporin family make up the majority of the β-lactam antibiotics. In general, the β-lactam antibiotics are considered bactericidal and work by inactivating enzymes involved with bacterial cell wall synthesis.
- In general, cephalosporins are grouped into generations based on their spectrum of activity.
  - The first generation cephalosporins are active against gram-positive aerobes and typically have poor activity against gram-negative organisms. However, some strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Shigella* may be susceptible.
  - Second generation cephalosporins have greater activity against *Haemophilus influenza* (*H.flu*) and enhanced activity against gram-negative organisms in vitro compared to first generation cephalosporins.
  - The third generation cephalosporins are more active against gram-negative bacilli versus first or second generation cephalosporins. However, they are not as active against susceptible strains of staphylococci compared to first generation cephalosporins. With the exception of cefuroxime, the first and second generation cephalosporins are not able to effectively penetrate the cerebrospinal fluid and therefore should not be used to treat central nervous system infections. Conversely, the third generation cephalosporins do effectively penetrate the cerebrospinal fluid.
  - The fourth generation cephalosporins have enhanced activity against gram-negative bacteria compared to the first and second generation cephalosporins and have activity in vitro against gram-negative bacteria that are typically resistant to the third generation cephalosporins, including *Pseudomonas aeruginosa* and *Enterobacteriaceae*. The fourth generation currently includes only 1 parenteral agent, cefepime.
- The cephalosporin class reviews will focus on the oral first through third generation agents. More specifically, this class review will discuss the oral third generation cephalosporins.
- The third generation cephalosporin agents include cefdinir, cefditoren, cefixime, cefpodoxime and ceftibuten. Cefdinir is FDA (Food and Drug Administration) approved to treat respiratory (i.e. bronchitis, otitis media, sinusitis, pneumonia, pharyngitis and tonsillitis) and dermatological infections. Cefditoren is FDA approved for treatment of respiratory (i.e. bronchitis, pneumonia, pharyngitis and tonsillitis) and dermatological infections. Cefixime is approved to treat genitourinary and respiratory (i.e. bronchitis, otitis media, pharyngitis and tonsillitis) infections. Cefpodoxime is FDA approved for dermatological, genitourinary, and respiratory (i.e. bronchitis, sinusitis, pneumonia, otitis media, pharyngitis and tonsillitis) infections. Ceftibuten is FDA approved for respiratory (i.e. bronchitis, otitis media, pharyngitis and tonsillitis) infections. (See MedMetrics class Review, Table 3, pg. 2)
Common and Severe Adverse Reactions (See MedMetrics class review, Table 7, pg. 27):
As a class, the third generation cephalosporins have the following side effects in common: nausea, diarrhea, Stevens-Johnsons Syndrome and toxic epidermal necrolysis. Other common and severe adverse reactions include:

- **cefdinir**: abdominal pain, candida vaginitis, hepatitis, hepatotoxicity, and immune hypersensitivity reaction
- **cefditoren**: candida vaginitis, erythema multiforme, *Clostridium difficile* colitis, pseudomembranous enterocolitis, immune hypersensitivity reaction, acute renal failure, and interstitial pneumonia.
- **cefixime**: abdominal pain, flatulence, indigestion, loose stool, erythema multiforme, clostridium difficile colitis, anaphylaxis, acute renal failure, and angioedema
- **cefpodoxime**: diarrhea rash and *Clostridium difficile* colitis
- **ceftibuten**: vomiting, headache, serum blood urea nitrogen raised, melena, and psychotic disorder.

- The third generation cephalosporins are contraindicated in patients with a known allergy to the cephalosporin group of antibiotics. Careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins or other drugs before therapy with a third generation cephalosporin is initiated as caution should be exercised due to documented cross-sensitivity among β-lactam antibiotics which may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction occurs, discontinue the drug.

- *Clostridium difficile* associated diarrhea (CDAD) has been reported with the use of almost all antibacterial agents, ranging in severity from mild diarrhea to fatal colitis. Careful medical history is required as CDAD may occur over two months after administration of antibiotics. If CDAD is suspected or confirmed, ongoing antibiotics not intended to treat CDAD may have to be discontinued. An increased incidence of diarrhea associated with *C difficile* was observed in early trials of cefpodoxime in normal patients. *C difficile* or *C difficile* toxins were reported in 10% of the cefpodoxime-treated patients with diarrhea, though no specific diagnosis of pseudomembranous colitis was made in these patients. Reports of pseudomembranous colitis have been received in post-marketing experience with cefpodoxime. Additionally, the third generation cephalosporins should be used with caution in patients with a history of gastrointestinal disease and/or colitis.

- The third generation cephalosporins should be used with caution in patients with markedly impaired renal function. Careful monitoring and laboratory testing is recommended, and dose adjustment may be necessary. Specifically, the dose of cefixime should be adjusted in patients with renal impairment as well as those undergoing continuous ambulatory peritoneal dialysis and hemodialysis.

- Cephalosporins may be associated with a fall in prothrombin activity. Renal or hepatic impairment, poor nutritional state, patients receiving a protracted course of antibiotic therapy and patient previously stabilized on anticoagulant therapy are at an increased risk. Prothrombin time should be monitored in patients at risk. Patients receiving cefdinir, cefditoren and cefixime may show false-positive reactions for glucose in the urine with tests that use Benedict’s and Fehling’s solutions and also with Clinitest® tablets.

- Ceftibuten is not recommended when prolonged courses of antibiotics are needed. Other pivalate-containing compounds have caused clinical manifestations of carnitine deficiency when used over a period of months. No clinical effects of carnitine decrease have been associated with short-term treatment.

- Asmar et al performed a double-blind prospective randomized controlled trial that evaluated cefixime oral suspension 8mg/kg/day QD versus cefpodoxime oral suspension
10 mg/kg/day QD in patients aged 2 months to 17 years with acute suppurative otitis media. This trial included 368 participants for a duration of 10 days. On days 12 through 15, clinical cure or improvement was reported in 83 and 81% of patients treated with cefpodoxime and cefixime, respectively (P=0.541). Overall microbiologic susceptibility was reported as 89 and 86% in patients treated with cefpodoxime and cefixime, respectively (P=0.70). Drug-related adverse effects (e.g., diarrhea, diaper rash, vomiting and rash) occurred in 23.3 and 17.9% of patients treated with cefpodoxime and cefixime, respectively (no P values reported). Van Zyle L et al performed a double-blind prospective randomized controlled trial that evaluated cefditoren 200 mg BID versus cefditoren 400 mg BID versus cefpodoxime 200 mg BID. This trial included patients 12 years of age and older with community acquired pneumonia. The trial duration was 7 to 14 days post-treatment and included 851 participants. Clinical cure rates were similar between groups at both the post-treatment (48 hours post-treatment) and follow-up visits (seven to 14 days post-treatment). The overall clinical cure rates for cefditoren 200 mg, cefditoren 400 mg and cefpodoxime were 90.5, 89.7 and 92.2% respectively at the post-treatment visit (no P values reported).


The 2010 Global Initiative for Chronic Obstructive Lung Disease (COPD) guidelines recommend the use a second or third generation cephalosporin as an alternative to penicillin, ampicillin, amoxicillin, tetracycline or sulfamethoxazole/trimethoprim in patients with chronic obstructive pulmonary disease and mild exacerbations with no risk of a poor outcome.

**RECOMMENDATION**

Cephalosporins are grouped into generations based on their spectrum of activity. The third generation cephalosporins include cefdinir, cefditoren, cefixime, cefpodoxime and ceftibuten. The third generation cephalosporins are active against streptococci, Haemophilus influenza and Moraxella catarrhalis and are more active against gram-negative bacilli compared to other cephalosporins. However, they are not as active against susceptible strains of staphylococci compared to first generation cephalosporins. Treatment guidelines identify third generation cephalosporins as alternative empiric agents for the treatment of community acquired pneumonia, and as treatment options for infections due to Enterobacteriaceae. These agents are also considered alternative agents for the treatment of otitis media in patients with non-type 1 penicillin allergies. Additionally guidelines recommend 3rd generation cephalosporins as an alternative agent in patients with COPD and mild exacerbations with no risk of poor outcome. In the treatment of lower respiratory tract infections including community acquired pneumonia, no consistently significant differences were observed when compared with agents within the class. Therefore it is recommended that at least 3 third generation cephalosporin agents are available that will allow for full antibacterial coverage within the class. Additionally, a liquid formulation should be available for the pediatric population.

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**RE-REVIEW: 3RD GENERATION CEPHALOSPORINS**

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<td>cefditoren (compares to Spectracef®)</td>
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References


RE-REVIEW: TETRACYCLINES

BACKGROUND

- The tetracycline agents include demeclocycline, doxycycline, minocycline, and tetracycline.
- Tetracyclines have a broad spectrum of activity and are active against most Rickettsia, Chlamydia, Mycoplasma and many other gram-negative and gram-positive bacteria. Although there are some slight differences in the relative degree of activity against certain organisms, the tetracycline agents are essentially the same.
- The tetracyclines reversibly bind to the 30S ribosomal unit, thus inhibiting protein synthesis. Tetracyclines are primarily bacteriostatic. However, in high concentrations tetracyclines can possess bactericidal effects.
- Tetracyclines are FDA approved to treat dermatological, gastrointestinal, genitourinary conditions, ophthalmic, respiratory, rickettsial, sexually transmitted infections and other miscellaneous infections (i.e. periodontitis, relapsing fever, tularemia). Additionally, all of these agents are FDA approved as alternative treatments for the following conditions: uncomplicated gonococcal infections, syphilis, Vincent’s infection, listeriosis (immediate release minocycline and demeclocycline only) and Yaws. Tetracyclines are often used for treatment of acne vulgaris and as adjuncts in the treatment of periodontitis. The action of tetracyclines in the treatment of acne vulgaris is not fully understood but is thought to be due to their antibacterial actions in addition to other mechanisms. Tetracyclines inhibit growth of susceptible organisms on the surface of the skin and reduce the concentration of free fatty acids in sebum. The mechanism of action of these agents in the treatment of periodontitis is unknown, but it is believed that tetracyclines work by inhibiting collagenase which breaks down connective tissue and leads to the separation of the gum from the tooth.
  - Doxycycline hyclate 20mg tablet has a sole indication for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.
  - Demeclocycline has the ability to antagonize the actions of anti-diuretic hormone, vasopressin at the collecting duct in the nephron, thus causing a nephrogenic diabetes insipidus. As a result of this side effect, the agent has been utilized off-label as the preferred alternative pharmacological treatment for chronic forms of Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH).
Minocycline extended release formulation is only FDA approved for the treatment of non-nodular moderate to severe acne vulgaris with inflammatory lesions in patients 12 years of age or older.

- **Common and Severe Adverse Reactions** (see MedMetrics class review, table 7, pg. 20): Tetracyclines as a class may cause photosensitivity and/or phototoxicity. Therefore an increased risk of sunburn may occur with exposure to sunlight or other light sources. Therapy should be discontinued if skin erythema occurs. Additionally, tooth discoloration and enamel hypoplasia may occur and therefore, tetracyclines are contraindicated in children during tooth development (i.e., less than 8 years of age).
  - **Demeclocycline**: nephrogenic diabetes insipidus
  - **Doxycline**: diarrhea, nasopharyngitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, clostridium difficile, diarrhea, hepatotoxicity, immune hypersensitivity reaction, bulging fontanelle, and pseudotumor cerebri (intracranial hypertension)
  - **Minocycline**: dizziness, vertigo, anaphylaxis, drug hypersensitivity syndrome, immune hypersensitivity reaction, systemic lupus erythematosus, bulging fontanelle, and pseudotumor cerebri
  - **Tetracycline**: acidosis, azotemia, increased serum blood urea nitrogen, bulging fontanelle, pseudotumor cerebri, and raised intracranial pressure
  - **Demeclocycline** is contraindicated with concurrent use of methoxyflurane anesthetic to avoid potential renal toxicity. Additionally, outdated demeclocycline and tetracycline may cause nephropathy.

- **Significant Drug-Drug Interactions** (See MedMetrics class review, Table 8, pg. 23):
  - The coadministration of aluminum, bismuth (liquid formulation), calcium, iron, magnesium and zinc salts decreases tetracycline serum levels, thus possibly reducing the anti-infective response.
  - Coadministration of tetracyclines with digoxin or anticoagulants may cause an increase in the interacting drug’s serum levels, possibly causing digoxin toxicity and increased warfarin pharmacological effect.
  - Coadministration of tetracyclines with penicillins causes a decreased pharmacologic effect.
  - Retinoids given in conjunction with tetracyclines may increase intracranial hypertension.
  - Coadministration of urinary alkalinizers may decrease tetracycline drug serum levels.

- A double blind randomized clinical trial performed by Daniels et al evaluated doxycycline 200 mg/day for 7 days versus placebo. This trial included hospitalized patients ≥45 years of age with an acute exacerbation of COPD. This trial included 223 participants with a 30 day duration. The clinical response at 30 days showed success rates of 61% (n=78) in patients receiving doxycycline and 53% (n=72) in the patients receiving placebo. (OR, 1.3; 95% CI, 0.8 to 2.0; P=0.32).

- Another, double-blind randomized controlled trial performed by Maesen et al evaluated doxycycline 100mg BID for 7 days versus minocycline 100mg BID for 7 days. Patients admitted to the hospital due to purulent exacerbations of chronic respiratory disease were included in the trial. This trial included 41 participants for a 15 day duration. The bacteriological and clinical assessment before and immediately after treatment showed no differences between doxycycline and minocycline, nor did further evaluation after seven days follow up show any difference (P values not reported).

- The 2007 Infectious Diseases Society of America and American Thoracic Society guidelines for the management of community acquired pneumonia in adults recommend a macrolide with doxycycline mentioned as an alternate option for patients with no risk factors for drug resistance. A fluoroquinolone is a treatment option for patients in an area with a high rate of macrolide resistance.
- The Infectious Diseases Society of America 2011 guidelines recommend a tetracycline (doxycycline or minocycline) along with other antibiotic options (i.e. clindamycin,
SMX/TMP, linezolid) for empiric therapy in community associated MRSA (Methicillin-Resistant Staphylococcus Aureus) skin and soft-tissue infections in adults and children.

**RECOMMENDATION**

The tetracyclines are FDA approved for use in various infectious diseases based on their activity against certain microorganisms. They work by inhibiting bacterial protein synthesis. These agents may be considered therapeutic alternatives to one another, as clinical trials have not exhibited any clinically significant differences within the class. However, minocycline and doxycycline may possess some advantages which may contribute to their high utilization, such as once to twice daily dosing as a result of longer elimination half-lives compared to the other agents within the class. Doxycycline may cause less photosensitivity and binds calcium to a lesser extent compared to tetracycline. Given that demeclocycline is the preferred alternative pharmacological treatment for chronic SIADH, it should be accessible for this subgroup of patients. Therefore it is recommended that at least doxycycline be available, with demeclocycline available for patients with SIADH. Doxycycline hyclate 20mg tablet has a sole indication for use as an adjunct in patients with adult periodontitis. Additionally, minocycline extended release formulation is only FDA approved for the treatment of non-nodular moderate to severe acne vulgaris with inflammatory lesions in patients 12 years of age or older. Therefore both doxycycline hyclate 20mg tablets and the minocycline extended release formulation should be subject to clinical criteria to ensure their appropriate use.

**COMMITTEE VOTE:**

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**Clinical Criteria for demeclocycline:**

Will be approved without requiring previous trials of preferred agents if being used for the treatment of SIADH

**COMMITTEE VOTE:**

APPROVED  DISAPPROVED  APPROVED with MODIFICATION
**ANTI-INFECTIVE AGENTS**

**Clinical Criteria for doxycycline hyclate 20mg (Periostat®):**

Will be approved when BOTH of the following conditions are met:

- When used as an adjunct to scaling and root planing to promote attachment level gain and reduce pocket depth for adult periodontitis.
- In patients with any of the following:
  - Multiple sites unresponsive to mechanical debridement
  - Acute infections
  - Medically compromised patients
  - Tissue-invasive organisms and ongoing disease progression

**COMMITTEE VOTE:**

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**Clinical Criteria for minocycline ER (Solodyn®):**

Will be approved if ALL of the following are true:

- Diagnosis is for the treatment of non-nodular moderate to severe acne vulgaris with inflammatory lesions.
- Recipient has failed, has an intolerance, contraindication or adverse reaction to at least two of the following topical agents:
  - Metronidazole (Metrogel®)
  - Azelaic acid (Azelex®, Finacea®)
  - Erythromycin (A/T/S® solution, gel)
  - Clindamycin (Cleocin T®)
  - Topical keratolytic agents (such as benzoyl peroxide, salicylic acid preparations)
- Recipient requires long-term therapy with an oral tetracycline
- Recipient must be less than 21 years old

**COMMITTEE VOTE:**

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**Quantity Limits:**

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**References**

RE-REVIEW: MACROLIDES

BACKGROUND

- The macrolide family of antibiotics includes azithromycin, clarithromycin, erythromycin and fidaxomicin. This class review will focus on fidaxomicin, the only new chemical entity in this class since the previous review by the PAC committee.
- The macrolides work by binding to the 50S subunit of bacterial ribosomes, ultimately inhibiting bacterial protein synthesis.
- The macrolides are approved to treat a wide variety of infections caused by susceptible organisms including but not limited to upper and lower respiratory tract infections, skin and skin structure infections, sexually transmitted diseases, *Helicobacter pylori* infection and duodenal ulcer disease, listeriosis, diphtheria, pertussis, and intestinal amebiasis. Fidaxomicin is approved only for the treatment of *Clostridium difficile*-associated diarrhea.
- Gastrointestinal symptoms, including abdominal pain, nausea and vomiting, were the most common adverse events associated with the use of fidaxomicin in clinical trials. Other common adverse events included anemia and neutropenia. Serious adverse events associated with the use of fidaxomicin include bowel obstruction and gastrointestinal hemorrhage.
  - Since there is minimal systemic absorption of fidaxomicin, it is not effective for systemic infections.
  - No drug-drug interactions have been identified with fidaxomicin.
- Fidaxomicin was compared to vancomycin in a randomized controlled trial of 629 patients with a diagnosis of *C difficile* infection. Rates of clinical cure with fidaxomicin were noninferior to those with vancomycin (88.2 vs 85.8%). Additionally, significantly fewer fidaxomicin-treated patients had recurrence of infection (15.4 vs 25.3%; 95% CI, -16.6 to -2.9; P=0.005) and fidaxomicin resulted in significantly higher rates of global cure (resolution of diarrhea without recurrence) (74.6 vs 64.1%; 95% CI, 3.1 to 17.7; P=0.006).
- Current guidelines from the Infectious Diseases Society of America (IDSA) recommend oral metronidazole as the drug of choice for the initial episode of mild to moderate *C difficile* infection and oral vancomycin as the drug of choice for the initial episode of severe *C difficile* infection. Currently, clinical treatment guidelines have not incorporated the use of fidaxomicin in the treatment of *C difficile* diarrhea.

RECOMMENDATION

The macrolide antibiotics are used to treat a variety of infections caused by susceptible organisms including but not limited to upper and lower respiratory tract infections, skin and skin structure infections, sexually transmitted diseases, *Helicobacter pylori* infection and duodenal ulcer disease, listeriosis, diphtheria, pertussis and intestinal amebiasis. Treatment guidelines recommend the use of macrolide antibiotics (excluding fidaxomicin) as the preferred empiric treatment for community acquired pneumonia in otherwise healthy patients and they are primary treatment options for various skin and soft tissue infections, various sexually transmitted diseases, and pertussis as well as primary and secondary prophylaxis and treatment of *Mycobacterium avium* Complex disease. Overall, the macrolide antibiotics have demonstrated efficacy for their respective indications and available head-to-head studies do not consistently demonstrate the "superiority" of one macrolide over another. However, due to varying indications and spectrums of activity, it is recommended erythromycin, azithromycin and clarithromycin should be available.
Fidaxomicin is the newest agent approved in the macrolide class and is a narrow-spectrum agent approved for the treatment of *Clostridium difficile*-associated diarrhea. For the treatment of *Clostridium difficile* diarrhea, fidaxomicin was shown to be non-inferior to vancomycin though it was also shown to have significantly lower rates of recurrence and higher rates of global cure. Current guidelines recommend metronidazole as the treatment of choice for the initial episode of mild to moderate *C difficile* infection, with oral vancomycin reserved for the treatment of severe *C difficile* infection. Due to its narrow-spectrum of activity and lack of endorsement by current clinical guidelines, it is recommended fidaxomicin should be subject to clinical criteria.

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### RE-REVIEW: MACROLIDES

**PREFERRED**
- azithromycin
  - azithromycin suspension
  - clarithromycin (compares to Biaxin)
  - erythromycin generic products
  - erythromycin/sulfisoxazole

**NON-PREFERRED**
- Biaxin (clarithromycin)
- Biaxin XL, clarithromycin ER
- clarithromycin ER (compares to Biaxin XL)
- Dificid (fidaxomicin)
- erythromycin brand products
- Zithromax, azithromycin
- Zmax (azithromycin extended release)

**Clinical Criteria for azithromycin suspension**
- No PA required for 11 years old & younger.
- All others: Will be approved for patients unable to swallow tablets.

**COMMITTEE VOTE:**

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**Clinical Criteria for Dificid**
- Dificid will be approved for recipients meeting the following criteria:
  - Diagnosis of *Clostridium difficile* (C. diff) associated diarrhea
  - Trial and failure of oral vancomycin within the past 30 days

**NOTE:** Individuals started on Dificid therapy in the hospital will be approved for this agent following hospital discharge in order to allow for completion of the course of therapy.

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References

RE-REVIEW: KETOLIDES

BACKGROUND

- Telithromycin is the first member of the ketolide group of antibiotics which is related to the macrolide group of antibiotics. It was developed to target respiratory pathogens resistant to the macrolides.
- Telithromycin works by binding to two sites on the 50S ribosomal subunit. Compared to the macrolides, structural modifications enable it to bind more tightly to bacterial ribosomes. These modifications result in decreased resistance, an improved pharmacokinetic profile and increased potency.
- Telithromycin is FDA approved to treat community acquired pneumonia due to Streptococcus pneumoniae, including multi-drug resistant isolates, Haemophilus influenzae, Moraxella catarrhalis, Chlamydophila pneumoniae and Mycoplasma pneumoniae.
- Adverse reactions most commonly associated with the use of telithromycin include diarrhea, nausea, vomiting, dizziness and headache. Less common, but severe, adverse reactions include prolonged QT interval, Torsades de Pointes, visual disturbances, loss of consciousness, hepatotoxicity, and respiratory failure.

  - Telithromycin carries a black box warning regarding its contraindication in patients with myasthenia gravis. Fatal and life-threatening respiratory failure has been reported in patients with myasthenia gravis associated with the use of Ketek®.
  - In addition to its contraindication in patients with myasthenia gravis, telithromycin is contraindicated in patients with previous history of hepatitis and/or jaundice associated with the use of the agent or any macrolide antibiotic.
  - On January 20, 2006, the FDA issued a public health advisory regarding the risk of liver injury in patients taking telithromycin, and in June of 2006, warnings regarding the risk of acute hepatic failure and severe, potentially fatal liver injury were strengthened in telithromycin’s product labeling. The hepatic reactions which have been reported include fulminant hepatitis and hepatic necrosis necessitating liver transplant in some patients.
  - Telithromycin may prolong the QT interval in some patients, leading to an increased risk for ventricular arrhythmias including torsades de pointes. Avoid the use of telithromycin in patients with congenital QT prolongation and in patients with pro-arrhythmic conditions such as hypokalemia, hypomagnesemia, clinically significant bradycardia and in patients receiving Class IA or Class III antiarrhythmic agents.
Prescribing telithromycin in the absence of proven or strongly suspected bacterial infection or prophylactic indication is unlikely to provide benefit and increases the risk of development of drug-resistant bacteria.

Concurrent administration of telithromycin with cisapride or pimozide is contraindicated. Concurrent administration of telithromycin with colchicine in patients with renal or hepatic impairment is contraindicated. See Table 8 in MedMetrics therapeutic class review for other clinically significant drug-drug interactions.

Overall, telithromycin has demonstrated efficacy in the treatment of community acquired pneumonia. Open-label studies demonstrate efficacy in clinical and bacteriologic response, including the treatment of erythromycin-resistant *Streptococcus pneumoniae* and penicillin-resistant *Streptococcus pneumoniae*.

A randomized, controlled trial compared telithromycin to clarithromycin for the treatment of acute community-acquired pneumonia in 448 patients. No significant difference was observed between groups in clinical cure rates at the post-therapy test-of-cure visit (88.3% for telithromycin and 88.5% for clarithromycin).

Current guidelines on the management of community-acquired pneumonia from the Infectious Diseases Society of America/American Thoracic Society recommend a macrolide (azithromycin, clarithromycin or erythromycin) for treatment of previously healthy patients with no risk factors for drug resistant *Streptococcus pneumoniae* infection. A respiratory fluoroquinolone (moxifloxacin, gemifloxacin or levofloxacin) is the treatment option in regions with a high rate of macrolide-resistant *S pneumoniae*, or for patients with comorbidities. Safety concerns with telithromycin have prompted the FDA to conclude that the risks of therapy outweigh the benefits in the treatment of minor illnesses. In patients with mild to moderate community acquired pneumonia, telithromycin should be reserved as a second-line agent to other antimicrobial agents.

RECOMMENDATION
Telithromycin is FDA approved to treat community acquired pneumonia due to *Streptococcus pneumoniae*, including multi-drug resistant isolates, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. Clinical trial demonstrate efficacy in clinical and bacteriologic response, including the treatment of erythromycin-resistant *S pneumoniae* and penicillin-resistant *S pneumoniae*. However, no significant differences were observed in clinical or bacteriologic response rates when comparing 10 days of therapy with either telithromycin or clarithromycin. Telithromycin is associated with significant safety risks, including hepatotoxicity, prompting the FDA to conclude that the risks of therapy outweigh the benefits in the treatment of minor illnesses. Currently clinical guidelines for the treatment of community-acquired pneumonia recommend a macrolide for the treatment of most patients with respiratory quinolones recommended in regions with a high rate of macrolide-resistant *S pneumoniae*, or for patients with comorbidities. In patients with mild to moderate community acquired pneumonia, telithromycin should be reserved for patients failing other antimicrobial agents. Due to its significant safety concerns as well as place in therapy it is recommended telithromycin should be subject to step therapy.

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February 23, 2012 Tennessee PAC
### Step Therapy for Ketek®:

Approved for treatment of community-acquired pneumonia in patients with previous trial (within 28 days) and failure of *at least TWO of the following:* a penicillin, cephalosporin, sulfonamide, advanced macrolide, quinolone, or doxycycline.

### COMMITTEE VOTE:

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### References


### BACKGROUND

- Vancomycin is a bactericidal antibiotic that binds to the bacterial cell wall causing immediate inhibition of cell wall synthesis and secondary damage to the cytoplasmic membrane.
- Oral vancomycin is FDA approved for the treatment of enterocolitis due to *Staphylococcus aureus* (including methicillin-resistant strains) or antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile*.
- Nausea and vomiting are the most common adverse events associated with oral administration of vancomycin. Ototoxicity and nephrotoxicity are the most serious adverse events of parenteral vancomycin therapy. Clinically significant serum concentrations have been reported in some patients that have taken multiple oral doses, and monitoring of serum concentrations may be appropriate in some instances (e.g., patients with renal insufficiency and/or colitis). In addition, some patients with inflammatory disorders of the intestinal mucosa may have significant systemic absorption and be at risk for adverse events associated with the intravenous formulation of vancomycin. The risk may be exacerbated by renal impairment.
  - Vancomycin should be used with caution and monitored regularly in patients with renal insufficiency, due to a greater risk of toxicity when blood concentration levels are high.
  - Concurrent use of vancomycin and aminoglycosides may cause additive ototoxicity and nephrotoxicity.
- For the treatment of pseudomembranous colitis caused by *Clostridium difficile* infection, Zar et al compared vancomycin to metronidazole in a double-blind, randomized trial and stratified the results by severity of disease. For mild disease there was no significant differences in cure rate between vancomycin and metronidazole (98 vs 90%, *P*=0.36).
ANTI-INFECTIVE AGENTS

However, the cure rate in severe disease was significantly higher with vancomycin (97 vs 76%, P=0.02). There was no significant difference between the treatments in relapse rates.

- Current guidelines from the Infectious Diseases Society of America (IDSA) recommend oral metronidazole as the drug of choice for the initial episode of mild to moderate *Clostridium difficile* infection and oral vancomycin as the drug of choice for the initial episode of severe *C difficile* infection. For the treatment of Intra-abdominal infections, IDSA recommends use of oral vancomycin if methicillin-resistant *Staphylococcus aureus* is proven or suspected as the causative organism.

**RECOMMENDATION**

Oral vancomycin is FDA-approved for the treatment of enterocolitis due to *Staphylococcus aureus* or *Clostridium difficile* pseudomembranous colitis. Clinical trials have demonstrated the similar efficacy between vancomycin and metronidazole in the treatment of mild *C difficile* pseudomembranous colitis. Current guidelines recommend metronidazole as the treatment of choice for the initial episode of mild to moderate *C difficile* infection with oral vancomycin reserved for the treatment of severe *C difficile* infection. Due to concerns regarding the emergence of resistance, it is recommended oral vancomycin should be subject to clinical criteria to ensure appropriate use.

**COMMITTEE VOTE:**

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### RE-REVIEW: ORAL GLYCOPEPTIDES

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<tr>
<td>N/A</td>
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**Clinical Criteria for Vancocin®:**

Approval will be granted for individuals meeting **ALL** of the following criteria:

- Diagnosis of enterocolitis caused by *Staphylococcus aureus*, OR
- Diagnosis of pseudomembranous colitis caused by *C. difficile*, AND trial and failure of, contraindication, adverse reaction or drug-drug interaction to oral metronidazole **unless there is a contraindication, adverse reaction, or drug to drug interaction that would preclude its use.**

The following is a common list (not all inclusive) of reasons why metronidazole may not be appropriate:

- Recipient is either pregnant or a child under the age of 10
- Recipient is severely ill
- Recipient is receiving an alcohol related compound (interaction with metronidazole)
- Recipient is allergic to metronidazole
- The organism is resistant to metronidazole
- There is evidence suggesting the diarrhea is caused by *Staphylococcus aureus*
- The recipient failed metronidazole in the past
- The diarrhea is suspected recurrent *C. difficile* colitis

**COMMITTEE VOTE:**

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

**References**


RE-REVIEW: LINCOSAMIDES

BACKGROUND

- Clindamycin is the only orally available lincosamide.
- Clindamycin exerts its effect by binding to the 50S ribosomal subunit of bacteria, ultimately disrupting bacterial protein synthesis.
- Clindamycin is FDA approved to treat serious respiratory tract, skin and skin structure infections caused by susceptible strains of streptococci and staphylococci. Also serious respiratory tract infections caused by susceptible strains of pneumococci and serious infections caused by susceptible anaerobic bacteria; including but not limited to intra-abdominal infections and infections of the female genital tract.
- Common adverse reactions associated with the use of oral clindamycin include rash, nausea, diarrhea and abdominal pain. Less common, but severe, reactions may include pseudomembranous colitis, Clostridium difficile associated diarrhea (CDAD), agranulocytosis, increased liver function tests and jaundice.
  - Clindamycin carries a black box warning regarding the risk of CDAD. CDAD has been reported with use of nearly all antibacterial agents, including clindamycin and may range in severity from mild diarrhea to fatal colitis. Because clindamycin therapy has been associated with severe colitis which may end fatally, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate.
  - Clindamycin should be prescribed with caution in patients with a history of gastrointestinal disease, particularly colitis. Clindamycin should be prescribed with caution in atopic patients. Prescribing clindamycin in the absence of proven or strongly suspected bacterial infection or prophylactic indication is unlikely to provide benefit and increases the risk of development of drug-resistant bacteria.
  - Gastrointestinal absorption is delayed for clindamycin when administered with kaolin-pectin antidiarrheals. Administer kaolin-pectin suspension two hours before clindamycin.
- Overall, clindamycin has shown efficacy for its approved indications.
  - In the treatment of group A β-hemolytic streptococcus infection, oral clindamycin therapy was associated with a significantly higher cure rate at day 12 compared to amoxicillin/clavulanic acid (92.6% vs 85.2%, p<0.003). However, no significant difference between groups was observed in cure rates at three months and no significant difference in bacteriologic efficacy was observed at day 12 or at three months.
- Lincosamides are generally reserved for situations when penicillin should not be used, such as patients with penicillin allergies and/or resistant organisms. For the treatment of community acquired pneumonia, treatment guidelines from the Infectious Diseases Society of America (IDSA) identify clindamycin as recommended therapy in patients infected with anaerobic bacteria and as an alternative agent for infections involving Streptococcus pneumonia, methicillin-susceptible Staphylococcus aureus and Bacillus anthracis (inhalation). The American Academy of Pediatrics (AAP) recommends clindamycin as an alternative agent for the treatment of acute otitis media and sinusitis in patients with a type-1 allergy to penicillin. For the treatment of skin and soft tissue
infections, IDSA states clindamycin, along with semisynthetic penicillins, first or second generation oral cephalosporins or macrolides, may be used as empiric therapy, though clindamycin resistance rates may be as high as 50% in patients with methicillin-resistant *S aureus* (MRSA) infections. Additionally, IDSA recommends clindamycin as an initial or alternative agent for various types of skin and skin structure infections, including but not limited to human bites, animal bites, cellulitis, and necrotizing infections.

**RECOMMENDATION**

Clindamycin is the only orally available lincosamide and is FDA approved to treat serious respiratory tract, skin and skin structure infections caused by susceptible bacteria, as well as serious infections caused by susceptible anaerobic bacteria. Clindamycin has shown efficacy for its approved indications; however it also carries a black box warning regarding its association with potentially fatal colitis. As such, it should be reserved for serious infections where less toxic antibiotics are inappropriate. Current clinical guidelines recommend clindamycin as initial or alternative therapy in a number of infections including, but not limited to, community acquired pneumonia, acute otitis media, sinusitis, and various types of skin and skin structure infections. Lincosamides are generally reserved for anaerobic coverage or situations when penicillin should not be used, such as patients with penicillin allergies and/or resistant organisms. Given their role in the treatment of various infections, particularly in patients with penicillin allergy, it is recommended oral clindamycin, including the pediatric dosage form, should be available for use.

**COMMITTEE VOTE:**

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**RE-REVIEW: LINCOSAMIDES**

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<td>Cleocin Pediatric&lt;sup&gt;®&lt;/sup&gt; (clindamycin pediatric solution)</td>
<td>Cleocin&lt;sup&gt;®&lt;/sup&gt; (clindamycin)</td>
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**Clinical Criteria for Cleocin Pediatric<sup>®</sup> (clindamycin pediatric solution)**

- No PA required for 11 years old & younger.
- All others: Will be approved for patients unable to swallow tablets.

**COMMITTEE VOTE:**

APPROVED          DISAPPROVED          APPROVED with MODIFICATION

**References**

RE-REVIEW: OXAZOLIDINONES

BACKGROUND

- Linezolid is the only agent in the oxazolidinone class of antibiotics.
- Linezolid is bacteriostatic against enterococci and staphylococci, and bactericidal against most strains of streptococci. It acts early in translation by binding to a site on the bacterial 23S ribosomal ribonucleic acid of the 50S subunit and preventing the formation of a functional 70S initiation complex, which is an essential component of the bacterial translation process.
- Linezolid is FDA-approved for the treatment of uncomplicated and complicated skin and skin structure infections and community- and hospital-acquired pneumonia, as well as vancomycin-resistant Enterococcus (VRE) infections.
- Diarrhea, nausea, vomiting, rash, headache and fever are the adverse reactions most commonly associated with the use of linezolid. Myelosuppression, elevated liver tests, peripheral or optic neuropathy, seizures and lactic acidosis have also been reported.
  - Unless blood pressure is closely monitored, linezolid should not be used in patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or taking directly or indirectly acting sympathomimetic agents, vasopressive agents or dopaminergic agents. Linezolid should also not be administered to patients with carcinoid syndrome and/or patients taking serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists, meperidine or buspironone unless they are carefully monitored for serotonin syndrome.
  - Linezolid has no activity against gram-negative pathogens and appropriate therapy should be administered if a concomitant gram-negative pathogen is found.
- Linezolid has demonstrated efficacy compared to other agents used for the same FDA-approved indications. Specifically, linezolid has similar efficacy to vancomycin for the treatment of community-acquired and nosocomial pneumonia and complicated and uncomplicated skin and skin structure infections. For the treatment of vancomycin-resistant Enterococcus faecium, linezolid did not have a significantly different clinical response compared to quinupristin/dalfopristin.
  - Linezolid was compared to vancomycin or teicoplanin for the treatment of nosocomial pneumonia in 2,329 patients. There were no significant differences in clinical cure (RR, 1.01; 95% CI, 0.93 to 1.10; P=0.83), microbiological eradication (RR, 1.10; 95% CI, 0.98 to 1.22; P=0.10) and mortality (RR, 0.95; 95% CI, 0.76 to 1.18; P=0.63). There was also no significant difference in microbiological eradication in patients with MRSA between linezolid and vancomycin or teicoplanin (RR, 1.10; 95% CI, 0.87 to 1.38; P=0.44).
  - Linezolid was compared to vancomycin in 813 patients with skin and soft tissue infections due to MRSA. There was no significant difference in clinical cure between linezolid and vancomycin treated patients (RR, 0.34; 95% CI, 0.04 to 2.89; P=0.32).
  - Linezolid was compared to quinupristin/dalfopristin in 40 patients with VRE infections. Clinical response at the end of therapy were not significantly different between patients receiving quinupristin/dalfopristin and patients receiving linezolid (P=0.6). There was no statistically significant difference between the
number of deaths caused by infection, relapse, or microbiological response between the two treatment arms (all P>0.05). The rate of myalgias/arthritis in patients receiving quinupristin/dalfopristin was 33% as compared to 0% in patients receiving linezolid (P<0.01). All other reports of adverse effects were found to be not significant (P>0.05).

- Clinical guidelines from the Infectious Diseases Society of America (IDSA) recommend linezolid for the treatment of community-acquired pneumonia and skin and soft-tissue infections when the causative organism is methicillin-resistant *Staphylococcus aureus* (MRSA). Linezolid is also recommended to be included as empiric therapy for hospital-acquired pneumonia, ventilator-associated pneumonia or healthcare-associated pneumonia in patients with late onset of disease or known risk factors for multidrug-resistant pathogens. Additionally, IDSA recommends linezolid as the preferred agent for the treatment of systemic infection confirmed due to ampicillin- and vancomycin-resistant *Enterococcus faecalis/faecium*.

**RECOMMENDATION**
The only drug contained in the oxazolidinone class is linezolid. It is indicated for skin and skin structure infections, pneumonia and vancomycin-resistant *Enterococcus* infections. Linezolid is effective against methicillin-resistant *Staphylococcus aureus* (MRSA) and multi-drug resistant *Streptococcus pneumoniae*. Linezolid has demonstrated similar efficacy compared to other agents used for the same FDA-approved indications. To minimize the emergence of resistance, guidelines recommend reserving linezolid use for infections caused by methicillin-resistant *Staphylococcus aureus* or ampicillin- and vancomycin-resistant *Enterococcus faecalis/faecium*. Therefore, it is recommended linezolid be subject to clinical criteria to ensure judicious use.

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**RE-REVIEW: OXAZOLIDINONES**

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**Clinical Criteria for Zyvox®:**

For oral therapy, the patient must have been diagnosed as follows:

- Vancomycin Resistant *Enterococcus faecium* infections, OR
- Vancomycin Resistant *Enterococcus faecalis* infections, OR
- Healthcare-associated Methicillin-Resistant *Staph aureus* (MRSA) infections or community-acquired MRSA with poly-resistance.

**Note:** The patient must have culture documentation of diagnoses. Individuals started on Zyvox® therapy in the hospital will be approved for the agent following hospital discharge in order to allow for completion of the course of therapy.

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**Quantity Limits:**

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<th>Zyvox®</th>
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**COMMITTEE VOTE:**

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ANTI-INFECTIVE AGENTS

References

RE-REVIEW: ORAL AMINOGLYCOSIDES

BACKGROUND
- Neomycin is the only agent in the oral aminoglycosides class. Neomycin is a broad spectrum antibiotic that is bactericidal against both gram-negative and some gram-positive bacteria.
- The antibacterial properties of neomycin result from the inhibition of bacterial protein synthesis by irreversibly binding to the 30S ribosomal subunit.
- Oral neomycin is FDA-approved to inhibit ammonia-forming bacteria in the gastrointestinal tract in conjunction with protein restriction and supportive therapy in patients with hepatic encephalopathy. The oral tablet is also approved for use as an adjunct to mechanical cleansing of the large intestine in patients undergoing colorectal surgery.
- Adverse events most commonly associated with oral neomycin include diarrhea, nausea and vomiting. As with other aminoglycosides, ototoxicity, neurotoxicity and nephrotoxicity have been reported with neomycin.
  - Neomycin carries a black box warning regarding the potential for ototoxicity, neurotoxicity and nephrotoxicity.
  - Neomycin is contraindicated in patients with intestinal obstruction as well as patients with inflammatory or ulcerative gastrointestinal disease.
  - The risk of nephrotoxicity and ototoxicity due to neomycin is greater in patients with impaired renal function. Aminoglycosides should be used with caution in patients with muscular disorders such as myasthenia gravis or parkinsonism due to the potential to aggravate muscle weakness.
o Concurrent and/or sequential systemic, oral, or topical use of other aminoglycosides and other potentially nephrotoxic and/or neurotoxic drugs such as bacitracin, cisplatin, vancomycin, amphotericin B, polymyxin B, colistin, and viomycin should be avoided because the toxicity may be additive. The concurrent use of neomycin with potent diuretics such as ethacrynic acid or furosemide should be avoided since certain diuretics by themselves may cause ototoxicity. Neomycin inhibits the gastrointestinal absorption of digoxin, methotrexate, penicillin V, oral vitamin B-12, and 5-fluorouracil.

- When comparing antibiotic regimens for surgical prophylaxis, a trial by Lewis et al compared systemic antibiotic prophylaxis (metronidazole plus amikacin) only and systemic prophylaxis combined with oral antibiotics (metronidazole and neomycin). There were significantly fewer wound infections in the combined group compared to the systemic only group (5 vs 17, P<0.01).
- Neomycin has been compared to lactulose for the treatment of hepatic encephalopathy. Trials by Orlandi et al and Atterbury et al did not demonstrate significant differences between the treatment groups in change of hepatic encephalopathy grade or neuropsychiatric signs.
- The National Surgical Infection Prevention Project’s advisory statement for antimicrobial prophylaxis for surgery recommends oral neomycin plus oral erythromycin or oral neomycin plus oral metronidazole along with administration of a mechanical bowel preparation for patients undergoing colorectal surgery. The American College of Gastroenterology recommends lactulose as the first-line pharmacologic agent in the treatment of hepatic encephalopathy with antibiotics, including oral neomycin, reserved for patients who do not adequately respond to lactulose.

RECOMMENDATION
Neomycin is the only agent in the oral aminoglycosides class. Efficacy of neomycin as an adjunct treatment for the prophylaxis of surgical infections and hepatic encephalopathy has been demonstrated in clinical trials, although systemic absorption may lead to toxic reactions, such as neurotoxicity, ototoxicity and nephrotoxicity. For prophylaxis of surgical infections, guidelines recommend oral neomycin with oral erythromycin along with mechanical bowel preparation as a treatment option for use prior to colorectal surgery. Oral neomycin is recommended as a second line option for hepatic encephalopathy in patients that do not respond adequately to lactulose. Therefore, it is recommended oral neomycin should be available for use.

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RE-REVIEW: ORAL AMINOGLYCOSIDES

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<td>Neo-Fradin® (neomycin solution)</td>
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References
6. Atterbury CE, Maddrey WC, Conn HO. Neomycin-sorbitol and lactulose in the treatment of
RE-REVIEW: ORAL NITROIMIDAZOLES

BACKGROUND

- Metronidazole and tinidazole are antiprotozoal drugs that belong to the 5-nitroimidazole or oral nitroimidazole class of antibiotics. These agents are bactericidal and exert their effects by diffusing into bacteria, thus undergoing intracellular reduction via mechanisms unique to anaerobic bacteria. The reduced form of these agents become cytotoxic and disrupts DNA's helical structure, thereby inhibiting bacterial nucleic acid synthesis resulting in bacterial cell death.

- **Indications (See MedMetrics class review, Table 3, pg 2):**

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<th>FDA-Approved Indications</th>
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<th>Tinidazole</th>
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<td>X</td>
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<tr>
<td>Giardiasis</td>
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- Metronidazole and tinidazole appear to have similar clinical cure rates in regards to their shared FDA-approved indications. Although pharmacokinetic data is unavailable for tinidazole, given the similarities in chemistry between the agents, the assumption that these agents may have similar properties is reasonable. Tinidazole is believed to be at least as effective as metronidazole and may have a more favorable side effect and tolerability profile. Metronidazole and tinidazole appear to have similar clinical cure rates in regards to their shared FDA-approved indications. Compared to metronidazole, tinidazole has a longer duration of action (11 to 15 hours vs. eight hours) allowing for less frequent dosing, and a shorter treatment duration.

- **Common and Severe Adverse Reactions, (see MedMetrics class review, Table 7, pg. 25):**

  - **Metronidazole:** nausea, Jarisch Herxheimer reaction, dizziness, headache, candida infection of genital region, vaginal discharge/irritation, Stevens-Johnson syndrome, toxic epidermal necrolysis, leukopenia, aseptic meningitis, encephalopathy, peripheral neuropathy, seizure, disorder of optic nerve, ototoxicity and hemolytic uremic syndrome.

  - **Tinidazole:** nausea, altered sense of taste, candida vaginitis, hypersensitivity reaction, numbness, paresthesia, peripheral neuropathy and seizure.
o Metronidazole has a black box warning regarding its carcinogenic effects in mice and rats. Although, specific data has not been reported for tinidazole, as a result of the two drugs being related structurally and possessing similar biologic effects; tinidazole has the same black box warning regarding the risk of carcinogenicity. Therefore, unnecessary use of the drug should be avoided. It should be reserved only for conditions for which it is approved.

o Metronidazole and tinidazole should be administered with caution to patients with diseases of the central nervous system, as convulsive seizures, encephalopathy, aseptic meningitis, optic and peripheral neuropathy (characterized as numbness or paresthesia of an extremity) have been reported in patients treated with nitroimidazoles.

o While taking metronidazole or tinidazole, alcoholic beverages should be avoided for at least one day after completion or discontinuation of treatment when using the tablets, and at least three days if using capsules or an extended-release formulation.

o The nitroimidazoles may produce transient leukopenia and neutropenia, so metronidazole and tinidazole should be used with caution in patients with blood dyscrasias.

o Significant Drug-Drug Interactions (See MedMetrics class review, Table 8, pg. 28):
Concomitant use of nitroimidazoles with the agents below may potentially result in the following:

- **CYP3A4 Inducers** (i.e. phenobarbital, rifampin, phenytoin and fosphenytoin): decreased plasma levels of metronidazole or tinidazole.
- **CYP3A4 Inhibitors** (cimetidine and ketoconazole): increased plasma levels of metronidazole or tinidazole.
- **Cholestyramine**: decreased effectiveness of the oral nitroimidazole.
- **Disulfiram**: may result in central nervous system toxicity (psychotic symptoms, confusion) as well as severe nausea, vomiting and abdominal cramping.
- **Fluorouracil or Lithium**: increased fluorouracil or lithium plasma levels and possible toxicity of the interacting agent.
- **Warfarin**: may prolong prothrombin time, resulting in increased risk of bleeding.
- **Amiodarone**: Concurrent use of amiodarone and metronidazole may result in an increased risk of cardiotoxicity.

- Simjee et al randomized 48 patients to receive metronidazole or tinidazole 2 g daily for five days for the treatment of intestinal amebiasis and amebic liver abscesses. A second course of the same drug was given if the patient showed no clinical improvement after 5 days. There was no difference in cure rates between both treatment groups, with a clinical cure rate of 100% (P= not significant). However, 7.4% and 19.0% of patients in the metronidazole and tinidazole treatment groups, respectively, required a second course of treatment (P value not reported).

- Schwebke et al compared metronidazole 500 mg twice-daily to tinidazole 500 mg or 1 g twice daily for seven days for the treatment of bacterial vaginosis. After 14 days, there was no difference in microbiologic cure rates between patients in the tinidazole 1 g BID group and the metronidazole 500 mg BID treatment group (73.0% vs 82.4%, respectively; P=0.08). The cure rate for patients who received tinidazole 500 mg BID was 75.3% (P value not reported). Additionally, no differences in rates of recurrence were reported (P=0.24).

- Treatment guidelines for parasitic infections involving mild, moderate or severe intestinal disease due to amebiasis recommend metronidazole 500mg to 750mg TID for 7 to 10 days as the drug of choice, with tinidazole listed as an alternative agent.
ANTI-INFECTIVE AGENTS

RECOMMENDATION

Metronidazole and tinidazole are antiprotozoal drugs that belong to the nitroimidazole class of antibiotics. All of the nitroimidazoles are considered effective agents for the management of various protozoal infections such as intestinal amebiasis, giardiasis, and trichomoniasis. Metronidazole has additional coverage for bacterial infections caused by susceptible gram negative anaerobes. Additionally, clinical guidelines recommend metronidazole as a first line agent for the treatment of mild to moderate *Clostridium difficile*. Although, tinidazole has a longer duration of action and better side effect profile, both agents are considered equally effective. Tinidazole is the only nitroimidazole FDA approved to treat giardiasis; however, clinical data has not established one agent as being superior over another, and guidelines recommend use of both agents. Therefore it is recommended that at least metronidazole is available for use.

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RE-REVIEW: ORAL NITROIMIDAZOLES

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References


RE-REVIEW: NON-ABSORBABLE RIFAMYCIN

BACKGROUND

- Rifaximin is a semi-synthetic, nonabsorbable, broad-spectrum antibiotic structurally related to rifampin. Rifaximin inhibits bacterial RNA synthesis by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase. Therefore, inhibiting the binding of the enzyme to DNA and blocking RNA transcription.
- Rifaximin is currently available in two strengths. Rifaximin 200 mg is Food and Drug Administration (FDA)-approved for the treatment of travelers' diarrhea caused by non-invasive strains of *Escherichia coli* (*E. coli*) in patients 12 years of age and older. The 550mg strength is approved for reduction in risk of overt hepatic encephalopathy (HE) recurrence in adult patients. The mechanism of action proposed in the treatment of hepatic encephalopathy involves the agent decreasing colonic bacteria with urease activities that catabolize amino acids into ammonia. This action reduces the gastrointestinal production and systemic absorption of ammonia.
Common and Severe Adverse Reactions (See MedMetrics class review, Table 7, pg. 8):

- **Rifaximin**:
  - **Common**: peripheral edema, abdominal pain, constipation, defecation urgency, flatulence, nausea, rectal tenesmus, vomiting, ascites, dizziness, fatigue and headache
  - **Serious**: immune hypersensitivity reaction
    - Rifaximin should be used cautiously in patients with severe hepatic impairment. Rifaximin is not effective in patients with traveler’s diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than *E. coli*.
    - Additionally, prophylactic use of this agent is not likely to provide a clinical benefit and use for traveler’s diarrhea in the absence of suspected bacterial infection may increase the risk of drug-resistance. Lastly, *clostridium difficile* associated diarrhea (CDAD) has been reported with rifaximin, with severity ranging from mild to diarrhea to fatal colitis. In suspected or confirmed cases of CDAD, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued.
    - Due to minimal systemic absorption, rifaximin has not been associated with any interactions with cytochrome P450 isoenzymes, as commonly seen with rifampin. An in vitro study suggests that rifaximin may induce CYP3A4. However, patients with normal liver function receiving rifaximin at the recommended dosing regimen are not expected to induce CYP3A4.

- A double-blind randomized controlled trial by Steffen et al, that compared rifaximin 200mg TID (600mg total) versus rifaximin 400mg TID (1,200mg total) versus placebo, showed the median time to last unformed stool was significantly shorter with both rifaximin groups 32.5 and 32.9 hours respectively compared to 60 hours for placebo. (P=0.0001).
- FDA approval of rifaximin 550mg BID was based on the safety and efficacy trial that evaluated the reduction in risk of overt HE recurrence in adult patients. This study performed by Bass et al showed rifaximin was associated with a lower incidence of breakthrough episodes of hepatic encephalopathy compared to placebo (22.1% vs. 45.9% respectively, P<0.001). Additionally, fewer patients in the rifaximin group experienced hospitalizations involving HE compared to the placebo group (13.6% vs. 22.6% respectively, P=0.01).
- The 2011 Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America guidelines recommend fluoroquinolones as first-line for traveler’s diarrhea, with rifaximin listed as an alternative option. Azithromycin is listed as an alternative option in areas with fluoroquinolone resistance. The CDC does not currently recommend prophylactic antibiotics for most patients, only patients who are high risk (i.e. immunocompromised pts.) or patients taking critical trips for which a short bout of diarrhea would affect the trip.
- The 2001 American College of Gastroenterology guidelines recommend lactulose as the first-line pharmacologic agent for the treatment of HE. Antibiotics, neomycin and metronidazole are listed as second-line agents. FDA approval of rifaximin for HE was received after these guidelines. However, the guidelines reserve antibiotics, such as rifaximin for patients who do not adequately respond to lactulose.

**RECOMMENDATION**
Rifaximin is the only nonabsorbable, broad-spectrum antibiotic FDA approved for the treatment of traveler’s diarrhea caused by noninvasive strains of *E. coli* and reduction in risk of overt hepatic encephalopathy recurrence in adult patients. Clinical guidelines list rifaximin as an alternative option for traveler’s diarrhea and specify antibiotics should be reserved as second-line agents for hepatic encephalopathy. Additionally, long-term clinical trial data beyond 6 months is not available. Therefore, it is recommended that rifaximin be subject to clinical criteria to ensure appropriate use.
COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

RE-REVIEW: NON-ABSORBABLE RIFAMYCIN

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<tr>
<td>n/a</td>
<td>Xifaxan® (rifaximin)</td>
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</table>

Clinical Criteria for Xifaxan®

Authorized if being used for ONE of the following:
- Treatment of traveler’s diarrhea caused by non-invasive strains of *Escherichia coli* (*E. coli*) that cannot be treated with another agent such as a fluoroquinolone or azithromycin.
- Treatment of hepatic encephalopathy for patients who do not adequately respond to lactulose.

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

References

RE-REVIEW: SULFONAMIDES

BACKGROUND
- The sulfonamide antibiotics include the single entity agents sulfadiazine and trimethoprim, as well as the combination product sulfamethoxazole/trimethoprim (SMZ/TMP).
- This class of antibiotics works by interfering with bacterial growth by inhibiting the production of bacterial folic acid, which is essential for nucleic acid and protein production. The sulfonamides are effective against a wide variety of aerobic gram-positive and gram-negative bacteria (see Table 2 in Therapeutic Class Review, pg. 2).
- The sulfonamide antibiotics are FDA-approved for the treatment of acute otitis media and urinary tract infections. Sulfadiazine is also approved for treatment of the following infections, alone or in combination with other anti-infective agents: chancroid, inclusive conjunctivitis, malaria, meningitis, nocardiosis, recurrent rheumatic fever, trachoma, and toxoplasmosis encephalitis. The combination SMZ/TMP is also approved for acute
exacerbations of chronic bronchitis, *Pneumocystis carinii* pneumonia, *Shigelllosis* and traveler’s diarrhea.

- Adverse events most commonly associated with the sulfonamides include rash and gastrointestinal symptoms, such as nausea, vomiting and abdominal pain. Less common, but severe, reactions include Stevens-Johnson syndrome, toxic epidermal necrosis, agranulocytosis and aplastic anemia.
  - Sulfadiazine is contraindicated with porphyria, sunscreens containing para-aminobenzoic acid and pregnancy.
  - Trimethoprim is contraindicated in patients with megaloblastic anemia due to folate deficiency, and sulfamethoxazole/trimethoprim is contraindicated in patients with megaloblastic anemia due to folate deficiency, as well as with marked hepatic damage or severe renal disease, pregnancy and breast feeding.
  - Sulfadiazine and sulfamethoxazole/trimethoprim should be discontinued at the first sign of rash because fatalities associated with severe reactions including agranulocytosis, aplastic anemia and other blood dyscrasias have occurred. Fatalities associated with severe reactions including Stevens-Johnson syndrome and toxic epidermal necrosis, as well as hepatic necrosis, have also occurred with sulfadiazine and sulfamethoxazole/trimethoprim.
  - Sulfamethoxazole/trimethoprim may cause hyperkalemia or hypoglycemia, particularly in malfnourished patients or in patients with renal or hepatic impairment.
  - Sulfamethoxazole/trimethoprim should be used with caution in patients with allergies, asthma or thyroid dysfunction. In addition, the incidence of adverse reactions with sulfamethoxazole/trimethoprim appears to increase in patients with acquired immunodeficiency syndrome and slow acetylators.

### Significant Drug-Drug Interactions:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Mechanism</th>
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</thead>
<tbody>
<tr>
<td>Sulfonamides (sulfadiazine, sulfamethoxazole/trimethoprim, trimethoprim)</td>
<td>Cyclosporine</td>
<td>The action of cyclosporine may be reduced, and sulfonamides may increase the risk of nephrotoxicity.</td>
</tr>
<tr>
<td>Sulfonamides (sulfadiazine, sulfamethoxazole/trimethoprim, trimethoprim)</td>
<td>Hydantoins</td>
<td>Serum hydantoin concentrations may be increased, resulting in increased pharmacologic and toxic effects.</td>
</tr>
<tr>
<td>Sulfonamides (sulfadiazine, sulfamethoxazole/trimethoprim)</td>
<td>Methotrexate</td>
<td>Sulfonamides may increase the risk of methotrexate-induced bone marrow suppression. Methotrexate may predispose patients to sulfamethoxazole/trimethoprim-induced anemia.</td>
</tr>
<tr>
<td>Sulfonamides (sulfamethoxazole/trimethoprim, trimethoprim)</td>
<td>Angiotensin II receptor blockers</td>
<td>Coadministration may increase the risk of hyperkalemia, especially in elderly patients.</td>
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<tr>
<td>Sulfonamides (sulfamethoxazole/trimethoprim, trimethoprim)</td>
<td>Angiotensin converting enzyme inhibitors</td>
<td>Coadministration may increase the risk of hyperkalemia, especially in elderly patients.</td>
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<tr>
<td>Sulfonamides (sulfamethoxazole/trimethoprim, trimethoprim)</td>
<td>Dapsone</td>
<td>Serum dapsone and trimethoprim concentrations may be increased, possibly increasing the pharmacologic and toxic effects.</td>
</tr>
<tr>
<td>Sulfonamides (sulfamethoxazole/trimethoprim, trimethoprim)</td>
<td>Dofetilide</td>
<td>Serum dofetilide concentrations may be increased, increasing the risk of ventricular arrhythmias, including torsades de pointes.</td>
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<tr>
<td>Sulfonamides (sulfamethoxazole/trimethoprim, trimethoprim)</td>
<td>Procainamide</td>
<td>Serum procainamide concentrations may be increased, increasing the pharmacologic effects.</td>
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</table>
### ANTI-INFECTIVE AGENTS

<table>
<thead>
<tr>
<th>Sulfonamides (sulfamethoxazole/trimethoprim)</th>
<th>Sulfonylureas</th>
<th>Coadministration may increase the half-life of sulfonylureas, resulting in hypoglycemia.</th>
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</thead>
<tbody>
<tr>
<td>Sulfonamides (sulfamethoxazole/trimethoprim)</td>
<td>Warfarin</td>
<td>The anticoagulant effect of warfarin may be enhanced, resulting in hemorrhage.</td>
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</table>

- The sulfonamide antibiotics are effective against a wide variety of aerobic gram-positive and -negative bacteria, but due to the development of widespread resistance, use of the sulfonamide antibiotics has decreased. The majority of treatment guidelines for the FDA-approved indications for the sulfonamide antibiotics list the sulfonamide antibiotics as alternative treatments. However, sulfadiazine is recommended in the treatment of *Toxoplasma gondii* encephalitis, when used in combination with first line therapies pyrimethamine and leucovorin, and SMZ/TMP is the recommended agent for prophylaxis against *Toxoplasma gondii* encephalitis in HIV patients. SMZ/TMP is recommended by the American College of Obstetricians and Gynecologists (ACOG) as well as the Infectious Diseases Society of America (IDSA) as first line in the treatment of uncomplicated bacterial cystitis; however, for the treatment of acute pyelonephritis SMX/TMP is only recommended if the pathogen is known to be susceptible. Current guidelines from Centers for Disease Control and Prevention (CDC) recommend SMX/TMP as the preferred agent for the prevention and treatment of *Pneumocystis carinii* pneumonia in patients infected with HIV.

**RECOMMENDATION**
The sulfonamide antibiotics represent a group of agents whose coverage encompasses a wide variety of aerobic gram-positive and gram-negative bacteria, and are FDA-approved for the treatment of various infections. The development of widespread resistance to sulfonamide antibiotics has led to the majority of treatment guidelines for their FDA-approved indications listing the sulfonamide antibiotics as alternative treatments. However, the SMZ/TMP combination is still recommended first line in the treatment of urinary tract infections and in the treatment and prevention of *Pneumocystis carinii* pneumonia in patients infected with HIV. Sulfadiazine is recommended in combination with first line therapies pyrimethamine and leucovorin for the treatment of *Toxoplasma gondii* encephalitis. Due to its place as first-line therapy for the treatment of specified infections, it is recommended at least the combination SMZ/TMP should be available for use. Additionally, sulfadiazine should be available for the treatment of *Toxoplasma gondii* encephalitis.

**COMMITTEE VOTE:**

APPROVED DISAPPROVED APPROVED with MODIFICATION

### RE-REVIEW: SULFONAMIDES

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<tr>
<td>SMZ/TMP (compares to Bactrim®, Bactrim® DS, Septra®, Septra® DS)</td>
<td>Bactrim® DS (SMZ/TMP)</td>
</tr>
<tr>
<td></td>
<td>Primsol® (trimethoprim)</td>
</tr>
<tr>
<td></td>
<td>Septre® (SMZ/TMP)</td>
</tr>
<tr>
<td></td>
<td>Septre® DS (SMZ/TMP)</td>
</tr>
</tbody>
</table>

**Clinical Criteria for sulfadiazine:**
- Sulfadiazine will be approved for the treatment of *Toxoplasma gondii* encephalitis in combination with pyrimethamine.

**COMMITTEE VOTE:**

APPROVED DISAPPROVED APPROVED with MODIFICATION
ANTI-INFECTIVE AGENTS

References

RE-REVIEW: ORAL NITROFURANS

BACKGROUND

- Nitrofurantoin is the only agent in the nitrofuran class. Nitrofurantoin macrocrystals are a larger crystal form of nitrofurantoin, allowing for slower absorption and less excretion. Nitrofurantoin monohydrate/macrocrystals are made up of 75% nitrofurantoin monohydrate and 25% macrocrystalline nitrofurantoin, which allows a slower rate of dissolution and absorption compared to 100% nitrofurantoin monohydrate.
- Nitrofurantoin's activity is believed to be related to interference with bacterial enzyme systems; it appears to inhibit vital biochemical processes of protein synthesis, aerobic energy metabolism, deoxyribonucleic acid, ribonucleic acid and cell wall synthesis.
- Nitrofurantoin and nitrofurantoin macrocrystals are indicated for the treatment of urinary tract infections and are also used as suppressive therapy; however, nitrofurantoin monohydrate/macrocrystals is only indicated for acute treatment.
- Adverse reactions commonly associated with the use of nitrofurantoin macrocrystalline include nausea, vomiting and decreased appetite while nitrofurantoin monohydrate macrocrystalline is commonly associated with nausea and headache.
  - All formulations of nitrofurantoin are contraindicated in patients with anuria, oliguria or significant impairment of renal function because of an impaired excretion that can lead to an increased risk of toxicity. Due to the risk of hemolytic anemia, all formulations of nitrofurantoin are contraindicated in the following: pregnant patients at term, during labor and delivery, when the onset of labor is imminent, or neonates less than one month of age. All formulations of nitrofurantoin are also contraindicated in patients with a history of cholestatic jaundice or hepatic dysfunction associated with nitrofurantoin.
  - All formulations of nitrofurantoin have been associated with acute, subacute or chronic pulmonary reactions (diffuse interstitial pneumonitis and/or pulmonary fibrosis). Rarely, hepatic reactions, including hepatitis, cholestatic jaundice, chronic active hepatitis and hepatic necrosis have occurred. Severe or irreversible peripheral neuropathy has occurred. Additionally, optic neuritis has been reported rarely. All formulations of nitrofurantoin have induced cases of hemolytic anemia and may be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of affected patients.
**ANTI-INFECTIVE AGENTS**

- Concomitant administration of any formulations of nitrofurantoin with magnesium trisilicate antacids reduces the rate and extent of absorption of nitrofurantoin.
- There are currently no head-to-head trials comparing the different nitrofurantoin formulations. The efficacy of the different formulations of nitrofurantoin has been demonstrated in clinical trials and is similar to other agents used in the treatment of urinary tract infections. In a meta-analysis by Zalmanovici Trestioreanu et al of agents commonly used for the treatment of urinary tract infections, there was no difference demonstrated in symptomatic cure between the treatment groups. Adverse events were also similar between the groups; though, nitrofurantoin had less occurrence of rash compared to sulfamethoxazole/trimethoprim.
- Current guidelines from the American College of Obstetrics and Gynecologist (ACoG) state that preferred treatment option for urinary tract infections is sulfamethoxazole/trimethoprim (SMX/TMP). Other treatment options include: trimethoprim, ciprofloxacin, levofloxacin, norfloxacin, gatifloxacin, nitrofurantoin macrocrystals, nitrofurantoin monohydrate/macrocrystals and fosfomycin tromethamine. Similarly, the Infectious Diseases Society of America (IDSA) recommends nitrofurantoin monohydrate/macrocrystals, SMX/TMP, or fosfomycin for the treatment of acute, uncomplicated bacterial cystitis.

**RECOMMENDATION**

Nitrofurantoin is the only agent in the nitrofuran class; however, it is available as nitrofurantoin suspension, nitrofurantoin macrocrystalline and nitrofurantoin monohydrate/macrocrystalline. All formulations of nitrofurantoin are indicated for the treatment of urinary tract infections. Nitrofurantoin and nitrofurantoin macrocrystalline are also indicated for prophylaxis in patients with frequent UTIs; however, nitrofurantoin monohydrate/macrocrystalline is indicated only for acute treatment. Clinical trials have demonstrated efficacy of all formulations of nitrofurantoin and have shown them to be similar to other agents used for the treatment of urinary tract infections. Additionally, current clinical guidelines from ACoG and IDSA recommend nitrofurantoin macrocrystals and nitrofurantoin monohydrate/macrocrystals as treatment options for acute, uncomplicated UTIs. Due to its indication for both treatment and prophylaxis of UTIs, it is recommended at least nitrofurantoin macrocrystalline should be available for use. Additionally, nitrofurantoin suspension should be available for use in the pediatric population as well as for those with difficulty swallowing.

**COMMITTEE VOTE:**

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### RE-REVIEW: ORAL NITROFURANS

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<tr>
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<tr>
<td>nitrofurantoin macrocrystalline (compares to Macrodantin®)</td>
<td>Furadantin® (nitrofurantoin suspension)</td>
</tr>
<tr>
<td>nitrofurantoin monohydrate/macrocrystalline (compares to Macrobid®)</td>
<td>Macrodantin® (nitrofurantoin macrocrystalline)</td>
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<tr>
<td>nitrofurantoin suspension (compares to Furadantin®)</td>
<td>Macrobid® (nitrofurantoin monohydrate/macrocrysstalline)</td>
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**Clinical Criteria for nitrofurantoin suspension:**

- No PA required for 11 years old & younger.
- All others: Will be approved for patients unable to swallow tablets.

**COMMITTEE VOTE:**

| APPROVED | DISAPPROVED | APPROVED with MODIFICATION |
References

RE-REVIEW: MISCELLANEOUS AGENTS FOR UTI

BACKGROUND
- Urinary Tract Infections (UTIs) are one of the most common diagnoses in the United States and account for eight million office visits annually. Fosfomycin is the only agent in the miscellaneous agents for UTIs.
- Fosfomycin exerts its bactericidal activity by inactivating the enzyme enolpyruvyl transferase, thereby inhibiting cell wall synthesis.
- Fosfomycin is FDA- approved for the treatment of uncomplicated UTIs (acute cystitis) in women due to susceptible strains of *Escherichia coli* and *Enterococcus faecalis*.
- The most common adverse events associated with the use of fosfomycin are headache, diarrhea, vomiting, vaginitis and rhinitis. Rare, but serious, adverse events include: aplastic anemia, cholestatic jaundice, hepatic necrosis and angioedema.
  - *Clostridium difficile* associated diarrhea has been reported with use of nearly all antibacterial agents, including fosfomycin, and may range in severity from mild diarrhea to fatal colitis.
  - More than one single dose of fosfomycin should not be used per episode of acute cystitis. Increased dosing did not improve outcomes, but did increase incidence of adverse effects.
  - Metoclopramide increases gastrointestinal motility which lowers serum concentrations and urinary excretion of fosfomycin.
- In general, no significant differences were observed in clinical trials comparing treatment with fosfomycin and other agents used to treat uncomplicated urinary tract infections. Fosfomycin demonstrated similar efficacy to nitrofurantoin, sulfamethoxazole/trimethoprim, cephalexin and fluoroquinolones.
  - A randomized, controlled trial compared fosfomycin 3 gram single dose to nitrofurantoin monohydrate/macrocrystals for 7 days in 749 females with symptoms of acute uncomplicated UTI. The bacteriologic cure rate at visit two (five to 11 days after initial treatment dose) was 78.1% with fosfomycin and 86.3% with nitrofurantoin monohydrate/macrocrystals (P=0.02); at visit three (five to 11 days after the last day of medication) the cure rate was 86.9% with fosfomycin and 80.9% with nitrofurantoin monohydrate/macrocrystals (P=0.17); at visit four (four to six weeks after last day of medication) the cure rate was 96.0% with fosfomycin and 91.1% with nitrofurantoin monohydrate/macrocrystals (P=0.18). There were no statistically significant differences between fosfomycin and nitrofurantoin monohydrate/macrocrystals in terms of clinical outcomes at any visit (P=0.3 to 0.91).
A randomized, controlled trial compared fosfomycin 3 gram single dose to ciprofloxacin for 5 days in 142 females with diagnosed uncomplicated UTI. At day seven, 83.1% of fosfomycin treated patients had clinical and bacteriological cure. In the ciprofloxacin group, 81.0% had clinical cure and 78.4% had bacteriological cure. There was no significant difference between clinical cure and bacteriological cure rates between the groups (P>0.05).

Current guidelines from the American College of Obstetrics and Gynecology (ACoG) state that preferred treatment option for urinary tract infections is sulfamethoxazole/trimethoprim (SMX/TMP). Other treatment options include: trimethoprim, ciprofloxacin, levofloxacin, norfloxacin, gatifloxacin, nitrofurantoin macrocrystals, nitrofurantoin monohydrate/macrocystals and fosfomycin tromethamine. Similarly, the Infectious Diseases Society of America (IDSA) recommends nitrofurantoin monohydrate/macrocystals, SMX/TMP, or fosfomycin for the treatment of acute, uncomplicated bacterial cystitis.

RECOMMENDATION
Fosfomycin is FDA-approved for single-dose therapy of uncomplicated UTIs (acute cystitis) in women due to susceptible strains of Escherichia coli and Enterococcus faecalis. Current clinical guidelines recommend fosfomycin as a treatment option for uncomplicated urinary tract infections, along with SMX/TMP, nitrofurantoin and quinolones; however, SMX/TMP is generally considered the preferred agent for treatment. In general, no significant differences were observed in clinical trials comparing treatment with fosfomycin and other agents used to treat uncomplicated urinary tract infections. Therefore, due to its higher relative cost, it is recommended fosfomycin should be subject to clinical criteria restricting its use to patients who are not candidates for other less costly treatment options.

COMMITTEE VOTE:
APPROVED  DISAPPROVED  APPROVED with MODIFICATION

RE-REVIEW: MISCELLANEOUS AGENTS FOR UTI

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<tr>
<td>N/A</td>
<td>Monurol® (fosfomycin)³⁵, ⁴⁴, ⁴⁶</td>
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</table>

Clinical Criteria for Monurol®:
Will be authorized if the recipient is pregnant and has a urinary tract infection, or the recipient has a previous failure, contraindication, intolerance or resistance to at least 2 of the following agents: or previous failure with sulfamethoxazole/trimethoprim, or is infected with an organism resistant to sulfamethoxazole/trimethoprim.
- Sulfamethoxazole/trimethoprim
- Quinolones
- Nitrofurantoin

COMMITTEE VOTE:
APPROVED  DISAPPROVED  APPROVED with MODIFICATION

Quantity Limits:
Monurol® 1 packet (3 g) per course of therapy

COMMITTEE VOTE:
APPROVED  DISAPPROVED  APPROVED with MODIFICATION
References


RE-REVIEW: METHENAMINE & COMBINATIONS

BACKGROUND

- Methenamine exhibits antibacterial activity by conversion of methenamine to formaldehyde in the presence of acidic urine. Formaldehyde is a nonspecific antibacterial agent which is typically bactericidal in action. The addition of acidic salts to methenamine, such as hippuric acid and madelic acid, helps to keep the urine acidic. The acid salts have shown some antibacterial activity as well.

- The primary role of methenamine is for prophylaxis or suppression of urinary tract infections (UTIs), especially when long term therapy is considered necessary. The combination methenamine products are utilized primarily for relief of symptoms associated with urinary tract infections.

- Methenamine and the methenamine combination products are generally well tolerated. Adverse events most commonly reported with use of methenamine are nausea, rash and dysuria. Large doses of methenamine have caused bladder irritation, painful and frequent micturition, albuminuria and gross hematuria.
  - Methenamine hippurate is contraindicated with renal insufficiency, severe hepatic insufficiency and severe dehydration. Methenamine mandelate is contraindicated in patients with renal insufficiency.
  - Use of methenamine hippurate in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. In addition, care should be taken to maintain an acid pH of the urine, especially when treating infections due to urea-splitting organisms such as Proteus and strains of Pseudomonas.
  - Benefits of methenamine combination antibiotics should be carefully considered with the following medical problems: cardiac disease, gastrointestinal tract obstructive disease, glaucoma and myasthenia gravis.
Methenamine preparations are contraindicated in patients taking sulfonamides because some sulfonamides may form an insoluble precipitate with formaldehyde in the urine.

The majority of clinical trials compared treatment with methenamine single entity antibiotics to either no antibiotic therapy or placebo, and results consistently demonstrated that methenamine single entity antibiotics are safe and effective for the prevention of urinary tract infections. There are currently no clinical trials involving the methenamine combination products.

A randomized, controlled trial compared methenamine hippurate, nitrofurantoin and trimethoprim in 290 patients with recurrent UTI. UTIs recurred in 63.2% of patients receiving placebo compared to 34.2% of patients receiving methenamine hippurate, 25.0% of patients receiving nitrofurantoin, and 10.4% of patients receiving with trimethoprim (P values not reported).

Methenamine hippurate was compared to nitrofurantoin in 99 female patients suffering from recurrent UTI. Fifty-eight percent of patients receiving nitrofurantoin remained free of symptoms compared to 27% of patients receiving methenamine hippurate (P value not reported). Ninety-nine percent of nitrofurantoin-treated patients remained abacteriuric while on therapy vs 67% of methenamine hippurate-treated patients (P value not reported).

Current guidelines for the management of urinary tract infections and uncomplicated acute bacterial cystitis and acute pyelonephritis in women do not make recommendations regarding the use of methenamine and combination antibiotics. The American College of Obstetricians and Gynecologists guideline on the treatment of urinary tract infections in nonpregnant women note that methenamine salts (hippurate and mandelate) have long been used for the prevention of urinary tract infections. It should be noted, use of methenamine should be only after the urinary tract infection has been eradicated by other appropriate antibiotics.

**RECOMMENDATION**

The primary role of methenamine is for prophylaxis or suppression of urinary tract infections (UTIs), especially when long term therapy is considered necessary. The combination methenamine products are utilized primarily for relief of symptoms associated with urinary tract infections. Clinical trials demonstrate that methenamine single entity antibiotics are safe and effective for the prevention of urinary tract infections. There is limited clinical information regarding the place in therapy of these agents; however, the American College of Obstetricians and Gynecologists guideline on the treatment of urinary tract infections in nonpregnant women note that methenamine salts (hippurate and mandelate) have long been used for the prevention of urinary tract infections. All agents in this class can be considered therapeutic alternatives. Therefore, it is recommended at least one methenamine single agent product and one methenamine combination product should be available for use.

**COMMITTEE VOTE:**

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**RE-REVIEW: METHENAMINE & COMBINATIONS**

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<tr>
<td>All generic combinations of methenamine, hyoscyamine, methylene blue, phenylsalicylate, etc methenamine hippurate (compares to Hiprex®) methenamine mandelate</td>
<td>All brand name combinations of methenamine, hyoscyamine, methylene blue, phenylsalicylate, etc Hiprex® (methenamine hippurate) Uroqid Acid #2®</td>
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</tbody>
</table>
ANTI-INFECTIVE AGENTS

References

RE-REVIEW: ANTIFUNGALS FOR OROPHARYNGEAL CANDIDIASIS

BACKGROUND

- This class review will focus on antifungal agents that are approved for the treatment of oropharyngeal candidiasis, specifically clotrimazole, miconazole, and nystatin. In addition to the agents covered in the class review, it should be noted that itraconazole oral solution, fluconazole and posaconazole also carry this indication; however due to their additional indications, these agents will be covered in the class review for oral systemic antifungals.
- All of the agents in the class work through differing mechanisms to alter the function of the fungal cell membrane.
- All of the agents in the class are FDA-approved for the treatment of oropharyngeal candidiasis. Clotrimazole is also approved to prevent oropharyngeal candidiasis in immunocompromised patients.
- The most common adverse reactions associated with clotrimazole & miconazole include nausea, vomiting, diarrhea and altered taste. Additionally, miconazole is commonly associated with headache. The most common adverse reactions with nystatin are rash and hypersensitivity reactions, which can rarely include Stevens-Johnson Syndrome.
  - These agents are not indicated for the treatment of systemic mycoses.
  - Abnormal liver function test have been reported with use of clotrimazole.
  - All agents in this class are Pregnancy Category C.
  - Safety and efficacy has not been established with clotrimazole in children less than 3 years of age or with miconazole in children less than 16 years if age.
- In general, all agents in this class are effective for the treatment of oropharyngeal candidiasis. Head-to-head trials for the treatment of oropharyngeal candidiasis show conflicting results.
  - Numerous studies have compared fluconazole and itraconazole for the treatment of oropharyngeal and/or esophageal candidiasis with varying results. Several studies have demonstrated no significant differences between treatments in patients with oropharyngeal or esophageal candidiasis, with or without HIV. Conversely; some studies have shown significantly better rates of clinical cure with fluconazole compared to itraconazole. Hernandez-Sampelayo and colleagues demonstrated no significant differences between fluconazole and ketoconazole in the treatment of pediatric patients with HIV/AIDS and oropharyngeal candidiasis. Studies comparing fluconazole and nystatin have also shown conflicting results, with some studies demonstrating no difference between treatments and others showing significantly better rates of clinical and mycological response with fluconazole. Studies comparing itraconazole and clotrimazole troches for the treatment of oropharyngeal candidiasis have demonstrated conflicting results.
o Miconazole buccal tablet was compared to clotrimazole troches for the treatment of oropharyngeal candidiasis in 578 HIV patients. Clinical cure rate at test of cure visit for miconazole-treated patients was non-inferior to clotrimazole-treated patients in both the intention-to-treat (61 vs 65%) and per protocol (68 vs 74%) populations (P values not reported).

- In their 2009 update for the management of candidiasis, the Infectious Disease Society of America (IDSA) recommends clotrimazole troches, nystatin suspension or fluconazole for the treatment of oropharyngeal candidiasis, with itraconazole solution, posaconazole, and voriconazole as alternative therapies.

**RECOMMENDATION**

All of the agents in the class are FDA-approved for the treatment of oropharyngeal candidiasis. Clotrimazole is also approved to prevent oropharyngeal candidiasis in immunocompromised patients. Data from head-to-head clinical trials does not consistently demonstrate superiority of one agent over another in this class. Current IDSA treatment guidelines recommend clotrimazole troches, nystatin suspension or fluconazole for the treatment of oropharyngeal candidiasis. Of the agents in this class only nystatin is approved for use in children of all ages. Therefore, it is recommended at least two antifungals for the treatment of oropharyngeal candidiasis should be available for use, one of which should be nystatin suspension due to its use in children.

**COMMITTEE VOTE:**

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

### RE-REVIEW: ANTIFUNGALS FOR OROPHARYNGEAL CANDIDIASIS

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>clotrimazole troches</td>
<td>Oravig® (miconazole)</td>
</tr>
<tr>
<td>nystatin</td>
<td></td>
</tr>
</tbody>
</table>

**References**

BACKGROUND

- This review will focus on oral antifungal agents used for the treatment of systemic infections and includes fluconazole, flucytosine, griseofulvin, itraconazole, ketoconazole, posaconazole, and voriconazole.
- Fluconazole, itraconazole, ketoconazole, posaconazole and voriconazole are azole antifungal agents which have a broad spectrum of activity. The azole antifungals alter the fungal cell membrane by inhibiting ergosterol synthesis. Flucytosine is a pyrimidine antifungal agent which works by inhibiting fungal deoxyribonucleic acid synthesis. Griseofulvin exerts its fungistatic activity by disrupting the mitotic spindle structure of the fungal cell, which causes an arrest of metaphase of cell division.
- The azole antifungals have a broad spectrum of activity and a wide variety of indications including but not limited to aspergillosis, Candida infections, dermatophyte infections and cryptococcal infections. Flucytosine is active against strains of Candida and Cryptococcus and is indicated to treat infections due to these fungi in combination with amphotericin B. It should not be used as monotherapy due to the emergence of resistance. Griseofulvin has activity against Epidermphyton, Microsporum, and Trichophyton species and is indicated to treat tinea infections including tinea barbae, capitis, corporis, cruris, pedis and unguium. Refer to table 3, pages 3-5 of Med Metrics complete therapeutic class review for a complete listing of FDA-approved indications.
- The most common adverse reactions associated with the azole antifungals include nausea, vomiting and headache. Other common and severe adverse reactions are as follows:
  - Fluconazole:
    - Severe: QT interval prolongation, Torsades de pointes, Stevens-Johnson Syndrome, Toxic epidermal necrolysis, agranulocytosis, anaphylaxis, seizure
  - Flucytosine:
    - Common: abdominal pain, diarrhea, nausea, vomiting, confusion, headache, hallucinations
    - Severe: cardiotoxicity, leukopenia, myelosupression, thrombocytopenia, renal failure
  - Griseofulvin:
    - Common: photosensitivity, rash, urticarial, diarrhea, nausea, vomiting, headache
    - Severe: acroparesthesia, elevated liver function tests, jaundice
  - Itraconazole:
    - Common: rash, rhinitis, sinusitis, upper respiratory infection
    - Severe: congestive heart failure, Stevens-Johnson syndrome, pancreatitis, hepatotoxicity, anaphylaxis, hearing loss
  - Ketoconazole:
    - Severe: hepatotoxicity, anaphylaxis, hypersensitivity reaction
  - Posaconazole:
    - Common: hypokalemia, diarrhea, fever
    - Severe: prolonged QT interval, Torsades de pointes, cholestasis, liver failure
  - Voriconazole:
    - Common: rash, visual disturbance, hallucinations, fever
    - Severe: hepatitis, liver failure, optic neuritis, papilledema, prolonged QT interval, Torsades de pointes, acute renal failure, pancreatitis, exfoliative cutaneous reactions including Stevens-Johnson Syndrome, photosensitivity
o Black Boxed Warnings:
  - Flucytosine carries a black boxed warning regarding its use in patients with impaired renal function, due to potential accumulation of the drug.
  - Itraconazole carries a black boxed warning regarding the risk of congestive heart failure, stating it should not be administered for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure or a history of congestive heart failure. Itraconazole also carries a black boxed warning regarding drug interactions which may result in serious cardiovascular events, including QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest and/or sudden death. Co-administration of cisapride, pimozide, quinidine, dofetilide or levacetylmethadol (levomethadyl) with itraconazole is contraindicated.
  - Ketoconazole carries a black box warning regarding the risk of hepatotoxicity. It also carries a black box warning regarding the risk drug interactions with astemizole, cisapride and terfenadine due to the potential for serious cardiovascular adverse events.

o Contraindications:
  - Griseofulvin is contraindicated in patients with porphyria and hepatocellular failure. Griseofulvin is also contraindicated in pregnancy; therefore additional contraceptive measures should be taken during treatment with griseofulvin and for one month after cessation of treatment. Males should wait at least six months after cessation of therapy to father a child.

o Precautions:
  - Fluconazole should be administered with caution in patients with liver or renal dysfunction. It has been associated with rare cases of serious hepatic toxicity including fatalities, usually in patients with serious underlying medical conditions.
  - Flucytosine should be used with extreme caution in patients with bone marrow depression.
  - Griseofulvin is derived from a species of penicillin which may result in cross-sensitivity.
  - Rare cases of torsades de pointes have been reported in patients taking posaconazole and voriconazole. These agents should be administered with caution in patients with potentially proarrhythmic conditions.
  - Photosensitivity may occur with use of griseofulvin or voriconazole. Patients should avoid intense or prolonged exposure to direct sunlight.

o Significant Drug-Drug Interactions are listed in the table below. For a complete listing on drug-drug interactions please refer to table 8 on pages 80-85 of MedMetrics complete therapeutic class review.

### Drug-Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azole antifungals</td>
<td>Cisapride</td>
<td>Increased cisapride plasma concentrations resulting in cardiotoxicity may occur. Coadministration is contraindicated.</td>
</tr>
<tr>
<td>Azole antifungals</td>
<td>Benzodiazepines</td>
<td>Increased serum levels of benzodiazepines with central nervous system depression and psychomotor impairment is possible. Coadministration of alprazolam or triazolam with itraconazole or ketoconazole is contraindicated. Consider dose adjustment when administering a benzodiazepine with fluconazole.</td>
</tr>
<tr>
<td>Azole antifungals</td>
<td>Cyclosporine</td>
<td>Cyclosporine levels and toxicity may increase and persist more than one week after stopping antifungal therapy. Close monitoring of cyclosporine levels is recommended. If administering with posaconazole, decrease the cyclosporine dose by 25%.</td>
</tr>
<tr>
<td>-------------------</td>
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<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Azole antifungals</td>
<td>HMG-CoA reductase inhibitors</td>
<td>Increased plasma levels of HMG-CoA reductase inhibitors and adverse reactions (rhabdomyolysis) may occur. Close monitoring is recommended. Itraconazole is contraindicated with CYP3A4 substrates. Posaconazole is contraindicated with simvastatin. Pravastatin may be the safest choice.</td>
</tr>
<tr>
<td>Azole antifungals</td>
<td>Nisoldipine</td>
<td>Increased nisoldipine levels and adverse reactions may occur. Close monitoring is recommended. Itraconazole is contraindicated with nisoldipine.</td>
</tr>
<tr>
<td>Azole antifungals</td>
<td>Sirolimus</td>
<td>Increased levels and adverse effects of sirolimus may occur. Close monitoring is recommended.</td>
</tr>
<tr>
<td>Fluconazole, itraconazole, ketoconazole, miconazole, voriconazole</td>
<td>Warfarin</td>
<td>Anticoagulant effect of warfarin may be increased. Close monitoring is recommended.</td>
</tr>
<tr>
<td>Fluconazole, itraconazole, ketoconazole, voriconazole</td>
<td>Oral contraceptives</td>
<td>Therapeutic efficacy of oral contraceptives may be decreased. An alternative method of contraception is recommended.</td>
</tr>
<tr>
<td>Fluconazole, itraconazole, ketoconazole, posaconazole</td>
<td>Tacrolimus</td>
<td>Increased levels and adverse effects of tacrolimus may occur. Close monitoring is recommended.</td>
</tr>
<tr>
<td>Itraconazole, ketoconazole, posaconazole, voriconazole</td>
<td>Dronedarone</td>
<td>Dronedarone concentrations may be increased. Coadministration is contraindicated.</td>
</tr>
<tr>
<td>Itraconazole, ketoconazole, posaconazole, voriconazole</td>
<td>Pimozide</td>
<td>The risk of life-threatening arrhythmias is increased. Coadministration is contraindicated.</td>
</tr>
<tr>
<td>Fluconazole, itraconazole, ketoconazole</td>
<td>Carbamazepine</td>
<td>Increased carbamazepine levels and increased adverse effects may occur. Close monitoring is recommended.</td>
</tr>
<tr>
<td>Fluconazole, itraconazole, voriconazole</td>
<td>Hydantoins (ethotoin, fosphenytoin, phenytoin)</td>
<td>Increased phenytoin levels and toxicity may occur, and concentrations of azoles may be decreased. Close monitoring is recommended.</td>
</tr>
<tr>
<td>Itraconazole, posaconazole, voriconazole</td>
<td>Quinidine</td>
<td>Quinidine levels may be increased, increasing the risk of cardiovascular events. Coadministration is contraindicated.</td>
</tr>
<tr>
<td>Itraconazole, ketoconazole</td>
<td>Conivaptan</td>
<td>Increased levels and adverse effects of conivaptan may occur. Coadministration is contraindicated.</td>
</tr>
<tr>
<td>Itraconazole, ketoconazole</td>
<td>Dofetilide</td>
<td>Increased levels and adverse effects of dofetilide may occur, including ventricular arrhythmias and torsades de pointes. Coadministration is contraindicated.</td>
</tr>
</tbody>
</table>
### Anti-Infective Agents

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Interacting Drug</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole, ketoconazole</td>
<td>Eplerenone</td>
<td>Increased eplerenone plasma concentrations may occur, increasing the risk of hyperkalemia and serious arrhythmias. Coadministration is contraindicated.</td>
</tr>
<tr>
<td>Itraconazole, ketoconazole</td>
<td>Tolvaptan</td>
<td>Tolvaptan concentrations may increase. Coadministration is contraindicated.</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Food (cola beverages, grapefruit juice, orange juice)</td>
<td>Plasma levels of itraconazole may be increased when co-administered with cola or food and decreased when co-administered with grapefruit or orange juice. Monitoring of therapeutic effect is recommended. Avoid coadministration with grapefruit juice or orange juice.</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Antacids (aluminum hydroxide, aluminum/magnesium hydroxide, magnesium hydroxide, sodium bicarbonate)</td>
<td>Ketoconazole effects may be decreased. Administer antacids at least two hours after ketoconazole.</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Ritonavir</td>
<td>Therapeutic effects of voriconazole may be decreased. Coadministration is contraindicated.</td>
</tr>
</tbody>
</table>

- Numerous studies have evaluated the use of fluconazole in the treatment of systemic *Candida* infections. When compared to amphotericin B and/or amphotericin B plus flucytosine, no significant differences have been observed in clinical response and/or mycologic elimination. Mondal and colleagues compared fluconazole and itraconazole in pediatric patients with signs of sepsis and positive blood cultures for *Candida*. Statistically similar cure rates were observed between groups.
- Studies evaluating the oral antifungal agents as prophylaxis against fungal infections in immunocompromised patients have compared various agents head-to-head.
  - Cornely et al compared fluconazole, itraconazole solution and posaconazole in patients after remission-induction chemotherapy. Significantly fewer invasive fungal infections occurred with posaconazole compared to fluconazole and itraconazole. Also of note, significantly fewer cases of invasive aspergillosis were observed and significantly fewer patients experienced treatment failure with posaconazole.66 Similarly, a study comparing fluconazole and posaconazole in patient with graft-vs-host-disease after hematopoietic stem cell transplantation demonstrated a significantly lower incidence of aspergillosis in the posaconazole group compared to the fluconazole group. Breakthrough fungal infections occurred in more patients in the fluconazole group.67
- Current clinical guidelines recommend the use of various oral antifungal agents as first- or second-line treatment options for various infections. The Infectious Diseases Society of America (IDSA) recommends the use of voriconazole as initial therapy in patients with pulmonary aspergillosis. Posaconazole is recommended for aspergillus prophylaxis in hematopoietic stem cell transplant patients with graft-vs-host-disease as well as in neutropenic patients with cancer. IDSA recommends fluconazole as the treatment of choice in neutropenic and non-neutropenic patients with candidiasis.
RECOMMENDATION
The oral antifungal agents are FDA-approved to treat a wide variety of infections, including but not limited to aspergillosis, blastomycosis and histoplasmosis, candidiasis, cryptococcal infections and dermatophyte infections. Clinical trials demonstrate efficacy within the FDA-approved indications and current clinical guidelines recommend the use of various oral antifungal agents as first- or second-line treatment options for various infections. Due to the relative safety and efficacy of fluconazole, ketoconazole, and griseofulvin in the treatment of fungal infections, it is recommended these agents should be available. Itraconazole, posaconazole and voriconazole are all effective for their respective FDA-approved indications; however, these agents are associated with significant adverse events and/or have very specific FDA-approved indications; therefore, these agents should be subject to clinical criteria. Due to the emergence of resistance, flucytosine is only indicated to be given in combination with amphotericin B; therefore, this agent should be subject to clinical criteria.

COMMITTEE VOTE:

APPROVED | DISAPPROVED | APPROVED with MODIFICATION
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<table>
<thead>
<tr>
<th>PREPARED</th>
<th>NON-PREFERRED</th>
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<tbody>
<tr>
<td>fluconazole® (compares to Diflucan)</td>
<td></td>
</tr>
<tr>
<td>Grifulvin V® (griseofulvin)</td>
<td></td>
</tr>
<tr>
<td>griseofulvin</td>
<td></td>
</tr>
<tr>
<td>Gris-Peg® (griseofulvin)</td>
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<tr>
<td>ketoconazole</td>
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<tr>
<td>Ancobon® (flucytosine)</td>
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</tr>
<tr>
<td>Diflucan® (fluconazole)</td>
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<tr>
<td>flucytosine (compares to Ancobon®)</td>
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</tr>
<tr>
<td>itraconazole® (compares to Sporanox®)</td>
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<tr>
<td>Noxafil® (posaconazole)</td>
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<td>Sporanox® (itraconazole)</td>
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<tr>
<td>Vfend® (voriconazole)</td>
<td></td>
</tr>
<tr>
<td>voriconazole (compares to Vfend®)</td>
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</tbody>
</table>

NOTE: Clinical criteria & quantity limits for itraconazole/Sporanox will be presented with the agents for onychomycosis.

Clinical Criteria for flucytosine/Ancobon®
Individuals started on flucytosine therapy in the hospital will be approved for this agent following hospital discharge in order to allow for completion of the course of therapy.

COMMITTEE VOTE:

APPROVED | DISAPPROVED | APPROVED with MODIFICATION
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Clinical Criteria for Noxafil®
Noxafil® will be approved if used for ANY of the following:

- As indicated for the prophylaxis of invasive *Aspergillus* and/or *Candida* in patients who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoetic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD) or recipients with hematologic malignancies (leukemia, lymphoma, myelodysplastic syndromes) with prolonged neutropenia from chemotherapy
- Treatment of *Fusariosis* disease
- Treatment of *Zygomycetes* disease
- Treatment of other fungal infections or molds that are refractory or resistant to, or in patients who have a contraindication or intolerance to itraconazole or voriconazole, or in patients who are intolerant to these medicinal products

Note: If started as an inpatient hospital regimen and this is a continuation of therapy, via home health or in a nursing home, then the drug is approvable.

COMMITTEE VOTE:
Clinical Criteria for voriconazole/Vfend®

Voriconazole will be approved for the following diagnoses:
- Treatment of invasive aspergillosis
- Serious fungal infections caused by *S. apiospermum* and *Fusarium* species including *F. solani*
- Part of standard anti-fungal regimen in febrile neutropenic patients
- Other fungal infections that are refractory or resistant to other oral triazole agents (i.e. fluconazole, ketoconazole, itraconazole)

**Note:** If started as an inpatient hospital regimen and this is a continuation of therapy, then the drug is approvable.

COMMITTEE VOTE:

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<tr>
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<th>APPROVED with MODIFICATION</th>
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</table>

Quantity Limits:

<table>
<thead>
<tr>
<th>Fluconazole (Diflucan) 150 mg</th>
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COMMITTEE VOTE:

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<th>APPROVED with MODIFICATION</th>
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</thead>
</table>

References

BACKGROUND

- This class review focuses on the oral antifungal agents used for the treatment of onychomycosis, including terbinafine and itraconazole. The mechanism of action, adverse events, and other general drug information for itraconazole have been discussed in the Oral Systemic Antifungals class review and will not be repeated here for the sake of brevity.
- Terbinafine is an allylamine antifungal agent which works by inhibiting the biosynthesis of ergosterol, increasing the permeability of the fungal cell membrane.
- Terbinafine is FDA-approved to treat onychomycosis of the toenails and fingernails, and the oral granules are approved to treat tinea capitis in patients four years of age and older. Itraconazole is FDA-approved for the treatment of onychomycosis of the toenails and fingernails, only in non-immunocompromised patients.
- The most common adverse events associated with the use of terbinafine are diarrhea, nausea, indigestion, taste disturbance, and headache. Less common, but severe, adverse events include agranulocytosis, neutropenia, Stevens Johnson Syndrome, Toxic epidermal necrolysis, systemic lupus erythematosus, and liver failure.
  - Cases of liver failure, some fatal, have occurred with terbinafine in patients with and without preexisting liver disease. Terbinafine is not recommended in patients with chronic or active liver disease.
  - Systemic terbinafine inhibits hepatic isoenzyme CYP2D6, and thus may inhibit the clearance of drugs metabolized by this isoenzyme.
- Terbinafine was compared to continuous itraconazole in a randomized, controlled trial for the treatment of onychomycosis in 170 patients with a 40 week post-treatment follow-up. Mycological cure rates were 81% in the terbinafine group and 63% in the itraconazole group (P<0.01).
- Current guidelines from the British Associated on Dermatologists recommend that treatment for onychomycosis should be commenced only when mycological infection has been confirmed. Terbinafine is more effective than itraconazole for dermatophyte infection of the nails and should be considered first-line treatment. Itraconazole may be considered second-line treatment.

RECOMMENDATION

The two oral agents currently FDA approved for the treatment of onychomycosis are terbinafine and itraconazole. Clinical trials demonstrate the clinical superiority of terbinafine compared to itraconazole and clinical guidelines consider terbinafine first-line therapy for the treatment of onychomycosis. Therefore, terbinafine can be considered a superior agent within this class. However, treatment for onychomycosis should be commenced only when mycological infection has been confirmed; therefore, all agents in this class should be subject to clinical criteria. In addition, because onychomycosis can be considered cosmetic in many cases, and cosmetic agents are excluded from coverage through the TennCare program, it is recommended that agents in this class be approved for onychomycosis only when an individual’s health could be compromised without treatment.

COMMITTEE VOTE:

APPROVED     DISAPPROVED     APPROVED with MODIFICATION
Clinical Criteria for terbinafine (Lamisil®, Terbinex®)

- Terbinafine will not be approved for cosmetic use.
- Terbinafine will be authorized for the treatment of nail fungal infections (onychomycosis) if the following are present:
  o Positive diagnostic microbiological or histological test (i.e. KOH preparation, periodic acid Schiff (PAS) stain, or lab culture), AND
  o Underlying disease (i.e. diabetes, peripheral vascular disease, poor circulation, immunocompromised recipients)
- Terbinafine granules will be authorized for the treatment of tinea capitis.

COMMITTEE VOTE:
APPROVED DISAPPROVED APPROVED with MODIFICATION

Clinical Criteria for itraconazole (Sporanox®)

- Itraconazole is unrestricted for Blastomycosis, Histoplasmosis, Aspergillosis, Cryptococcosis, Coccidiomycosis, febrile neutropenia, oropharyngeal/esophageal candidiasis, Candida krusei infections, and any other systemic fungal infection.
- Also unrestricted for prevention of histoplasmosis or any other invasive fungal infection (including cryptococcosis, coccidiomycosis) in HIV or immunocompromised patients.
- For onychomycosis will be authorized if ALL of the following are true:
  o Positive diagnostic microbiological or histological test (including KOH preparation, periodic acid Schiff (PAS) stain, or lab culture), AND
  o Underlying disease (i.e. diabetes, peripheral vascular disease, poor circulation, immunocompromised recipients, etc.), AND
  o Recipient has tried and failed or has an intolerance or contra-indication to terbinafine.

COMMITTEE VOTE:
APPROVED DISAPPROVED APPROVED with MODIFICATION

Quantity Limits:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>itraconazole</td>
<td>4/day</td>
</tr>
<tr>
<td>Lamisil®</td>
<td>4/day</td>
</tr>
<tr>
<td>Sporanox®</td>
<td>4/day</td>
</tr>
<tr>
<td>terbinafine</td>
<td>84/year</td>
</tr>
<tr>
<td>Terbinex®</td>
<td>2 kits/year</td>
</tr>
</tbody>
</table>

COMMITTEE VOTE:
APPROVED DISAPPROVED APPROVED with MODIFICATION

References