Proposed
Preferred Drug List

with

Clinical Criteria

Proposal for TennCare

May 24, 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 **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)

---

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

- Included in this review are the prescription vaginal antifungals miconazole, nystatin, sulfanilamide and terconazole.
- Vaginal formulations of miconazole, sulfanilamide and terconazole are FDA approved for the treatment of vulvovaginal candidiasis (VVC). Vaginal nystatin is FDA approved for the treatment of vaginal infections.
- Adverse events with the vaginal antifungals are usually limited to local side effects including burning, itching and irritation.
  - Miconazole vaginal products should be discontinued if sensitivity or irritation occurs. Terconazole vaginal products should be discontinued if sensitization, irritation, fever, chills or flu-like symptoms are reported during use. Because sulfonamides are absorbed from the vaginal mucosa, the usual precautions for oral sulfonamides apply in patients receiving sulfanilamide vaginal cream. Patients should be observed for skin rash or evidence of systemic toxicity, and if these develop, the medications should be discontinued.
  - All agents in this class are Pregnancy Category C, except for nystatin which is Pregnancy Category A.
  - No clinically significant drug interactions have been documented with miconazole, nystatin, sulfanilamide or terconazole vaginal products.
- Clinical trials evaluating the safety and efficacy of the vaginal antifungal products overall demonstrate treatment is superior to placebo, and in line with current treatment guidelines. Head-to-head trials do not consistently demonstrate one vaginal antifungal product or regimen to be consistently superior to another, though nystatin may be less effective than theazole antifungals.
  - Miconazole was compared to intravaginal nystatin in a randomized, controlled trial of 116 patients with mycologically confirmed VVC. Cure rates were higher with miconazole compared to nystatin (91.1 vs 76.6%, respectively; P=0.05).
  - Young, et al conducted a systematic review of 10 randomized controlled trials of pregnant patients receiving any topical treatment for VVC. According to data from five trials, topical azoles achieved greater cure rates compared to nystatin (OR, 0.21; 95% CI, 0.06 to 0.29).
- Guidelines from the Centers for Disease Control and Prevention (CDC) recommend OTC intravaginal antifungal products, prescription intravaginal antifungal products and prescription oral antifungals for the treatment of uncomplicated vulvovaginitis candidiasis. Of the agents included in this review, nystatin, miconazole and terconazole are recognized as potential treatment options; sulfanilamide is not addressed within the guidelines. Additionally, the CDC guidelines state that topically applied azoles are more effective than nystatin. Current guidelines from the Infectious Diseases Society of America list intravaginal miconazole, nystatin and terconazole among the antifungal agents effective for the treatment of VVC and state that no one agent is clearly superior.

RECOMMENDATION

All of the vaginal antifungals are approved for the treatment of vulvovaginal candidiasis (VVC), with the exception of nystatin, which is FDA approved for the treatment of vaginal infections. Clinical trials consistently demonstrate that the vaginal antifungal products are safe and effective in the management of vulvovaginitis candidiasis. Clinical guidelines for the treatment of VVC recommend intravaginal antifungal products, including intravaginal miconazole, nystatin and terconazole; sulfanilamide is not addressed within the guidelines. The CDC guidelines state that topically applied azoles are more effective than nystatin; however, overall there is no available evidence to consistently demonstrate the superiority of any vaginal antifungal. Therefore, the agents within this class can be considered therapeutic alternatives. Nystatin is the only agent within this class with a Pregnancy Category A. It is recommended at least nystatin and one
vaginal azole antifungal should be available for use. In addition, it is recommended that at least one cream and one suppository formulation be available.

COMMITTEE VOTE:

APPROVED   DISAPPROVED  APPROVED with MODIFICATION

<table>
<thead>
<tr>
<th>RE-REVIEW: ANTIFUNGALS: VAGINAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PREFERRED</strong></td>
</tr>
<tr>
<td>miconazole-3 kit</td>
</tr>
<tr>
<td>nystatin</td>
</tr>
<tr>
<td>terconazole (compares to Terazol®)</td>
</tr>
<tr>
<td>Zazole® (terconazole, compares to Terazol®)</td>
</tr>
</tbody>
</table>

References
4. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines. MMWR. 2010 Dec 17;59(No. RR-12):[1-110].

RE-REVIEW: VAGINAL ANTIBIOTICS

BACKGROUND

- Bacterial vaginosis is a polymicrobial syndrome resulting from the replacement of normal, predominant hydrogen peroxide producing Lactobacillus species in the vagina with high concentrations of anaerobic gram negative rods. Included in this review are the vaginal antibiotics clindamycin and metronidazole.
- Both metronidazole and clindamycin are FDA approved for the treatment of bacterial vaginosis. Clindamycin vaginal cream is indicated for use in nonpregnant women and pregnant women during the second and third trimester, while clindamycin vaginal suppository and metronidazole vaginal gel are indicated for use in nonpregnant women only.
- The most common adverse effects are localized effects which may include vaginal pain and vaginal discharge.
  - Clindamycin vaginal cream and vaginal suppositories are contraindicated with a history of regional enteritis, ulcerative colitis or antibiotic-resistant colitis.
  - Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin, and may range in severity from mild to life-threatening. Diarrhea, bloody diarrhea and colitis have been reported with the use of orally, parenterally and topically administered clindamycin. Therefore it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of clindamycin, even when administered intravaginally, because approximately five percent of the clindamycin dose is systematically absorbed.
from the vagina. Additionally, the use of clindamycin vaginal cream and vaginal suppository may result in the overgrowth of nonsusceptible organisms in the vagina.

- Health care professionals should be aware that clindamycin vaginal cream might be associated with adverse outcomes if used in the latter half of pregnancy.
- Metronidazole vaginal gel should be used with caution with central nervous system diseases. Discontinue treatment promptly if a patient develops abnormal neurologic signs.
- Use of oral metronidazole is associated with psychotic reactions in alcoholic patients who were using disulfiram concurrently. Do not administer metronidazole vaginal gel to patients who have taken disulfiram within the last two weeks. Use of oral metronidazole is also associated with a disulfiram-like reaction to alcohol. Discontinue alcohol consumption during and for at least three days after therapy with metronidazole vaginal gel.

- Clinical trials consistently demonstrate that these agents are effective and safe in the management of bacterial vaginosis.
  - In a head-to-head trial comparing clindamycin vaginal suppository and metronidazole vaginal gel in patients with bacterial vaginosis (N=119), the rate of clinical response did not differ between the two treatments at any of the three follow up visits up to 90 days post-treatment (seven to 12 days; P=0.3, 35 to 45 days; P=0.5 and 70 to 90 days; P=0.8). In addition, a second head-to-head trial comparing clindamycin vaginal cream, metronidazole vaginal gel and oral metronidazole demonstrated no difference between the three treatments in terms of cure rates (P=0.548).
  - A Cochrane review demonstrated that clindamycin, oral metronidazole and oral and vaginal tablets of lactobacillus are effective in the treatment of nonpregnant women with bacterial vaginosis. Furthermore, clindamycin and metronidazole demonstrated identical rates of treatment failure, regardless of regimen type, with clindamycin being associated with a lower incidence of adverse events.

- In their 2010 guidelines, the Centers for Disease Control and Prevention recommend oral metronidazole, metronidazole vaginal gel and clindamycin vaginal cream as first line treatment options for bacterial vaginosis in nonpregnant females. Alternative regimens include oral tinidazole, oral clindamycin and clindamycin vaginal suppository. Recommended treatment regimens for pregnant women include oral metronidazole and clindamycin. Oral therapy is preferred in pregnant women due to the possibility of subclinical upper genital tract infection. Of note, clindamycin vaginal cream may be associated with adverse outcomes if used in the latter half of pregnancy.

RECOMMENDATION
Both metronidazole and clindamycin phosphate are FDA approved for the treatment of bacterial vaginosis. Current guidelines recommend oral metronidazole, metronidazole vaginal gel and clindamycin vaginal cream as first line treatment options for bacterial vaginosis in nonpregnant females. Clinical trials consistently demonstrate that the recommended treatment regimens are effective and safe in the management of bacterial vaginosis. Therefore, all agents in this category can be considered therapeutic alternatives to one another for the effective treatment of bacterial vaginosis. However, due to their differing adverse event profiles, it is recommended at least one metronidazole and one clindamycin phosphate product should be available for use.

COMMITTEE VOTE:
APPROVED  DISAPPROVED  APPROVED with MODIFICATION
RE-REVIEW: VAGINAL ANTIBIOTICS

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleocin\textsuperscript{®} suppositories clindamycin 2% cream (compares to Cleocin\textsuperscript{®}) metronidazole 0.75% gel (compares to MetroGel\textsuperscript{®} Vaginal) Vandazole\textsuperscript{®} (metronidazole, compares to MetroGel Vaginal\textsuperscript{®})</td>
<td>Cleocin\textsuperscript{®} cream (clindamycin) MetroGel Vaginal\textsuperscript{®} (metronidazole)</td>
</tr>
</tbody>
</table>

References
7. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines. MMWR. 2010 Dec 17;59(No. RR-12):[1-110].

RE-REVIEW: ORAL ANTIPARASITICS

BACKGROUND

- Included in the oral anti-parasitic review are anthelmintic, antimalarial, and miscellaneous antiprotozoal agents. The anthelmintic agents include albendazole, ivermectin, and praziquantel. The antimalarial agents include chloroquine, mefloquine, primaquine, pyrimethamine, quinine sulfate, and the fixed-dose combination products artemether/lumefantrine and atovaquone/proguanil. The miscellaneous antiprotozoal agents include atovaquone and nitazoxanide.
- Each anthelmintic agent included in this review has a specific FDA-approved indication. All antimalarial agents included in this review are approved for prophylaxis and/or treatment of malaria. Of note, only primaquine is FDA-approved for radical cure of \textit{P vivax} malaria. Atovaquone is approved for use in both the prevention and treatment of \textit{Pneumocystis carinii} pneumonia. Nitazoxanide is approved for the treatment of diarrhea caused by \textit{Giardia lamblia} or \textit{Cryptosporidium parvum}. See table below for details on specific FDA-approved indications.
## Anti-Infective Agents

<table>
<thead>
<tr>
<th>Indications</th>
<th>Single Entity Agents</th>
<th>Combination Products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alben-d-azole</td>
<td>Atova-quine</td>
</tr>
<tr>
<td>Prevention of <em>Pneumocystis carinii</em> pneumonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radical cure (prevention of relapse) of <em>vivax</em> malaria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suppressive treatment of malaria</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Treatment for acute attacks of malaria</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Treatment of diarrhea caused by <em>Giardia lamblia</em> or <em>Cryptosporidium parvum</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of <em>Enterobius vermicularis</em>, <em>Ascaris lumbricoides</em>, <em>Necator americanus</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of extraintestinal amebiasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of Hydatid disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of schistosoma infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of liver flukes, <em>Clonorchis sinensis/</em> <em>Opisthorchis viverrini</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of intestinal Strongyloidiasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of neurocysticercosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of Onchocerciasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of <em>Pneumocystis carinii</em> Pneumonia</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Treatment of toxoplasmosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of uncomplicated <em>Plasmodium falciparum</em> malaria</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Prevention of PCP in patients who are not tolerant to sulfamethoxazole/trimethoprim.
† Recommended only for radical cure of *vivax* malaria, the prevention of relapse in *vivax* malaria, or following termination of chloroquine phosphate suppressive therapy in *vivax* malaria endemic area.
‡ Due to *Plasmodium vivax*, *P malariae*, *P ovale*, and susceptible forms of *P falciparum*.
§ Prophylaxis of *P falciparum* and *P vivax* malaria infections, including prophylaxis of chloroquine-resistant strains of *P falciparum*.
‖ Indicated for chemoprophylaxis of malaria due to susceptible strains of plasmodia. However, resistance to pyrimethamine is prevalent; not suitable as prophylactic agent for travelers to most areas.
¶ Prophylaxis of *P falciparum* malaria, including in areas where chloroquine resistance has been reported.
# Treatment of mild-to-moderate acute malaria caused by mefloquine-susceptible strains of *P falciparum* or by *P vivax*.
** Should not be used along to treat acute malaria.
†† Treatment of mild-to-moderate PCP.
‡‡ When used conjointly with a sulfonamide, since synergism exists with this combination.
§§ Indicated for the treatment of acute, uncomplicated malaria infections due to *P falciparum* in patients of 5 kg bodyweight and above.
|| Treatment of acute, uncomplicated *P falciparum* malaria.
Primaquine carries a black box warning that health care providers should completely familiarize themselves with the contents of the monograph before prescribing. Quinine sulfate carries a black box warning that use for the treatment or prevention of nocturnal leg cramps may result in serious and life-threatening hematologic reactions, including thrombocytopenia and hemolytic uremic syndrome/thrombotic thrombocytopenic purpura. The risk associated with quinine use in the absence of evidence of its effectiveness in the treatment or prevention of nocturnal leg cramps outweighs any potential benefit.

Mefloquine should not be prescribed for prophylaxis in patients with active depression; a recent history of depression, generalized anxiety disorder, psychosis or schizophrenia or other major psychiatric disorders; or with a history of convulsions. Praziquantel is contraindicated in patients receiving rifampin who need immediate treatment for schistosomiasis. Primaquine is contraindicated in acutely ill patients suffering from systemic disease manifested by tendency to granulocytopenia, in patients receiving concurrently other potentially hemolytic drugs or depressants of myeloid elements of bone marrow, and with recent use of quinacrine. Pyrimethamine is contraindicated with documented megaloblastic anemia due to folate deficiency. Quinine sulfate is contraindicated with prolonged QT interval, glucose-6-phosphate dehydrogenase deficiency, myasthenia gravis, and optic neuritis. Atovaquone/proguanil is contraindicated with severe renal impairment when used for prophylaxis of Plasmodium falciparum malaria.

Precautions:

- Rare fatalities with albendazole treatment have been reported due to granulocytopenia or pancytopenia. The agent has been shown to cause bone marrow suppression, aplastic anemia, and agranulocytosis in patients with or without underlying hepatic dysfunction. Albendazole should not be used in pregnant women except in clinical circumstances where no alternative management is appropriate. Furthermore, patients should not become pregnant for at least one month following cessation of albendazole therapy.

- Rare cases of hepatitis, elevated liver function tests and one case of fatal liver failure have been reported in patients receiving atovaquone. If it is necessary to treat patients with severe hepatic impairment, caution is advised and administration should be closely monitored.

- Due to the development of worldwide chloroquine resistance, before using chloroquine for prophylaxis of malaria it should be ascertained whether chloroquine is appropriate for use in the region to be visited by the traveler. Chloroquine should not be used for treatment with P falciparum infections acquired in areas of chloroquine resistance or malaria occurring in patients where chloroquine prophylaxis has failed. Irreversible retinal damage has been observed in some patients who had received long-term or higher-dosage 4-aminoquinoline therapy. Use of chloroquine in patients with psoriasis may precipitate a severe attack of psoriasis, and when used in patients with porphyria the condition may be exacerbated. In patients with pre-existing auditory damage, chloroquine should be administered with caution. Chloroquine should be used with caution in patients with hepatic disease or alcoholism or in conjunction with known hepatotoxic drugs. Patients with a history of epilepsy should be advised about the risk of chloroquine provoking seizures.

- Patients treated with ivermectin for onchocerciasis may experience cutaneous and/or systemic reactions of varying severity and ophthalmological reactions.

- In patients with epilepsy, mefloquine may increase the risk of convulsions. Mefloquine should be used with caution in patients with psychiatric disturbances because the agent has been associated with
emotional disturbances. Mefloquine may cause psychiatric symptoms in a number of patients, ranging from anxiety, paranoia, and depression to hallucinations and psychotic behavior. The benefits of mefloquine should be weighed against the possibility of adverse effects in patients with cardiac disease.

- Caution with praziquantel should be exercised in patients with moderate to severe liver dysfunction. Praziquantel should not be administered in patients with a history of epilepsy and/or signs of potential central nervous systems involvement such as subcutaneous nodules suggestive of cysticercosis.

- It is advisable to make routine blood examinations during therapy with primaquine. Treatment should be discontinued immediately if marked darkening of the urine or sudden decrease in hemoglobin concentration or leukocyte count occurs.

- The dosage of pyrimethamine required for the treatment of toxoplasmosis is 10 to 20 times the recommended antimalarial dosage and approaches the toxic level. Pyrimethamine should be kept out of reach of children as they are extremely susceptible to adverse events from an overdose. Pyrimethamine should be used with caution in patients with impaired renal or hepatic function or in patients with possible folate deficiency, such as individuals with malabsorption syndrome, alcoholism, or pregnancy, and in those receiving therapy affecting folate levels.

- Quinine sulfate has been rarely associated with potentially fatal cardiac arrhythmias, including torsades de pointes, and ventricular fibrillation. Quinine stimulates release of insulin from the pancreas, and patients may experience clinically significant hypoglycemia.

- Artemether/lumefantrine has been associated with prolongation of the QT interval. Therefore, treatment should be avoided in patients with congenital prolongation of QT interval or any other clinical condition known to prolong the QTc interval, with a family history of congenital prolongation of the QT interval or sudden death, with known disturbances of electrolyte balance, concurrent use of other drugs that prolong the QT interval, and concurrent use of medications that are metabolized by the cytochrome enzyme CYP2D6.

- Elevated liver function tests and rare cases of hepatitis have been reported with prophylactic therapy with atovaquone/proguanil.

**Drug-Drug Interactions:**

- Halofantrine and ketoconazole should not be administered with mefloquine or within 15 weeks of the last dose of mefloquine due to the risk of a potential fatal prolongation of the QTc interval. Concomitant administration of mefloquine and quinine or quinidine may produce electrocardiographic abnormalities. In addition, concomitant administration of mefloquine and quinine or chloroquine may increase the risk of convulsions.

- Quinine sulfate is not recommended for use with other drugs known to cause QT prolongation. Treatment failures may result from the concurrent use of rifampin with quinine sulfate, due to decreased plasma concentrations of quinine, and concomitant use of these medications should be avoided.

- See Table 8, page 76 of Med Metrics Therapeutic Class Review for listing of other Drug-Drug Interactions.

- The use of oral anti-parasitic agents in the management of malaria is well-established. Decisions regarding prophylaxis and treatment of malaria depend on both the form of *Plasmodium* species identified and resistance rates in the specific region. There are
numerous clinical trials evaluating the safety and efficacy of these agents with no one agents demonstrating consistent superiority over another.

- All of the anthelmintic agents included in this review are safe and effective in their respective FDA-approved indications.
- Several clinical trials have demonstrated the safety and efficacy of nitazoxanide for the treatment of diarrhea caused by both Cryptosporidiosis and Giardiasis.
  - Nitazoxanide was compared to metronidazole for the treatment of Giardiasis in 110 children aged 2 to 11 years old. Diarrhea had resolved in 80 and 85% of the children treated with metronidazole and nitazoxanide, respectively, before day seven follow-up visit (P=0.6148).
- According to the Centers for Disease Control and Prevention (CDC), recommended first-line agents for the treatment of chloroquine-resistant, uncomplicated *P. falciparum* malaria include atovaquone/proguanil, artemether/lumefantrine, quinine sulfate, and mefloquine. All options are recommended equally; however, because of a higher rate of severe neuropsychiatric reactions seen at treatment doses, mefloquine is recommended only if other options cannot be utilized. Patients with chloroquine-susceptible *P. falciparum* infection should receive treatment with either chloroquine or hydroxychloroquine.
- Each anthelmintic agent included in this review has a specific FDA-approved indication and their use is supported by current clinical guidelines. No one specific indication has two FDA-approved agents for use in eradicating the infection; however, guidelines note that other anthelmintic agents may be used as alternative therapies.
- Current guidelines from the CDC for the Prevention and Treatment of Opportunistic Infections in HIV-Infected patients recommend SMX/TMP as the agent of choice for treatment and prophylaxis of PCP. If SMX/TMP cannot be tolerated, alternative prophylactic regimens include dapsone; dapsone plus pyrimethamine plus leucovorin; aerosolized pentamidine and atovaquone. Alternative treatment regimens in mild to moderate PCP disease include dapsone plus TMP, primaquine plus clindamycin or atovaquone suspension. Additionally, the CDC recommends atovaquone as an alternative regimen to SMX/TMP for *Toxoplasma gondii* encephalitis prophylaxis.
- According to treatment guidelines found the Medical Letter's “Drugs for Parasitic Infections”, nitazoxanide is considered the drug of choice for the treatment of Cryptosporidiosis. For the treatment of Giardiasis, metronidazole, tinidazole or nitazoxanide are considered the drugs of choice.

**RECOMMENDATION**

Included in the oral anti-parasitics class are anthelmintic, antimalarial, and miscellaneous antiprotozoal agents:

All antimalarial agents in this class are approved for prophylaxis and/or treatment of malaria. Decisions regarding prophylaxis and treatment of malaria depend on both the form of Plasmodium species identified and resistance rates in the specific region. The CDC recommended first-line agents for the treatment of chloroquine-resistant, uncomplicated *P. falciparum* malaria include atovaquone/proguanil, artemether/lumefantrine, quinine sulfate, and mefloquine. All options are recommended equally; however, because of a higher rate of severe neuropsychiatric reactions seen at treatment doses, mefloquine is recommended only if other options cannot be utilized. Patients with chloroquine-susceptible *P. falciparum* infection should receive treatment with either chloroquine or hydroxychloroquine. Clinical trial data supports the recommendations for current clinical guidelines. Therefore, it is recommended at least chloroquine plus at least two other antimalarial agents for use in chloroquine-resistant *P. falciparum malaria* should be available for use. Additionally, as only primaquine is FDA-approved for radical cure of *P. vivax* malaria, primaquine should also be available for use.

Each anthelmintic agent included in this review has a specific FDA-approved indication and their use is supported by current clinical guidelines. No one specific indication has two FDA-approved agents for use in eradicating the infection; however, guidelines note that other anthelmintic agents may be used as alternative therapies. Therefore, it is recommended at least two anthelmintic agents should be available for use.
Atovaquone is approved for use in both the prevention and treatment of *Pneumocystis carinii* pneumonia. Current CDC guidelines consider atovaquone a second-line agent for the treatment and prevention of PCP and *Toxoplasma gondii* encephalitis in patients who cannot tolerate SMX/TMP. Therefore, it is recommended atovaquone should be subject to clinical criteria to ensure its use as a second-line agent. Nitazoxanide is approved for the treatment of diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum*. Treatment guidelines state nitazoxanide is the drug of choice for Cryptosporidiosis. However, for the treatment of Giardiasis, metronidazole, tinidazole or nitazoxanide are considered the drugs of choice and no one agent is given preference over the others. Due to the relative increased cost compared to other first line agents for the treatment Giardiasis, it is recommended nitazoxanide should be subject to step therapy for this indication.

COMMITTEE VOTE:

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

**RE-REVIEW: ORAL ANTI-PARASITICS**

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>atovaquone/proguanil (compares to Malarone®)</td>
<td>Aralen® (chloroquine)</td>
</tr>
<tr>
<td>chloroquine (compares to Aralen®)</td>
<td>Coartem® (artemether/lumefantrine)</td>
</tr>
<tr>
<td>dapsone</td>
<td>Malarone® (atovaquone/proguanil)</td>
</tr>
<tr>
<td>Daraprim® (pyrimethamine)</td>
<td>melfloquine</td>
</tr>
<tr>
<td>primaquine</td>
<td>quinidine</td>
</tr>
<tr>
<td>Qualaquin® (quinine sulfate)</td>
<td>tetracycline</td>
</tr>
</tbody>
</table>

**RE-REVIEW: ANTIMALARIALS**

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albenza® (albendazole)</td>
<td>Biltricide® (praziquantel)</td>
</tr>
<tr>
<td>Biltricide® (praziquantel)</td>
<td>N/A</td>
</tr>
<tr>
<td>Stromectol® (ivermectin)</td>
<td></td>
</tr>
</tbody>
</table>

**RE-REVIEW: ANTHELMINTICS**

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albenza® (albendazole)</td>
<td>Biltricide® (praziquantel)</td>
</tr>
<tr>
<td>Albenza® (albendazole)</td>
<td>N/A</td>
</tr>
<tr>
<td>Biltricide® (praziquantel)</td>
<td></td>
</tr>
<tr>
<td>Stromectol® (ivermectin)</td>
<td></td>
</tr>
</tbody>
</table>

**RE-REVIEW: MISCELLANEOUS ANTIPROTOZOAL AGENTS**

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>Alinia® (nitazoxanide)</td>
</tr>
<tr>
<td></td>
<td>Mepron® (atovaquone)</td>
</tr>
</tbody>
</table>

**Clinical Criteria for Alinia®**

Alinia® will be authorized for treatment of:

- Diarrhea caused by *Cryptosporidium parvum* (or suspected *Cryptosporidium parvum* in immunocompromised recipients).
- Diarrhea caused by *Giardia lamblia* if the recipient has tried and failed metronidazole or has a contraindication, intolerance, adverse drug reaction, or other reason not to use drug-drug interaction to metronidazole.
- Diarrhea caused by *Clostridium difficile* if recipient has failed metronidazole or has a contraindication, intolerance, adverse drug reaction, or other reason not to use metronidazole.

COMMITTEE VOTE:

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

**Clinical Criteria for Mepron®**

Mepron® will be authorized if patient meets ALL of the following criteria:

- Diagnosis of prophylaxis against or treatment of *Pneumocystis carinii pneumonia* (PCP) or *Toxoplasmosis gondii* encephalitis, AND
- Contraindication, intolerance, or drug-drug interaction to sulfamethoxazole/trimethoprim
BACKGROUND

- Tuberculosis (TB) is a common and deadly infectious disease that usually affects the pulmonary system. The World Health Organization estimates that approximately nine million individuals develop active TB annually, resulting in two to three million deaths; therefore, making TB one of the leading causes of death worldwide. This review focuses on the single-entity (aminosalicylic acid, cycloserine, ethambutol (EMB), ethionamide, isoniazid (INH), pyrazinamide (PZA), rifabutin, rifampin (RIF), and rifapentine) and combination anti-TB agents (isoniazid/rifampin and isoniazid/rifampin/pyrazinamide) available in the United States.

- While all of the other agents in this class are indicated to treat TB in some capacity, rifabutin is only indicated for the prevention of disseminated Mycobacterium Avium Complex (MAC) Disease in patients with advanced HIV infection. See table 3 on page 3 of MedMetrics Therapeutic Class Review for complete listing of all FDA-approved indications.

- Common and severe adverse drugs reactions:
  - Aminosalicylic acid:
    - Common: Abdominal pain, diarrhea, nausea, vomiting, rash with fever
    - Severe: thrombocytopenia, hepatotoxicity
  - Cycloserine:
    - Common: confusion, dizziness, headache, somnolence
    - Severe: seizure
  - Ethambutol:
    - Common: hyperuricemia, nausea, vomiting, mania
    - Severe: neutropenia, thrombocytopenia, anaphylaxis, peripheral neuropathy, blindness, visual impairment, optic neuritis
  - Ethionamide:
    - Common: abdominal pain, diarrhea, metallic taste, nausea, stomatitis, vomiting
    - Serious: hepatitis, encephalopathy, optic neuritis, psychiatric symptoms
  - Isoniazid:
    - Common: neuropathy, psychiatric symptoms
Serious: rash, agranulocytosis, anemia, thrombocytopenia, hepatitis, hepatotoxicity, SLE, rhabdomyolysis, seizure

- **Pyrazinamide:**
  - Common: hyperuricemia, nausea, vomiting, arthralgia
  - Serious: anemia, hepatotoxicity

- **Rifabutin:**
  - Common: discoloration of skin & body fluids, diarrhea, rash, indigestion, loss of appetite, nausea, vomiting, increased ALT, uveitis
  - Serious: anemia, neutropenia, thrombocytopenia, SLE

- **Rifampin:**
  - Common: discoloration of body fluids, heartburn, loss of appetite, nausea, increased LFT, flu-like symptoms
  - Serious: thrombocytopenia, hepatotoxicity, nephrotoxicity

- **Rifapentine:**
  - Common: hyperuricemia, arthralgia, pyogenic proteinuria, discoloration of skin & body fluids, increased aminotransferase, ALT/AST

- **Isoniazid and the isoniazid-containing combination products** carry a black box warning regarding the risk of severe and sometimes fatal hepatitis associated with therapy which may occur or may develop even after many months of treatment. Additionally, isoniazid should be used carefully in daily users of alcohol, patients with active chronic liver disease or severe renal dysfunction, patients >35 years of age, concurrent use of any chronically administered medication, existence of peripheral neuropathy or conditions predisposing to neuropathy, pregnancy, injection drug use, women belonging to minority groups, and human immunodeficiency virus (HIV) seropositive patients.

- **Aminosalicylic acid** is contraindicated with severe renal disease. Cycloserine is contraindicated with epilepsy, depression, severe anxiety, psychosis, severe renal dysfunction, and excessive concurrent use of alcohol. Ethambutol is contraindicated with known optic neuritis, unless clinical judgment determines that it may be used, and in patients unable to appreciate and report visual side effects or changes in vision. Ethionamide is contraindicated with severe hepatic dysfunction. Isoniazid is contraindicated with previous isoniazid-associated hepatic injury, severe adverse reactions to isoniazid (e.g., drug fever, chills, arthritis), and acute liver disease of any etiology. Pyrazinamide is contraindicated with severe hepatic damage and acute gout. Precautions:
  - Patients should be advised that poor compliance in taking anti-TB medication often leads to treatment failure, and to the development of resistance of the organisms in the individual patient.
  - Cycloserine should be discontinued or the dosage reduced if the patient develops allergic dermatitis or symptoms of central nervous system toxicity, such as convulsions, psychosis, somnolence, depression, confusion, hyperreflexia, headache, tremor, vertigo, paresis, or dysarthria. Anticonvulsant drugs or sedatives may be effective in controlling symptoms of central nervous system toxicity. The risk of convulsions while receiving cycloserine is increased in chronic alcoholics. Patients should be monitored by hematologic, renal excretion, blood level, and liver function studies. Administration of cycloserine and other anti-TB drugs has been associated with vitamin B12 and/or folic acid deficiency, megaloblastic anemia, and sideroblastic anemia. If evidence of anemia develops during treatment, appropriate studies and therapy should be instituted.
  - Ethambutol may produce decreases in visual acuity due to optic neuritis. This effect may be related to dose and duration of treatment, and generally reversible when treatment is discontinued promptly. Of note, irreversible blindness has been reported with ethambutol. Physical examination should include ophthalmoscopy, finger perimetry, and
testing of color discrimination in patients receiving ethambutol. Liver toxicities, including fatalities have been reported; therefore, baseline and periodic assessment of liver function should be performed.

- Patients receiving pyrazinamide should have baseline serum uric acid function determinations. Pyrazinamide should be discontinued if hyperuricemia accompanied by acute gouty arthritis appear. Pyrazinamide should be used with caution in patients with a history of diabetes. Patients should be instructed to notify health care professionals promptly if fever, loss of appetite, malaise, nausea and vomiting, darkened urine, yellowish discoloration of the skin and eyes, pain or swelling of the joints develops while receiving pyrazinamide.
- Rifabutin must not be administered for MAC prophylaxis in patients with active TB. Due to the possible occurrence of uveitis, patients receiving rifabutin should also be carefully monitored if also receiving clarithromycin and/or fluconazole.
- Rifampin has been shown to produce liver dysfunction, with some cases being fatal; therefore, rifampin should only be given to patients with liver dysfunction in cases of necessity. Rifampin should be used with caution in patients with diabetes.
- Rifapentine should not be used as a once weekly continuation phase regimen in combination with isoniazid in HIV seropositive patients with pulmonary TB because of a higher rate of failure and/or relapse documented with the presence of rifampin-resistant organisms. Rifapentine has not been evaluated as part of the initial phase treatment regimen in HIV seropositive patients with pulmonary TB. Rifapentine should be used cautiously in patients with cavitary pulmonary lesions and/or positive sputum culture after the initial phase of treatment or in those with evidence of bilateral pulmonary disease due to higher rates of relapse. Patients with abnormal liver tests and/or liver disease should only be given rifapentine in cases of necessity and then with caution under strict medical supervision. Rifapentine should not be used with porphyria.

- Rifampin has enzyme induction properties that can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormones, and vitamin D. Rifampin and isoniazid have been reported to alter vitamin D metabolism. Rifampin is a known to induce the metabolism of drugs metabolized by CYP3A4 and therefore has numerous significant drug interactions. Rifampin is contraindicated with concurrent use of ritonavir-boosted saquinavir, atazanavir, darunavir, fosamprenavir, saquinavir, or tipranavir. See Table 8 (pages 33-35) of MedMetrics Therapeutic Class Review for complete listing of Drug-Drug Interactions.

- Overall, results from clinical trials consistently demonstrate that anti-TB agents are efficacious in decreasing relapse rates in patients with active infection and in preventing the progression to active infection in patients with latent TB infection. Furthermore, isoniazid, rifampin, and pyrazinamide, in addition to ethambutol and rifapentine, are typically recommended as the backbone to the majority of recommended treatment regimens for both active pulmonary TB and latent TB infection. As such, the majority of clinical trial data support the use of these agents over others in the class. Currently, there is no substantial clinical trial data indicating that anti-TB fixed-dose combination products are more efficacious when compared to single-entity agents administered together. Furthermore, there is no clinical trial data to demonstrate an improvement in patient compliance when fixed-dose combination therapy is used; therefore, it is recommended the combination products should be subject to clinical criteria.
- The primary goals of anti-tuberculosis therapy are to kill tubercule bacilli rapidly, prevent the emergence of drug resistance, and eliminate persistent bacilli from the host's tissue to prevent relapse. To accomplish these goals, current clinical guidelines focus on the
importance of multidrug regimens to treat TB. Clinical guidelines from the American Thoracic Society, Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA) recommend a combination of isoniazid, rifampin, pyrazinamide, and ethambutol as first line agents for the initial treatment phase of active TB, followed by a continuation phase of isoniazid plus either rifampin or rifapentine. Guidelines recommend the use of second-line agents, aminosalicylic acid, cycloserine and ethionamide, only when first-line agents cannot be tolerated or in the treatment of drug-resistant TB. The majority of guidelines do not specifically address the combination agents, but do stress the importance of compliance. Therefore, guidelines recommend the use of directly observed therapy to improve adherence in situations where a lack of compliance and/or therapy adherence is evident. In 2011, the CDC updated their recommendations for the treatment of latent TB infection and now prefer either 9 months of daily INH or 3 months of weekly INH + rifapentine given as direct observation therapy.

- Current CDC guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected patients state that clarithromycin and azithromycin are the preferred agents for primary prophylaxis against MAC disease with rifabutin as an alternative in patients who cannot tolerate the macrolides. Additionally, for the treatment of disseminated MAC, rifabutin may be added to a macrolide and EMB if a third drug is necessary.

**RECOMMENDATION**

All of the agents in this class, excluding rifabutin, are indicated to treat TB in some capacity. Rifabutin is only indicated for the prevention of disseminated *Mycobacterium Avium* Complex (MAC) Disease in patients with advanced HIV infection. Current clinical guidelines recommend a combination of isoniazid, rifampin, pyrazinamide, and ethambutol as first line agents for the initial treatment phase of active TB, followed by a continuation phase of isoniazid plus either rifampin or rifapentine. Therefore, it is recommended at least isoniazid, rifampin, pyrazinamide and ethambutol should be available for use. Additionally, due to its unique indication, rifabutin should be available for MAC treatment and prophylaxis. However, since current guidelines state that rifabutin is an alternative for primary prophylaxis against MAC disease in patients who cannot tolerate the macrolides, it is recommended rifabutin should be subject to clinical criteria. Currently, there is no substantial clinical trial data indicating that anti-TB fixed-dose combination products are more efficacious when compared to single-entity agents administered together. Furthermore, there is no clinical trial data to demonstrate an improvement in patient compliance when fixed-dose combination therapy is used; therefore, it is recommended the combination products should be subject to clinical criteria.

**COMMITTEE VOTE:**

APPROVED   DISAPPROVED  APPROVED with MODIFICATION

**RE-REVIEW: ORAL ANTI-TUBERCULOSIS**

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>cycloserine (compares to Seromycin®)</td>
<td>Isonar® (isoniazide/rifampin)</td>
</tr>
<tr>
<td>ethambutol (compares to Myambutol®)</td>
<td>Myambutol® (ethambutol)</td>
</tr>
<tr>
<td>isoniazid</td>
<td>Paser® (aminosalicylic acid granules)</td>
</tr>
<tr>
<td>Mycobutin® (rifabutin)</td>
<td>Priftin® (rifapentine)</td>
</tr>
<tr>
<td>pyrazinamide</td>
<td>Rifadin® (rifampin)</td>
</tr>
<tr>
<td>rifampin (compares to Rifadin®)</td>
<td>Rifamate® (isoniazid/rifampin)</td>
</tr>
<tr>
<td></td>
<td>Rifater® (isoniazid/rifampin/pyrazinamide)</td>
</tr>
<tr>
<td></td>
<td>Seromycin® (cycloserine)</td>
</tr>
<tr>
<td></td>
<td>Trecator® (ethionamide)</td>
</tr>
</tbody>
</table>
ANTI-INFECTIVE AGENTS

Clinical Criteria for Mycobutin®

Mycobutin® will be approved for recipients meeting the following criteria:

- Prophylaxis against MAC in patients with contraindication or intolerance to clarithromycin AND azithromycin
- Treatment of disseminated MAC in combination with a macrolide and ethambutol

COMMITTEE VOTE:

APPROVED       DISAPPROVED       APPROVED with MODIFICATION

References


RE-REVIEW: ANTIVIRALS: HERPES

BACKGROUND

- Herpes simplex virus (HSV)-1 and -2 and varicella-zoster virus (VZV) are herpes viruses that commonly infect humans. HSV-1 and -2 cause a wide variety of illnesses, including mucocutaneous infections, central nervous system infections and infections of the visceral organs. They are widely associated as the causative agent in orolabial and genital lesions, commonly referred to as cold sores and genital herpes, respectively. VZV causes two diseases: chickenpox and herpes zoster, commonly known as shingles. Acyclovir, famciclovir and valacyclovir are nucleosides antivirals with activity against various herpesviruses.
- These agents exert their antiviral effect against HSV and VZV by interfering with DNA and inhibiting viral replication. Acyclovir and famciclovir are synthetic purine and acyclic purine nucleoside analogs. Valacyclovir is a prodrug and after oral administration is rapidly converted to acyclovir. The bioavailability of oral acyclovir is relatively low (15 to 21%); however, the relative bioavailability of acyclovir is three to five times greater after ingestion of valacyclovir (54 to 70%).
- All of the agents in this class are FDA-approved for the treatment of various herpes viruses.
The most common adverse events associated with use of these agents include: headache, diarrhea, vomiting, and malaise. Less common, but severe, adverse events may include Stevens-Johnson Syndrome and thrombotic thrombocytopenic purpura. Thrombocytopenic purpura/hemolytic uremic syndrome has been reported in immunocompromised patients receiving acyclovir and valacyclovir. Acyclovir should be used with caution in patients receiving other nephrotoxic drugs. Furthermore, adequate hydration is required during treatment with acyclovir, as well as valacyclovir. Famciclovir tablets contain lactose; therefore, they should not be administered with galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption syndromes. Concomitant administration of acyclovir and theophylline may result in elevated theophylline levels.

Overall, several head-to-head trials have demonstrated comparable efficacy and safety among acyclovir, famciclovir and valacyclovir in the treatment of herpes simplex and zoster infections. For the treatment of genital herpes, no differences among the agents with regards to the time to complete healing, viral shedding and resolution of all symptoms were noted. For the treatment of herpes zoster, there were minimal differences between the agents with regards to time to complete healing and resolution of zoster-associated pain and/or abnormal sensation. While one agent may have achieved “superiority” over another for one particular outcome in one clinical trial, “superiority” of any agent was not consistently demonstrated.

Acyclovir was compared to valacyclovir in 204 adult patients with genital herpes who had ≥3 occurrences within the past 12 months. Mean healing times (defined as re-epithelialization of lesions) were 5.13 and 5.38 days with famciclovir and acyclovir (difference, 0.25 days; 95% CI, -0.32 to 0.82). Famciclovir was considered statistically equivalent to acyclovir.

Famciclovir was compared to valacyclovir in 1,179 immuno-competent adult patients with a history of recurrent genital herpes. Time to healing of nonaborted lesions in the ITT population was similar between the two treatments (4.25 vs 4.08 days). A median treatment difference (0.16 days) and its 95% CI demonstrated that famciclovir was noninferior to valacyclovir with respect to time to healing of all nonaborted genital herpes lesions. Consistent results were obtained for the PP population. The time to healing of all lesions (nonaborted and aborted) in the ITT population was similar with famciclovir and valacyclovir (3.07 vs 3.01 days; median difference, 0.00; 95% CI, 0.00 to 0.00; HR, 1.07; 95% CI, 0.91 to 1.25; P=0.42).

In their 2010 guidelines for the treatment of sexually transmitted diseases, the Centers for Disease Control and Prevention (CDC) state that antiviral therapy offers clinical benefits to most symptomatic patients with genital herpes and is the mainstay of management. Additionally, the CDC emphasizes that randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes and that all three agents appear equally effective for episodic treatment of genital herpes. Guidelines from the CDC, National Institutes of Health and the HIV Medicine Association of the Infection Diseases Society of America recommend acyclovir, famciclovir or valacyclovir for the treatment of uncomplicated varicella. Additionally, these guidelines state that recommended treatment options for acute localized dermatomal herpes zoster in HIV infected patients are oral acyclovir, famciclovir or valacyclovir; with famciclovir or valacyclovir preferred due to improved pharmacokinetic profiles and resulting simplified dosing schedules.

RECOMMENDATION
Acyclovir, famciclovir and valacyclovir are antiviral agents FDA approved for the treatment of the herpesviruses herpes simplex virus (HSV) and varicella-zoster virus (VZV). The agents in this class are all well-established treatment options for both HSV and VZV infections and have demonstrated comparable efficacy. While the bioavailability of acyclovir is improved after ingestion of valacyclovir, head-to-head clinical trials support treatment guidelines in that acyclovir,
famciclovir and valacyclovir all provide clinical benefit to patients with HSV or VZV infection and that all three agents appear equally effective. Therefore, all agents in this class can be considered therapeutic alternatives to one another. It is recommended at least two agents in this class should be available for use.

COMMITTEE VOTE:

APPROVED       DISAPPROVED       APPROVED with MODIFICATION

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>acyclovir (compares to Zovirax®)</td>
<td>Famvir® (famciclovir)</td>
</tr>
<tr>
<td>famciclovir (compares to Famvir®)</td>
<td>Valtrex® (valacyclovir)</td>
</tr>
<tr>
<td>valacyclovir (compares to Valtrex®)</td>
<td>Zovirax® (acyclovir)</td>
</tr>
</tbody>
</table>

References

BACKGROUND

- The spectrum of human illness caused by cytomegalovirus (CMV), a member of the herpes virus family, is diverse and mostly dependent on the host. Infections in immunocompromised patients can lead to substantial morbidity and mortality, especially among transplant recipients and human immunodeficiency virus (HIV)-infected patients. Included in this review are the oral formulations of the antiviral agents ganciclovir and valganciclovir.
- The exact mechanism of action of ganciclovir in the prevention and treatment of CMV is not fully understood; however, it is believed to be related to the inhibition of deoxyribonucleic acid (DNA) synthesis via competition with deoxyguanosine for incorporation into viral DNA. The active phosphorylated form of ganciclovir can both competitively inhibit viral DNA polymerase and be incorporated into growing DNA chains as a false nucleotide; thereby inhibiting viral replication. Valganciclovir is a prodrug of ganciclovir.
- Ganciclovir capsules are FDA-approved for the prevention of CMV disease in patients with advanced HIV infection at risk for developing CMV disease, for the prevention of CMV disease in solid organ transplant recipients, and for maintenance treatment of CMV retinitis in immunocompromised patients. Please note, oral ganciclovir is indicated as an alternative to intravenous ganciclovir sodium for maintenance treatment of CMV retinitis in immunocompromised patients, in whom retinitis is stable following appropriate
induction therapy and for whom the risk of more rapid progression is balanced by the benefit of avoiding daily IV infusions. Valganciclovir is FDA-approved for the prevention of CMV disease in solid organ transplant recipients at high risk and for the treatment of CMV retinitis in adult patients with acquired immunodeficiency syndrome. Valganciclovir is not indicated for use in liver transplant patients and the oral solution is approved only for the prevention of CMV disease.

- Adverse effects commonly associated with the use of ganciclovir and valganciclovir include diarrhea, vomiting, anemia, neutropenia, thrombocytopenia, increased serum creatinine and fever. Serious adverse effects with either agent may include renal failure or retinal detachment. Additionally, serious adverse effects associated with the use of ganciclovir may include cardiac arrest, pancreatitis, liver failure, rhabdomyolysis and Stevens-Johnsons Syndrome.

- Ganciclovir carries a black box warning regarding the clinical toxicities of use, including granulocytopenia, anemia, and thrombocytopenia. The warning also includes language that ganciclovir was carcinogenic, teratogenic, and caused aspermatogenesis in animal studies. Since valganciclovir is a prodrug of ganciclovir, it also carries these same black box warnings. Ganciclovir's black box warning also includes language about the more rapid rate of CMV retinitis progression with the use of ganciclovir capsules compared to intravenous infusions.

- Ganciclovir and valganciclovir should be used with caution in patients with pre-existing cytopenias or with a history of cytopenic reactions to other drugs, chemicals, or irradiation. These agents should not be administered with absolute neutrophil counts <500 cells/μL, platelet counts <25,000/μL, or hemoglobin levels <8 g/dL.

- Acute renal failure may occur in elderly patients, with or without reduced renal function, receiving valganciclovir, patients who receive concomitant nephrotoxic drugs, or inadequately hydrated patients. Use with caution in elderly patients or those taking nephrotoxic drugs, and reduce the dosage in patients with renal impairment. In addition, renal function should be monitored.

- Concurrent use of ganciclovir or valganciclovir with didanosine increases the risk of didanosine toxicity and CD4 cell loss or failure of CD4 cell recovery. Life-threatening hematologic toxicity may occur with concurrent use of ganciclovir and zidovudine.

- Both ganciclovir and valganciclovir have demonstrated safety and efficacy in the prevention of CMV disease in solid organ transplant recipients. Head-to-head trials comparing oral ganciclovir and valganciclovir demonstrate that even with significantly higher incidences of CMV viremia with ganciclovir, incidences of CMV disease were comparable between the two treatments. Safety data within these two trials is inconsistent with one reporting similar rates of adverse events between ganciclovir and valganciclovir, and the other reporting a significantly higher incidence of adverse events with valganciclovir.

- Oral ganciclovir was compared to oral valganciclovir in 372 solid organ transplant patients from a CMV positive donor. After six months, CMV disease occurred in 15.2 and 12.1% of patients receiving ganciclovir and valganciclovir (95% CI, -0.042 to 0.110). The incidence of CMV viremia was comparable between the two treatments after six (43.2 vs 39.7%) and 12 months (48.8 vs 48.5%; P values not reported). Reported drug-related adverse events were comparable between the two treatments. The most commonly reported adverse events were diarrhea, tremor, graft rejection, and headache.

- Oral ganciclovir was compared to oral valganciclovir in 163 lung transplant patients who were seropositive for CMV. After one year, there was no difference between the incidence of CMV disease in patients receiving ganciclovir and valganciclovir (16.1 vs 7.9%; P value not significant). There was a significantly higher incidence of CMV viremia with ganciclovir compared to valganciclovir.
There was no difference in the incidence of CMV infection between ganciclovir and valganciclovir (34.5 vs 32.9%; P value not significant). The overall incidence of adverse effects was higher with valganciclovir compared to ganciclovir (6.9 vs 25.0%; P<0.01). Leukopenia was more frequent with valganciclovir (2.3 vs 15.8%; P<0.01). Treatment was discontinued in significantly more patients receiving valganciclovir (1.1 vs 11.8%; P<0.01).

For the treatment of CMV retinitis, a head-to-head trial comparing intravenous ganciclovir to valganciclovir demonstrated no difference between the two treatments in the progression of disease after four weeks of treatment (10.0 vs 9.9%; 95% CI, -9.7 to 10.0). In addition, there was no difference in the proportion of patients achieving a satisfactory response between the two treatments. In this trial, the median time to progression of retinitis was 125 and 160 days with intravenous ganciclovir and valganciclovir.

- Current clinical guidelines from the Center for Disease Control and Prevention, the National Institutes of Health and the Infectious Diseases Society of America for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents state that oral valganciclovir, intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, intravenous foscarnet, intravenous cidofovir, and the ganciclovir intraocular implant coupled with oral valganciclovir are all effective treatments for CMV retinitis. Initial therapy for CMV retinitis should be individualized based on the location and severity of the lesion(s) and the level of underlying immune suppression. The guidelines state that the ganciclovir intraocular implant plus oral valganciclovir is superior to once-daily intravenous ganciclovir for preventing relapse of retinitis.

- For the prevention of CMV in solid organ transplantation, the Transplantation Society International Cytomegalovirus Consensus Group recommends various antivirals, including oral ganciclovir and valganciclovir, depending on the specific organ transplanted, and no one antiviral agent is preferred or recommended over another.

**RECOMMENDATION**

Ganciclovir and valganciclovir are oral antiviral agents with activity against cytomegalovirus. While valganciclovir is a prodrug of ganciclovir, they do not carry the same FDA-approved indications. Ganciclovir capsules are FDA-approved for the prevention of CMV disease in patients with advanced HIV infection at risk for developing CMV disease, for the prevention of CMV disease in solid organ transplant recipients, and for maintenance treatment of CMV retinitis in immunocompromised patients. Valganciclovir is FDA-approved for the prevention of CMV disease in solid organ transplant recipients (excluding liver transplant) at high risk and for the treatment of CMV retinitis in adult patients with acquired immunodeficiency syndrome. According to current clinical guidelines, choice of initial therapy for CMV retinitis in HIV-infected patients should be individualized based on the location and severity of the lesion(s) and the level of underlying immune suppression. Both oral ganciclovir and valganciclovir, along with other antivirals, are effective treatment options. For the prevention of CMV in solid organ transplantation, depending on the specific surgery various antivirals are recommended, including oral ganciclovir and valganciclovir, and again no one agent is preferred or recommended over another. Both ganciclovir and valganciclovir have demonstrated efficacy for their approved indications; however, given their differences in approved indications, these agents cannot be considered therapeutic alternatives to one another. Therefore, it is recommended both ganciclovir and valganciclovir should be available for use.

**COMMITTEE VOTE:**

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

### RE-REVIEW: ANTIVIRALS: CYTOMEGALOVIRUS AGENTS

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>ganciclovir</td>
<td>N/A</td>
</tr>
<tr>
<td>Valcyte® (valganciclovir)</td>
<td></td>
</tr>
</tbody>
</table>

**References**


---

### RE-REVIEW: ANTI-INFECTIVES: HEPATITIS B

**BACKGROUND**

- An estimated 1.4 million Americans have chronic hepatitis B which is a leading cause of cirrhosis and hepatocellular carcinoma. This review includes five oral agents indicated for the treatment of chronic hepatitis B: the nucleoside reverse transcriptase inhibitors entecavir, lamivudine (Epivir-HBV®) and telbivudine and the nucleotide reverse transcriptase inhibitors adefovir and tenofovir.

- The nucleoside/nucleotide reverse transcriptase inhibitors are nucleoside/nucleotide analogs that possess antiviral activity due to their structural similarity to the basic building blocks of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA). The nucleoside/nucleotide reverse transcriptase inhibitors serve as substrates for and inhibit viral DNA or RNA polymerase during viral replication. Many of these agents may also be incorporated into viral DNA during synthesis, acting as a chain terminator of DNA synthesis.

- All of the agents in this class are FDA-approved for the treatment of chronic hepatitis B (lamivudine: ages 2 & older, adefovir: ages 12 & older, entecavir, telbivudine: ages 16 & older, tenofovir: adults only); tenofovir is also indicated for the treatment of human immunodeficiency virus (HIV) in combination with other antiretroviral agents. Similarly, lamivudine (Epivir®) is indicated for the treatment of HIV, but at a higher dose than is used for the treatment of hepatitis B virus (HBV).

- The most common adverse drug events observed with these agents are diarrhea, fatigue, headache, nausea, vomiting, rash and sleep disorders.
  - All of the agents in this class carry a boxed warning regarding potentially fatal lactic acidosis and severe hepatomegaly with steatosis. Also, all agents carry a black box warning regarding the risk of severe acute exacerbations of hepatitis B that have been reported in patients who have discontinued anti-hepatitis B therapy. Lamivudine (Epivir-HBV®) carries a black box warning stating that HIV counseling and testing should be offered to all patients prior to initiation of therapy and periodically during treatment. If treatment with Epivir-HBV® is prescribed for chronic hepatitis B for patients with unrecognized or untreated HIV infection, rapid emergence of HIV resistance is likely because of subtherapeutic dose and inappropriate monotherapy.
  - Adefovir and tenofovir carry general warnings about the risk of nephrotoxicity and require dose adjustments for declining creatinine clearance. Telsbivudine carries a warning regarding myopathy and a risk of neuropathy.
Lamivudine should be used cautiously in pediatric patients with a history of prior antiretroviral nucleoside exposure, pancreatitis or other significant risk factors for pancreatitis, since fatal pancreatitis has been reported in this population.

There is limited data available on the use of adefovir, entecavir, lamivudine and tenofovir in patients who are co-infected with HBV and HIV. It is recommended that HIV antibody testing be performed prior to initiating treatment. Use of entecavir is not recommended in co-infected patients who are not receiving highly active antiretroviral therapy. A higher dose of lamivudine indicated for HIV therapy should be administered as part of an appropriate combination regimen to co-infected patients.

In patients who have developed lamivudine-resistance, adefovir should be administered in combination with lamivudine and not as monotherapy in order to reduce the risk of resistance to adefovir. Dose modifications should be considered in patients with serum HBV DNA levels exceeding 1,000 copies / mL with continued treatment.

Co-administration of drugs that reduce renal function or compete for tubular secretion may increase the levels of adefovir, entecavir, lamivudine, telbivudine and tenofovir. See Table 7 (pages 25-26) of Therapeutic Class Review for complete listing of drug interactions.

Data from clinical trials support the use of the nucleoside/nucleotide reverse transcriptase inhibitors for the treatment of chronic hepatitis B. Two meta-analyses that evaluated the efficacy of all five nucleoside/nucleotide reverse transcriptase inhibitors, tenofovir and entecavir were shown to be the most effective and second most effective agents, respectively, in reducing serum HBV DNA levels.

Daikin, et al conducted a meta-analysis of 23 randomized, controlled trials (3,602 patients) of patients aged 18 and older with chronic hepatitis B who had no co-infection with HIV. In HBeAg-positive, nucleoside analog-naive patients, treatment with tenofovir was more likely to result in serum HBV DNA suppression at one year compared to lamivudine (OR, 3.51; 95% CI, 1.88 to 5.49; P<0.05), adefovir (OR, 3.06; 95% CI, 1.70 to 4.46; P<0.05), telbivudine (OR, 2.49; 95% CI, 0.78 to 4.36; P<0.05) and entecavir (OR, 1.99; 95% CI, 0.26 to 3.85; P<0.05). Telbivudine (OR, 1.02; 95% CI, 0.24 to 1.98; P<0.05) and entecavir (OR, 1.52; 95% CI, 0.80 to 2.47; P<0.05) also led to higher rate of viral suppression compared to lamivudine. Overall, tenofovir was associated with a 97.7% probability of being the best treatment for viral suppression.

Woo, et al conducted a meta-analysis of 20 randomized, controlled trials (4,786 patients) of patients aged 18 and older with chronic hepatitis B who had no co-infection with hepatitis C, D or HIV. In HBeAg-positive patients, tenofovir was the most effective treatment for serum HBV DNA suppression, ALT normalization, HBeAg seroconversion and HBsAg loss. Entecavir was the most effective treatment for histologic improvement and the second best option for serum HBV DNA suppression and ALT normalization. In HBeAg-negative patients, tenofovir was shown to be the most effective treatment for serum HBV DNA suppression and histologic improvement and the second best option for ALT normalization.

Current guidelines from the American Association for the Study of Liver Diseases (AASLD) state that therapy for the treatment of chronic hepatitis B can be initiated with any of the FDA-approved agents; however, entecavir, peginterferon alfa or tenofovir is preferred and that children should be initiated with interferon alfa or lamivudine. Subsequent treatment options are outlined by population, defined by resistance patterns and other patient specific factors.

**RECOMMENDATION**

All of the agents in this class are FDA-approved for the treatment of chronic hepatitis B; tenofovir is also indicated for the treatment of human immunodeficiency virus (HIV) in combination with other antiretroviral agents. According to the American Association for the Study of Liver Disease guidelines, therapy can be initiated with any of the FDA-approved agents; however, entecavir,
 peginterferon alfa and tenofovir are preferred, and data from clinical trials align with this recommendation. Additionally, lamivudine is indicated for use in children as young as two years of age and is one of the two preferred treatments in children. Therefore, it is recommended at least entecavir, lamivudine and tenofovir should be available for use.

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baraclude® (entecavir)</td>
<td>Hepsera® cc (adefovir)</td>
</tr>
<tr>
<td>Epivir HBV® (lamivudine)</td>
<td>Tyzeka® cc (telbivudine)</td>
</tr>
<tr>
<td>Viread® (tenofovir)</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Criteria for Hepsera®

Hepsera® will be approved for recipients meeting the following criteria:

- For patients aged 15 & less: requires inadequate treatment response (detectable HBV DNA level after 24 weeks of therapy), virologic breakthrough, resistance, intolerance or contraindication to lamivudine
- For patients aged 16 & older: requires inadequate treatment response (detectable HBV DNA level after 24 weeks of therapy), virologic breakthrough, resistance, intolerance or contraindication to entecavir OR tenofovir

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

Clinical Criteria for Tyzeka®

Tyzeka® approval requires inadequate treatment response (detectable HBV DNA level after 24 weeks of therapy), virologic breakthrough, resistance, intolerance or contraindication to entecavir OR tenofovir

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

References

BACKGROUND

- According to the Centers for Disease Control and Prevention (CDC), the most effective way to minimize the negative impact of influenza is through prophylaxis, by administration of the influenza vaccine. The use of chemotherapeutic agents for the prophylaxis and treatment of influenza is an important adjunct for disease control during outbreaks among unvaccinated individuals, or for individuals at risk for whom the vaccine is contraindicated or ineffective.

- Neuraminidase inhibitors work by blocking viral release mechanisms during the replication cycles of influenza A and B. Neuraminidase is an enzyme that is necessary for release of daughter virions from infected cells. Without the action of neuraminidase, the new virions are tethered to the cellular membrane glycoproteins of their parent cells and therefore, the virus will remain aggregated at the cell surface and cannot spread to other cells. Because the peak range for influenza virus replication is 24 to 72 hours after the onset of illness, oseltamivir and zanamivir must be administered as early as possible. The adamantanes work by preventing viral replication by blocking the viral M2 protein ion channel, which prevents fusion of the virus and host-cell membranes.

- The neuraminidase inhibitors, oseltamivir and zanamivir, are FDA-approved for the treatment and prophylaxis of influenza A and B. Rimantadine is FDA approved for the treatment of influenza A in patients 17 years of age or older and for prophylaxis of influenza A in adults and pediatric patients five years of age and older.

- The use of oseltamivir is generally well tolerated with the most common adverse events including abdominal pain, nausea and vomiting. Zanamivir is commonly associated with respiratory symptoms including cough, throat pain, nasal symptoms and fever. The neuraminidase inhibitors have both rarely been associated with serious skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. Adverse events common to rimantadine includes loss of appetite, nausea, xerostomia, dizziness, headache and insomnia.

- Precautions:
  - Clearance of rimantadine in those with severe liver dysfunction is lower than that of healthy individuals. Because of the potential for accumulation of rimantadine and its metabolites in plasma, caution should be exercised when patients with hepatic insufficiency are treated with rimantadine. In subjects with severe renal impairment, rimantadine systemic exposure is increased compared to healthy subjects. Because of the potential for increased accumulation of rimantadine metabolites in renally impaired subjects, caution should be exercised when these patients are treated with rimantadine and dosages should be reduced.
  - Rare occurrences of neuropsychiatric events (including confusion, seizures, delirium, hallucinations, and/or self-injury) have been reported with the neuraminidase inhibitors from post-marketing reports (mostly from Japan). These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. Patients with influenza should be closely monitored for signs of abnormal behavior. If neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient.
  - Zanamivir is not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease). Cases of bronchospasm, some fatal, have been reported in those with and without airway disease.

- Clinical trials have demonstrated that rimantadine is effective in both the prophylaxis and treatment of influenza A. Oseltamivir and zanamivir have been effective in both the prophylaxis and treatment of influenza A and B. Clinical trials have demonstrated reduced laboratory-confirmed influenza, decreased illness, fever duration, secondary
complications, as well as a reduction in household contacts with influenza infection. Numerous placebo-controlled trials have demonstrated the efficacy of oseltamivir and zanamivir individually; however head-to-head trials directly comparing the agents are limited.

- Current guidelines from the CDC state that annual influenza vaccination is the most effective method for preventing seasonal influenza virus infection and its complications. Antiviral treatment is recommended by the CDC as soon as possible for patients with confirmed or suspected influenza who have severe, complicated, or progressive illness or who require hospitalization and for outpatients with confirmed or suspected influenza who are at higher risk for influenza complications on the basis of their age or underlying medical conditions. The greatest benefit is when initiated within 48 hours of influenza onset. However, it may be beneficial in those with severe, complicated, or progressive illness and in hospitalized patients if administered >48 hours from onset. Recommended antiviral medications include oseltamivir and zanamivir. The CDC notes that amantadine and rimantadine should not be used because of the high levels of resistance to these drugs. Persons at higher risk for influenza complications recommended for antiviral treatment include:
  - Children aged <2 years.
  - Adults aged ≥65 years.
  - Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematological (including sickle cell disease), metabolic disorders (including diabetes mellitus), or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury).
  - Persons with immunosuppression, including that caused by medications or by human immunodeficiency virus (HIV) infection.
  - Women who are pregnant or postpartum (within two weeks after delivery).
  - Persons aged <19 years who are receiving long-term aspirin therapy.
  - American Indians/Alaska Natives.
  - Persons who are morbidly obese (i.e., body-mass index ≥40).
  - Residents of nursing homes and other chronic-care facilities.

**RECOMMENDATION**

The neuraminidase inhibitors and the adamantanes are FDA approved for the treatment and prophylaxis of influenza. Clinical trials have demonstrated that rimantadine is effective in both the prophylaxis and treatment of influenza A; however, due to a marked increase in resistant isolates, the CDC recommends that adamantanes not be used for the treatment of influenza, except in selected circumstances. Therefore, rimantadine can be considered an inferior product in this class. Numerous placebo-controlled trials have demonstrated the efficacy of oseltamivir and zanamivir individually; however limited within class comparisons prevent recommendation of one neuraminidase inhibitor over the other. The neuraminidase inhibitors have both demonstrated efficacy; however, safety issues may vary as zanamivir is not recommended for use in patients with underlying airway disease and oseltamivir is the only agent approved for use in children as young as one year of age. Current CDC guidelines recommend antiviral treatment with oseltamivir or zanamivir as soon as possible for patients with confirmed or suspected influenza who have severe, complicated, or progressive illness or who require hospitalization and for outpatients with confirmed or suspected influenza who are at higher risk for influenza complications on the basis of their age or underlying medical conditions. Therefore, it is recommended at least oseltamivir should be available for use; however, due to the need to initiate these agents within 48 hours of the onset of symptoms to ensure efficacy, it is recommended the influenza antivirals should be subject to clinical criteria.
COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION

RE-REVIEW: ANTIVIRALS: INFLUENZA

PREFERRED       NON-PREFERRED
N/A                                             Flumadine® (rimantadine)
Relenza® (zanamivir)
rimantadine (compares to Flumadine®)
Tamiflu® (oseltamivir)

Clinical Criteria for Relenza® & Tamiflu®
Will be approved if any of the following are true:
• Recipient has been clinically diagnosed with influenza A, B or H1N1 AND drug therapy will be initiated within 48 hours of the onset of symptoms. (For individuals at high risk of influenza complications, approvals may be granted outside the initial 48 hours.)
• Recipient requires prophylaxis for influenza due to having been in close contact with an individual known to have influenza A, B or H1N1.
• Recipient has a suspected case of avian influenza (optimal doses & duration of treatment are not known, but will be dealt with case by case if necessary)
Please Note: the following high risk populations are exempt from the PA requirement: children under age 5 years, adults aged 65 years and older, and pregnant women (identified by use of prenatal vitamins).

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION

Clinical Criteria for Flumadine® (rimantadine)
Will be approved if the following are true:
• Recipient has contraindication, intolerance or drug-drug interaction to both oseltamivir and zanamivir AND at least ONE of the following:
  o Recipient has been clinically diagnosed with influenza A
  o Recipient requires prophylaxis for influenza due to having been in close contact with an individual known to have influenza A

NOTE: The CDC recommends that rimantadine should not be used for treatment or prophylaxis of influenza due to high levels of resistance.

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION

Quantity Limits:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Relenza®</td>
<td>40 per 180 days</td>
</tr>
<tr>
<td>Tamiflu®</td>
<td>Tablets: 20 per 180 days</td>
</tr>
<tr>
<td></td>
<td>6mg/mL susp: 240mL per 180 days</td>
</tr>
<tr>
<td></td>
<td>12mg/mL susp: 100mL per 180 days</td>
</tr>
</tbody>
</table>

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION
References

RE-REVIEW: URINARY ALKALIZING AGENTS

BACKGROUND

- The urinary alkalizing agents, potassium citrate, sodium citrate and citric acid may also be classified as citrates. Following administration of urinary alkalizing agents, the citrate salts are metabolized to bicarbonates which increase urinary pH by promoting the urinary excretion of free bicarbonate ions. In treating metabolic acidosis, the resulting bicarbonates buffer excess hydrogen ion concentrations and raise blood pH.
- FDA Approved Indications (See MedMetrics class review, Table 2, page 6):

<table>
<thead>
<tr>
<th>Indication</th>
<th>Single Products</th>
<th>Combination Products</th>
<th>Tri-Citrate Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal tubular acidosis w/ Ca stones</td>
<td>Potassium Citrate</td>
<td>Potassium Citrate/Citric Acid</td>
<td></td>
</tr>
<tr>
<td>Hypocitraturic calcium oxalate nephrolithiasis</td>
<td>Potassium Citrate/Citric Acid</td>
<td>Sodium Citrate/Citric Acid</td>
<td></td>
</tr>
<tr>
<td>Uric acid lithiasis with or w/o Ca stones</td>
<td>Potassium Citrate/Sodium Citrate</td>
<td>Sodium Citrate/Citric Acid</td>
<td></td>
</tr>
<tr>
<td>Long-term maintenance of alkaline urine</td>
<td>Potassium Citrate/Sodium Citrate/Citric acid</td>
<td>Sodium Citrate/Citric Acid</td>
<td></td>
</tr>
<tr>
<td>metabolic acidosis</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Acidosis of certain renal tubular disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary alkali</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

- **Common and Severe Adverse Reactions** (See MedMetrics Class Review, Table 5, pg. 7): Some common and severe adverse reactions for the alkalizing agents includes:
  - **Potassium citrate**: abdominal discomfort, diarrhea, loose bowel movements, nausea and vomiting.
  - **Sodium citrate/citric acid**: diarrhea, loose bowel movements, hypernatremia and metabolic alkalosis.
  - **Potassium citrate/sodium citrate/citric acid**: alkalosis
    - **Potassium citrate** is contraindicated with hyperkalemia, peptic ulcer disease, active urinary tract infection, renal insufficiency, and in patients in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract.
    - **Potassium citrate/citric acid** is contraindicated with hypersensitivity to the formulation, severe renal impairment with oliguria or azotemia, untreated Addison's disease, acute dehydration, heat cramps, anuria, severe myocardial damage, and hyperkalemia.
    - **Sodium citrate/citric acid** is contraindicated with sodium-restricted diets, severe renal impairment, or known hypersensitivity to the individual agent(s). Also, this formulation should not be given concurrently with aluminum-based antacids. Additionally, patients should be directed to adequately dilute the formulation with water and should take after meals to avoid a saline laxative effect.
    - **Potassium citrate/sodium citrate/citric acid** is contraindicated with severe renal impairment with oliguria or azotemia, untreated Addison's disease, or severe myocardial damage. Aluminum-based antacids should not be given concurrently with this formulation as well.
  - **Significant Drug-Drug Interactions** (See MedMetrics Class Review, Table 6, pg. 8): Some significant drug-drug interactions with alkalization of the urine include:
    - **CNS stimulants**: may prolong the effects of CNS stimulants.
    - **Lithium**: reduces lithium plasma levels, resulting in decreased therapeutic response.
    - **Sympathomimetics**: may increase half-life and decrease elimination of ephedrine or pseudoephedrine, resulting in increased therapeutic response.
Potassium-sparing diuretics: increase potassium retention and can produce severe hyperkalemia.

Although, clinical guidelines addressing the role of urinary alkalizing agents are at best limited. The American Urological Association 2007 guidelines for uric acid stones, states manipulation of the urinary pH with oral potassium citrate, sodium citrate, or sodium bicarbonate to a level ranging from 6.0 to 7.0 may avoid the need for surgical intervention. As this treatment allows for stone dissolution in patients with controllable symptoms, prevents future uric acid stones and has been shown to enhance clearance with shock-wave lithotripsy.

Furthermore, clinical trial data demonstrating safety and efficacy is limited and clinical guidelines do not specifically recommend one agent over another. However, product selection may be determined with respect toward the potassium and sodium contents contained within the individual preparations.

**RECOMMENDATION**
The urinary alkalizing agents are utilized in conditions where long-term maintenance of alkaline urine is desired and in the management of chronic metabolic acidosis associated with chronic renal insufficiency or renal tubular acidosis. Clinical trial data demonstrating safety and efficacy is limited and clinical guidelines do not recommend one agent over another. However, treatment with urinary alkaliizers indicates these agents are efficacious in increasing urinary pH and preventing the formation of kidney stones. However, differences in the amount of sodium and potassium among the various products within the class may play a role in product selection for patients who are sodium restricted or concerned with potassium levels. Therefore, it is recommended that at least one tri-citrate product, at least one sodium citrate/citric acid product and at least one potassium citrate product is available for use.

**COMMITTEE VOTE:**

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

**RE-REVIEW: URINARY ALKALIZING AGENTS**

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>citric acid/ sodium citrate</td>
<td>Citrolith™ (potassium citrate/sodium citrate)</td>
</tr>
<tr>
<td>citric acid/potassium citrate</td>
<td>Cytra-K® crystals (compares to potassium citrate/citric acid)</td>
</tr>
<tr>
<td>Cytra-2® (citric acid/sodium citrate)</td>
<td>Oracit® (sodium citrate/citric acid)</td>
</tr>
<tr>
<td>Cytra-3® (K citrate/Na citrate/citric acid)</td>
<td>Polycitra-K® (potassium citrate/citric acid)</td>
</tr>
<tr>
<td>Cytra-K® solution (compares to potassium citrate/citric acid)</td>
<td>Tricitrates® (K citrate/Na citrate/citric acid)</td>
</tr>
<tr>
<td>potassium citrate (compares to Urocit-K®)</td>
<td>Urocit-K® (potassium citrate)</td>
</tr>
</tbody>
</table>

**References**

**RE-REVIEW: URINARY ACIDIFYING AGENTS**

**BACKGROUND**
- The urinary acidifying agents are used for a variety of medical situations that require an acidic urinary environment, including bladder irrigation, dissolution of renal calculi or when urinary phosphate levels need to be increased.
• Acetic acid has been shown to exert an antimicrobial action against a variety of microorganisms (especially ammonia-forming bacteria) that frequently gain access to the urinary bladder specifically in patients that require an indwelling urethral catheter for a prolonged time.
• Potassium phosphate is a sodium-free urinary acidifier and keeps calcium soluble and reduces odor and rash caused by ammonia in the urine. Additionally, the antibacterial activity of certain antibacterial agents is enhanced as a result of the acidic environment created with the use of potassium phosphate.
• Phosphates also play an important role in modifying steady-state tissue concentrations of calcium, buffering intracellular fluid, and are a key factor in hydrogen ion excretion via the kidneys. Potassium phosphate/sodium phosphate and potassium phosphate monobasic/sodium phosphate dibasic/sodium phosphate monobasic increase urinary phosphate and pyrophosphate. The relationship between phosphorus and calcium is reciprocal; therefore in patients with idiopathic hypercalciuria, administration of phosphate lowers urinary calcium levels.
• Citric acid/D-gluconic acid is approved for use for local irrigation and for dissolution of renal calculi composed of apatite or struvite. The mechanism of action of citric acid/D-gluconic acid on susceptible calculi involves an exchange of magnesium from the irrigating solution for the insoluble calcium contained in the stone matrix or calcification. The magnesium salts formed are soluble in the gluconocitrate irrigating solution, resulting in the dissolution of the calculus. It should be noted that citric acid/D-gluconic acid is not effective for dissolution of calcium oxalate, uric acid, or cystine stones. It should be noted that an infected stone can serve as a continual source of infection and sterile urine must be present prior to initiating therapy with citric acid/D-gluconic acid.
• **FDA-Approved Indications** (see MedMetrics class review, Table 2, page 2 for additional details)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Single Agent Products</th>
<th>Combination Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic Acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium Phosphate Monobasic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citric Acid/D-Gluconic Acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium Phosphate/Sodium Acid Phosphate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium Phosphate Monobasic/Sodium Phosphate Dibasic/Sodium Phosphate Monobasic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder irrigation</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Elevated urinary pH</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Local irrigation dissolution of renal calculi (apatite or struvite) in pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>not candidates for surgical removal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjunctive tx to dissolve residual apatite or struvite calculi after surgery or partial dissolution of renal calculi to facilitate surgical removal</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Dissolution of bladder calculi (apatite or struvite variety) by local intermittent irrigation through a urethral/cystostomy catheter as alternative/adjunct to surgical procedure</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Intermittent irrigating solution to prevent/minimize encrustations of indwelling urinary tract catheters</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Increase urinary phosphate and pyrophosphate</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

• **Adverse Drug Reactions** (See MedMetrics class review, Table 6, pg. 7 for a complete list)- Adverse drug reactions associated with urinary acidifying agents include the following:
  • **Acetic acid**- (rare) skin irritation, hematuria, superinfection and urethral pain
Potassium Phosphate Monobasic: irregular heartbeat, dizziness, mental confusion, diarrhea, nausea, vomiting, bone pain, joint pain, muscle cramps, osteomalacia, pain/weakness in hands/feet/legs, shortness of breath and numbness/tingling

Citric acid/D-Gluconic Acid: thrombophlebitis, nausea, ileus, vomiting, back, transient flank pain, elevated serum creatinine, hypermagnesemia, hyperphosphatemia, dysuria, UTI, transient hematuria, candidiasis and sepsis.

Potassium Phosphate/Sodium Acid Phosphate: (rare) nausea, vomiting, abdominal pain, headache and diarrhea.

Potassium Phosphate Monobasic/ Sodium Phosphate Dibasic/ Sodium Phosphate Monobasic: edema, tachycardia, dizziness, headache, mental confusion, abdominal pain, ileus, vomiting, arthralgia, bone pain, muscle cramps, osteomalacia, paresthesia, seizure, oliguria and dyspnea.

The use of potassium phosphate monobasic is contraindicated with infected phosphate stones; severe renal dysfunction, and in the presence of hyperphosphatemia and hyperkalemia. Additionally caution should be used when the regulation of potassium is required.

Citric acid/D-gluconic acid is contraindicated with urinary tract infections and should be discontinued immediately if fever, urinary tract infection, signs and symptoms consistent with urinary tract infection, persistent flank pain, hypermagnesemia or elevated serum creatinine develops.

Potassium phosphate monobasic/sodium phosphate dibasic/sodium phosphate monobasic is contraindicated with hyperphosphatemia, severe renal dysfunction, and infected phosphate stones.

Significant Drug-Drug Interactions (See MedMetrics class review, Table 7, pg. 9):

Acetic acid:
- Antacids: The use of magnesium, calcium or aluminum containing antacids with phosphate preparations may bind phosphate and prevent absorption.
  - Potassium-containing drugs: Concurrent use with potassium salts may cause hyperkalemia. Potassium levels should be monitored periodically.
  - Salicylates: Concurrent use may lead to increased salicylate levels due to reduced excretion in acidic urine. Serum salicylate levels should be monitored to avoid toxicity.

Citric acid/D-gluconic acid:
- Magnesium-containing drugs: concurrent use may cause hypermagnesemia.

The 2005 American Urological Association guidelines for the management of staghorn calculi list as an alternative treatment, irrigation of the collecting system with solutions such as citric acid/D-gluconic acid (Renacidin®) to dissolve struvite staghorn stones, as a primary method or following percutaneous nephrolithotomy. However, it warns that this treatment may be effective but requires prolonged hospitalization and is not widely used. Furthermore, the American Urological Association also states that there is not sufficient evidence to support the routine use of citric acid/D-gluconic acid (Renacidin®) irrigations to eradicate residual struvite fragments that may remain following percutaneous nephrolithotomy or shock-wave lithotripsy monotherapy.

RECOMMENDATION

The urinary acidifying agents may be used for a variety of medical situations that require an acidic urinary environment, including bladder irrigation, dissolution of kidney stones or when urinary phosphate levels need to be increased. Although, there is limited clinical information available regarding the use of urinary acidifying agents, the American Urological Association guidelines for the management of staghorn calculi list citric acid/D-gluconic acid (Renacidin®) irrigation as an alternative treatment. However, the American Urological Association also states there is not sufficient evidence to support routine use of this agent for eradicating residual struvite fragments.
Therefore it is recommended that at least one single entity agent and one combination urinary acidifying agent is available for use with citric acid/D-gluconic acid subject to clinical criteria to ensure appropriate use.

COMMITTEE VOTE:
APPROVED    DISAPPROVED    APPROVED with MODIFICATION

RE-REVIEW: URINARY ACIDIFYING AGENTS

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic acid</td>
<td>Renacidin® (Citric Acid/D-Gluconic Acid )&lt;sup&gt;CC&lt;/sup&gt;</td>
</tr>
<tr>
<td>K-Phos® (Potassium Phosphate Monobasic)</td>
<td></td>
</tr>
<tr>
<td>K-Phos #2® (Potassium Phosphate/Sodium Acid Phosphate)</td>
<td></td>
</tr>
<tr>
<td>K-Phos MF® (Potassium Phosphate/Sodium Acid Phosphate)</td>
<td></td>
</tr>
<tr>
<td>K-Phos Neutral® (Potassium Phosphate Monobasic/Sodium Phosphate Dibasic/Sodium Phosphate Monobasic)</td>
<td></td>
</tr>
<tr>
<td>Phospha 250 Neutral (Potassium Phosphate Monobasic/Sodium Phosphate Dibasic/Sodium Phosphate Monobasic)</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Criteria for Renacidin®
Renacidin® will be approved only for patients with a diagnosis of apatite and/or struvite calculi who:
- Have received antibiotic therapy, AND
- Not candidates for surgery or have residual calculi following surgery.

COMMITTEE VOTE:
APPROVED    DISAPPROVED    APPROVED with MODIFICATION

References

RE-REVIEW: URINARY ANALGESICS

BACKGROUND
- Phenazopyridine is a urinary tract analgesic used for the management of various conditions involving dysuria.
- The mechanism of action of phenazopyridine is not known. However, the agent is believed to promote topical analgesia on the mucosa of the urinary tract.
- Phenazopyridine is FDA (Food and Drug Administration) approved for symptomatic relief of pain, burning, urgency, frequency, and other discomforts arising from irritation of the lower urinary tract mucosa. This product is available as a prescription agent and as an OTC (over-the-counter) product as well.
• The most common adverse reactions experienced with the use of phenazopyridine include headache, gastrointestinal disturbance, pruritis and maculopapular rash.
  o Phenazopyridine is contraindicated in renal insufficiency as well as with known hypersensitivity to the agent.
  o Phenazopyridine is an azo dye and can discolor many bodily fluids. Patients should be informed of the possibility that phenazopyridine produces a reddish-orange discoloration of the urine and may stain fabric. Additionally, staining of contact lenses may also occur.
  o There are no clinically significant drug interactions with phenazopyridine that are mentioned or reported in the current drug literature.

• Charles et al performed a double-blind, randomized controlled trial in patients receiving surgery on the lower urinary tract. This study included 52 patients for a 10 day duration. Patients were given nitrofurantoin 200mg/day given in 4 doses versus phenazopyridine 100mg QID. The primary endpoint of incidence of complications and proportion of patients with fever showed there were more early complications (marked frequency, bladder spasms, hemorrhage, fever, etc) with phenazopyridine compared to nitrofurantoin. However, the difference was not significant (23 vs. 15%; P>0.05). Similar results were observed with late complications (12 vs. 4%; P value not reported) and total complications (35 vs. 19%; P>0.05). Early fever developed in 42% and 38% of patients receiving nitrofurantoin and phenazopyridine, respectively. (See MedMetrics class review, Table 4 for further details on clinical trials)

• The clinical literature does not provide any specific clinical guidelines for the management of dysuria. The American Urological Association 2011 guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome does not specifically list phenazopyridine as a first line treatment. However, it does state for first line treatments, self-care practices and behavioral modifications, including the administration of OTC agents that can improve symptoms should be discussed and implemented as feasible.

RECOMMENDATION
The urinary analgesics class is limited to phenazopyridine, which is FDA approved for symptomatic relief of pain, burning, urgency, frequency, and other discomforts arising from irritation of the lower urinary tract mucosa. Although there are few well-designed clinical trials evaluating the safety and efficacy of phenazopyridine in dysuria, the use of this agent is still utilized for the management of a number of conditions involving dysuria. Additionally, the American Urological Association guidelines do not specifically list phenazopyridine, it does however state that for first line treatments, self-care practices and behavioral modifications, including administration of OTC agents, such as phenazopyridine that can improve symptoms should be implemented as necessary. Therefore, it is recommended that phenazopyridine is available for use.

COMMITTEE VOTE:
APPROVED    DISAPPROVED    APPROVED with MODIFICATION

<table>
<thead>
<tr>
<th>RE-REVIEW: URINARY ANALGESICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREFERRED</td>
</tr>
<tr>
<td>phenazopyridine (Compares to Pyridium®)</td>
</tr>
<tr>
<td>Pyridium® (phenazopyridine)</td>
</tr>
</tbody>
</table>

References

RE-REVIEW: URINARY INTERSTITIAL CYSTITIS

BACKGROUND

- Interstitial cystitis, combined with bladder pain syndrome (IC/BPS) is defined as a recurring discomfort (pressure) or pain in the bladder and the surrounding pelvic region and associated with lower urinary tract symptoms. The urinary tract symptoms associated with IC/BPS last more than 6 weeks and typically occur in the absence of infection or other identifiable causes. IC/BPS is typically known to occur in the fourth decade of life or sometime thereafter and is more prevalent in female patients. Symptoms associated with IC/BPS include urinary frequency, urinary urgency or a combination of these symptoms. Pain may change in intensity as the bladder fills with urine or with the intake of specific foods or drinks.

- The urinary interstitial cystitis agents include pentosan polysulfate sodium (Elmiron®) and irrigating solution, dimethyl sulfoxide (RIMSO-50®). The exact mechanism of action for both of these agents is unknown. Pentosan polysulfate sodium is a low molecular weight heparin-like compound that possesses anticoagulant and fibrinolytic effects.

- Pentosan polysulfate sodium (pentosan) is FDA approved for relief of bladder pain or discomfort associated with IC in patients 16 years of age or older. Pentosan has been shown to adhere to the bladder wall and act as a buffer to control cell permeability, thereby preventing irritating solutes in urine from reaching the cells. Dimethyl sulfoxide (DMSO) is FDA approved for symptomatic relief of IC. This agent has anti-inflammatory and analgesic effects and is thought to reduce inflammation and block pain. It may also prevent muscle contractions that cause pain, frequency, and urgency.

- The most common and severe adverse reactions for pentosan polysulfate sodium and dimethyl sulfoxide are listed below:

  - **pentosan polysulfate sodium:**
    - common: alopecia (4%), rash (up to 3%), abdominal pain (2%), diarrhea (2.3% to 4%), indigestion (up to 2%), nausea (2.3% to 4%), dizziness (1%) and headache (up to 3%)
    - severe: proctitis and rectal hemorrhage (6.3%)

  - **dimethyl sulfoxide (DMSO):**
    - common: garlic breath, garlic taste, abnormal body odor, chemical cystitis (transient), pain following administration of agent (moderate to severe)
    - severe: anaphylactoid reaction (rare)

- There are no known contraindications with DMSO. However, pentosan is contraindicated with known hypersensitivity to the agent or its excipients.

- Patients undergoing invasive procedures or having signs and symptoms of underlying coagulopathy or other increased risks of bleeding should be evaluated for hemorrhage when taking pentosan. Caution should also be exercised in patients with a history of heparin induced thrombocytopenia.

- Pentosan is classified as FDA pregnancy risk category B. Pentosan’s anticoagulant effect is relatively weak compared to other anticoagulants, but caution should be utilized when administering to pregnant women near the time of delivery as there may be an increased risk for peripartum bleeding.

- DMSO can initiate the release of histamine; hypersensitivity reactions have been reported in one patient receiving intravesical DMSO. If anaphylactoid symptoms should develop, appropriate therapy should be administered.

- Use DMSO cautiously in patients with cataracts. Full eye evaluations (i.e. slit lamp examinations) are recommended prior to and periodically during treatment.
with DMSO, as lens changes have been noted in animals. Additionally, biochemical screening, including complete blood count, liver and renal function tests are recommended every 6 months.

- The risk of using DMSO during pregnancy cannot be ruled out, as there are no adequate and/or well controlled studies of DMSO in pregnant females. Therefore DMSO should only be used during pregnancy if the benefit outweighs the potential risk to the fetus. Also, it should be noted that the safety and efficacy of DMSO has not been established in the pediatric population.

- There are no head-to-head trials comparing the urinary interstitial cystitis agents but both appear to have comparable efficacy and safety to other agents that may be utilized in the management of interstitial cystitis. Furthermore, clinical trials evaluating the safety and efficacy of the urinary interstitial cystitis agents are dated and commonly evaluate or assess quality of life.

- A double-blind multi-center randomized controlled trial evaluated pentosan 100 TID versus placebo in patients with interstitial cystitis. This trial included 148 patients and showed 32% of the patients receiving pentosan demonstrated significant improvement compared to 16% of patients receiving placebo (P=0.01). Additionally, patients receiving pentosan experienced a significant decrease in pain and urgency (P=0.04 and P=0.01) versus placebo. Also patients receiving pentosan demonstrated an increase > 20mL in voided urine versus placebo (P=0.02).

- Another randomized controlled cross-over trial evaluated patients with biopsies suggestive of interstitial cystitis. This trial included only 33 patients with a primary endpoint of response rate and side effect profile. Assessed subjectively, 53% of DMSO-treated patients were markedly improved compared to 18% of placebo-treated patients. With DMSO, 93% of patients had objective improvements compared to 35% of patients with placebo (P values not reported). Also, there were no significant side effects noted during the trial.

- Clinical guidelines state that conservative treatment strategies, such as patient education and behavioral modification, should be utilized as first-line treatment including the administration of over-the-counter (OTC) agents in patients with interstitial cystitis and that no one single treatment has been found effective for the majority of patients. Oral pentosan polysulfate and DMSO is recommended for the treatment of interstitial cystitis in patients who have failed on other therapeutic options. The American Urological Association 2011 guidelines recognize both, pentosan and DMSO as potential second-line treatment options and state acceptable symptom control may require trials of multiple therapeutic options.

**RECOMMENDATION**

Dimethyl sulfoxide (RIMSO-50®) is an intravesical administered agent, FDA approved for symptomatic relief of interstitial cystitis. However, safety and efficacy has not been established in pediatric patients. Pentosan polysulfate sodium (Elmiron®) is FDA approved for symptomatic relief of interstitial cystitis in patients 16 years of age or older. Although there are no head-to-head trials evaluating the urinary interstitial cystitis agents and clinical trials demonstrating safety and efficacy is lacking, clinical trial data does suggest that patients with interstitial cystitis, who are treated with DMSO and pentosan polysulfate achieve response to treatment and a decrease in symptoms. The 2011 American Urological Association guidelines state patient education and behavioral modification including administration of OTC agents should be utilized as first-line treatments in the management of interstitial cystitis. Additionally, clinical guidelines list DMSO and pentosan as potential second-line treatment options with the understanding that no one single treatment has been found effective for the majority of patients. In fact trials of multiple therapeutic options may be needed to achieve acceptable symptom control. Therefore, given that safety and efficacy has been established in children 16 years of age and older, it is recommended that at least pentosan is available for use.
COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

RE-REVIEW: URINARY INTERSTITIAL CYSTITIS

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elmiron® (pentosan polysulfate sodium)</td>
<td>N/A</td>
</tr>
<tr>
<td>RIMSO-50® (dimethyl sulfoxide)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

References

RE-REVIEW: KIDNEY STONE AGENTS

BACKGROUND

- Cystinosis is an autosomal recessive disorder characterized by an accumulation of the amino acid cystine, the building block of proteins. Excess cystine forms crystals that can build up and damage cells. These crystals negatively affect many systems in the body, especially the kidneys and eyes. Patients with cystinosis have an error of metabolism in which the transport of cystine out of lysosomes is abnormal. Cystinosis may further be classified into 3 different classifications based on age at presentation and degree of disease severity. These 3 classifications in decreasing order of severity include: nephropathic infantile form, nephropathic juvenile form, and non-nephropathic adult form. All three forms are due to a mutation of the CTNS (cystinosin lysosomal cystine transporter) gene and have phenotypic overlap. Mutations in this gene lead to a deficiency of a transporter protein called cystinosin, which moves cystine out of the lysosomes. In nephropathic infantile and nephropathic juvenile, the kidneys are the first affected organs, which progressively lose function of proximal tubular transporters. Thus, resulting in urinary loss of water, sodium, potassium, bicarbonate, calcium, magnesium, phosphate, amino acids, glucose, proteins, and many other solutes normally reabsorbed in this segment of the nephron. Patients with non-nephropathic or ocular cystinosis do not usually experience growth impairment or kidney malfunction. The only symptom is photophobia due to build-up of cystine crystals in the cornea.
- The kidney stone agents for the purposes of this class review includes: acetohydroxamic acid (Lithostat®), cysteamine bitartrate (Cystagon®), and tiopronin (Thiola®). Cysteamine bitartrate is a cystine depleting agent; therefore, decreases the amount of cystine in the lysosomes. Exogenous cysteamine enters the cell and converts cystine to cysteine and a cysteine-cysteamine complex. Cysteamine bitartrate works via this thiol-disulfide interchange reaction. This reaction that produces both cysteine and the cysteine-cysteamine complex are more readily transported out of the lysosome than cystine, resulting in a long-term depletion of lysosomal cystine. Cysteamine bitartrate is
Food and Drug Administration (FDA)-approved for the management of nephrotic cystinosis in children and adults. Based on clinical literature, the use of cysteamine bitartrate postpones and prevents the deterioration of renal function and the development of extra-renal complications in patients with cystinosis.

- Tiopronin is similar to cysteamine bitartrate in that it is an active reducing agent that also undergoes a thiol-disulfide exchange with cystine; however, tiopronin-cystine disulfide is formed, which has increased water solubility compared to cystine and is readily excreted. This agent is FDA-approved for the prevention of cystine (kidney) stone formation in patients with severe homozygous cystinuria. Treatment with tiopronin prevents the formation of urinary cystine calculi.

- Acetohydroxamic acid is somewhat different compared to the other two agents, as this agent does not directly affect cystine levels. As a urease inhibitor, acetohydroxamic acid reversibly blocks urease, a bacterial enzyme, and prevents the hydrolysis of urea and ammonia production in urine contaminated with urea-splitting bacteria. Therefore, causing the actions of acetohydroxamic acid to improve the potency of certain antibiotics and raise the cure rate in patients with urinary tract infections. Acetohydroxamic acid is FDA-approved as adjunctive therapy in patients with chronic urea-splitting urinary infections, but has the potential to be used off-label as prophylaxis treatment in urolithiasis. As, acetohydroxamic acid has been effective in preventing stone recurrence and arresting growth or causing partial or complete dissolution of stones.

- Some common and most severe adverse events found with the kidney stone agents include (for further details please MedMetrics class review, table 6, pg. 7):
  - **Cysteamine bitartrate** (common): rash, diarrhea, loss of appetite, vomiting, lethargy, somnolence, fever, (severe): skin lesion, gastrointestinal hemorrhage, gastrointestinal ulcer, encephalopathy, seizure and papilledema.
  - **Tiopronin** (common): skin disorder, pharyngitis, oral ulcers, gastrointestinal symptoms, altered taste/smell, immune hypersensitivity reaction (severe): aplastic anemia, leukopenia, thrombocytopenia, drug-induced lupus erythematosus, fever, arthralgia, lymphadenopathy and kidney disease.
  - **Acetohydroxamic** (common): loss of appetite, nausea, vomiting, hemolytic anemia, reticulocytosis, headache, anxiety, depression, mild malaise, and (severe): lower limb vein phlebitis.

- While both cysteamine bitartrate and tiopronin are classified as Pregnancy category C and contraindicated in pregnancy. Tiopronin may be used in severe cystinuria where the benefit of inhibiting stone formation clearly outweighs the potential hazards of treatment.
- Acetohydroxamic acid is classified as FDA pregnancy risk category X and is contraindicated in women who are pregnant or women not using appropriate contraception. Acetohydroxamic acid may cause fetal harm. Therefore, if the agent is used during pregnancy, or if the patient becomes pregnant while taking acetohydroxamic acid, the patient should be informed of the potential hazard to the fetus.
- Additionally, acetohydroxamic acid is contraindicated with patients whose physical state and disease are amenable to definitive surgery and appropriate antimicrobial agents, patients whose urine is infected by non-urease producing organisms, patients whose urinary infections can be controlled by culture-specific oral antimicrobial agents, and in patients whose renal function is poor.
- Cases of pseudomotor cerebri (benign increased intracranial pressure) and/or papilledema have been reported with cysteamine therapy. Pseudomotor cerebri may be more common in cystinotic patients because of concurrent medication and renal transplantation. Nonetheless, providers should monitor for pseudomotor cerebri in patients receiving cysteamine, even though a causal relationship has not been established. Also, physicians should instruct patients to report any of the following symptoms: headache, tinnitus, dizziness, nausea, diplopia, blurry vision, loss of vision, pain behind the eye, or pain with eye movement. To prevent vision loss, patients should receive periodic eye
examinations for early identification and timely treatment of pseudomotor cerebri and/or papilledema.

- There are a limited number of clinical trials available that demonstrate the safety and efficacy of the kidney stone agents as it relates to their FDA-approved indications. Although, the trials available are small in size and are primarily observational in design. Overall, cysteamine bitartrate and tiopronin have both demonstrated an ability to decrease cystine urinary concentration and 24-hour urinary cystine excretion.
  o Gahl performed an observational study that included 93 patients. This study evaluated cysteamine 51.3 mg/kg/day in children with nephropathic cystinosis. 82% of the patients exhibited cystine depletions from leukocytes. At trial end, creatinine clearance was higher with the cysteamine group compared to the control group that received ascorbic acid or placebo. On average the cysteamine group was 1.4 years older than the control group. Also, patients between 2-3 years of age grew at 93% of the normal velocity in the cysteamine group versus 54% among the control group. However, 14% of the patients could not tolerate the taste and smell of cysteamine.
  o A retrospective trial performed by Lindell et al evaluated 31 patients with homozygous cystinuria receiving tiopronin. A 69% decrease in frequency of renal stone episodes, a 60% decrease in frequency of new stone formation and a 72% decrease in the need for surgical procedures were exhibited.

- There is limited data regarding treatment outcomes on patients with cystinuria, typically these patients will have their first stone event early in life, are prone to recurrent stones and subject to repetitive stone removal procedures. Additionally, this group of patients is at risk for developing renal insufficiency over time. The American Urological Association (AUA) guidelines for ureteral calculi recommend prophylactic medical therapy and close follow-up to limit stone recurrence. While, the AUA guidelines for management of staghorn calculi state that patients with abnormal lower urinary tracts undergoing removal of infection related calculi are at highest risk of stone recurrence. Therefore a more aggressive approach that utilizes acetohydroxamic acid should be considered as a treatment option.

**RECOMMENDATION**

Cystinosis is an autosomal recessive disorder characterized by an accumulation of the amino acid cystine. Excessive accumulation of cystine crystals negatively affects many systems in the body, especially the kidneys and eyes. The kidney stone agents utilized for management of cystinosis include acetohydroxamic acid (Lithostat®), cysteamine bitartrate (Cystagon®), and tiopronin (Thiola®). Cysteamine bitartrate is FDA-approved for the management of nephrotic cystinosis in children and adults. According to clinical literature, the use of cysteamine bitartrate postpones and prevents the deterioration of renal function and the development of extra-renal complications in patients with cystinosis. Tiopronin is approved for the prevention of cystine (kidney) stone formation in patients with severe homozygous cystinuria. Treatment with tiopronin prevents the formation of urinary cystine calculi. Acetohydroxamic acid is a urease inhibitor, FDA-approved as adjunctive therapy in patients with chronic urea-splitting urinary infections. Specifically, acetohydroxamic acid has been effective in preventing stone recurrence and arresting growth or causing partial or complete dissolution of stones and has the potential to be used off label as prophylaxis treatment in urolithiasis.

There is limited guidance on the appropriate use of the kidney stone agents within clinical guidelines. According to the American Urological Association, typically patients with cystinosis who have their first stone event early in life, are prone to recurrent stones and subject to repetitive stone removal procedures. Additionally, this group of patients is at risk for developing renal insufficiency over time. Clinical guidelines recommend prophylactic medical therapy and close follow-up to limit stone recurrence. Given that cysteamine bitartrate postpones and prevents deterioration of renal function and extra-renal complications and is approved for management of nephrotic cystinosis in both pediatric and adult populations it is recommended that at least cysteamine bitartrate is available for use.
COMMITTEE VOTE:

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

RE-REVIEW: KIDNEY STONE AGENTS

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystagon® (cysteamine bitartrate)</td>
<td>N/A</td>
</tr>
<tr>
<td>Thiola® (Tiopronin)</td>
<td></td>
</tr>
<tr>
<td>Lithostat® (acetohydroxamic acid)</td>
<td></td>
</tr>
</tbody>
</table>

References


RE-REVIEW: VAGINAL ANTISEPTICS

BACKGROUND

- A basic component of a healthy vaginal ecosystem is the maintenance of an acidic vaginal environment (pH 4.0±0.5). The conversion of epithelial cell-derived glycogen primarily into lactate helps to maintain a vaginal acidic environment; this acidic environment has an antagonistic effect to most bacteria and viruses. Therefore, alkalization of the vaginal environment, by medical conditions or other factors such as menses, increases the risk of overgrowth of certain bacteria.
- Vaginal antiseptics, or acidifying agents, might serve as either a therapeutic or preventative means to the development of vaginal bacterial infections. The single-entity agent, acetic acid provides an acidic environment, possesses local antibacterial and antifungal properties. While the single-entity, oxyquinoline has topical antiseptic, mild fungistatic, bacteriostatic, anthelmintic and amebicidal properties.
- The vaginal antiseptic class includes acetic acid/oxyquinoline sulfate (Fem pH®). Fem pH is FDA (Food and Drug Administration) approved as adjunctive therapy in cases where restoration and maintenance of vaginal acidity is desired.
- Acetic acid/oxyquinoline (Fem pH®) is associated with local stinging and burning. Occasional cases have been reported with acetic acid/oxyquinoline sulfate
  - There are no known drug interactions as none have been reported.
- Unfortunately, there are no clinical trials available that demonstrate the safety and efficacy of the vaginal antiseptics class as it relates to it FDA approved indications. Additionally, clinical guidelines do not specifically address the role of vaginal antiseptics regarding its place in therapy.

RECOMMENDATION

The vaginal antiseptic class includes acetic acid/oxyquinoline sulfate (Fem pH®). A basic component of a healthy vaginal ecosystem is the maintenance of an acidic vaginal environment. Vaginal antiseptics, or acidifying agents, might serve as either a therapeutic or preventative means
to the development of vaginal bacterial infections. The single-entity agent, acetic acid provides an acidic environment, possesses local antibacterial and antifungal properties. While the single-entity, oxyquinoline has topical antiseptic, mild fungistatic, bacteriostatic, anthelmintic and amebicidal properties. Although, there is limited clinical information available for vaginal antiseptics and clinical guidelines do not specifically address their role. Acetic acid/oxyquinoline (Fem pH®) is FDA approved as adjunctive therapy where restoration and maintenance of vaginal acidity is desired. Therefore it is recommended that this agent is available for use.

COMMITTEE VOTE:

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

### RE-REVIEW: VAGINAL ANTISEPTICS

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fem pH® (acetic acid/oxyquinoline)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**References**