

ORAL CANDIDIASIS AND HIV DISEASE



preventing and treating fungal infections of the mouth and throat

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Oral candidiasis, which is also called *thrush*, is a fungal infection of the mouth and/or throat. Candidiasis of the throat is called *esophageal* candidiasis (see *Diagnosis on page 3*).

While oral candidiasis can sometimes occur without symptoms, the most common ones are discomfort and burning of the mouth and throat and an altered sense of taste (often described as “bad”). Creamy white or yellowish spots on the mouth and throat that can be

removed by light scraping are also common. These may be accompanied by cracking, redness, soreness and swelling at the corners of the mouth. A bad case can include mouth sores.

Oral candidiasis is rare if CD4+ cell counts are above 500. Outbreaks are more common as the count drops to 100. Oral candidiasis may be more difficult to treat when CD4+ cell counts fall below 50.

Cause

Oral candidiasis is caused by the fungus called *Candida*. Everyone has small quantities of the fungus in the mouth, vagina, digestive tract and skin. In healthy persons, “friendly” bacteria and the immune system prevent the fungus from causing disease. However, a damaged or weakened immune system, as can be the case in HIV disease, makes it easier for *Candida* to grow and cause disease.

Certain drugs can alter the natural organisms in the mouth, which can then promote the growth of *Candida*. These include the extended use of antibiotics, steroids and oral contraceptives with a high estrogen content. Other factors that may stimulate *Candida* growth include: diabetes, pregnancy, iron, folate, vitamin B12 or zinc deficiency and using antihistamines. Factors that may weaken the immune system—from cancer chemotherapy to stress and depression—can also cause candidiasis.

Diagnosis

Oral conditions are usually diagnosed by appearance and symptoms. Diagnosis can be confirmed by scraping a sore and examining it under a microscope. Further lab tests are usually performed if the infection does not clear up after drug treatment.

Candida infection of the throat (esophagus) is a serious condition. It is on the list of AIDS-defining illnesses, affecting up to 20% of people with AIDS. It often occurs together with oral candidiasis. Symptoms include chest pain, nausea and painful or difficult swallowing, causing people to not want to eat.

If symptoms do not improve with treatment, or problems with swallowing occur without oral candidiasis, an *endoscopy* is usually performed. This procedure is where a small tube is used to look at the esophagus for signs of infection.

treating oral candidiasis

Topical treatment (active only on the area where applied) is generally the first choice for oral candidiasis and usually works for mild-to-moderate cases. Topical treatments for oral candidiasis include lozenges (also called *trouches*) and mouth rinses.

One or two lozenges are taken for oral symptoms three to five times a day. They should be sucked slowly and not chewed or swallowed whole. Common brands are clotrimazole (Mycelex) and nystatin (Mycostatin).

Mouth rinses are generally less effective than lozenges since they are only in contact with the mouth for a short time. However, they may be the best choice for someone who has a very sore and dry mouth. Rinses are taken in between meals, in a measured amount and are held in the mouth for as long as possible. They should be swilled around in the mouth, then swallowed. They are used at least four times a day and should be continued for a few days after the symptoms have gone (generally two weeks). The most widely used rinse is nystatin (Mycostatin).

Systemic treatment (treatments that work throughout the body) are used for recurring candidiasis or outbreaks that do not clear up with topical treatment. They are also used for esophageal candidiasis.

Three antifungal drugs are approved for treating oral and esophageal candidiasis. They include ketoconazole (Nizoral), fluconazole (Diflucan) and itraconazole (Sporanox). Generally, doctors will start out with less aggressive therapies (like ketoconazole or itraconazole) and save the more potent fluconazole for later use, if necessary. If candidiasis does not improve with these drugs (i.e. becomes *azole* resistant), another drug, called amphotericin B (Fungizone) is often tried.

The dose of fluconazole is 200mg once a day for oral and esophageal candidiasis. Treatment typically lasts two weeks for oral candidiasis and three weeks for esophageal infection (or two weeks after symptoms clear up, whichever is longer).

Itraconazole is usually taken at a dose of 100mg once a day for oral candidiasis for 1–2 weeks and 200mg once a day for esophageal candidiasis for 2–3 weeks. It should

also be taken with food. Itraconazole oral solution gives higher levels of the drug in the blood than the capsule and has been shown to be more effective. There is a greater potential for interactions between itraconazole and many anti-HIV therapies. For more information on drug interactions, read Project Inform's publication, *Drug Interactions*, available at 1-800-822-7422 or www.projectinform.org.

Ketoconazole (Nizoral) is usually taken at a dose of 200mg once a day for oral candidiasis for 1–2 weeks and 400mg once a day for esophageal candidiasis for

2–3 weeks. It should be taken with food. It may not be well absorbed in people with gut problems or who cannot eat very much. Taking it with an acidic drink (such as cola) may help.

Amphotericin B is given by an oral solution (100mg a day four times daily) or through intravenous injection (generally .5mg/kg a day) for 2–3 weeks. Newer liposomal versions of the drug, such as amphotericin B lipid complex (Abelcet), is given by intravenous injection at a rate of 5mg/kg a day for 2–3 weeks.

drugs used to treat oral candidiasis

| DRUG NAME | DOSE | SIDE EFFECTS | NOTES |
|--|---|--|---|
| TOPICAL THERAPIES | | | |
| clotrimazole (Mycelex) trowches | 10mg 4–5 times daily for 1–2 weeks | May cause altered taste and stomach upset | Suck slowly; do not chew or swallow whole |
| nystatin (Mycostatin) pastille | 1–2 pastilles 4–5 times daily | May cause irritation in the mouth; nausea | Suck slowly; do not chew or swallow whole |
| nystatin (Mycostatin) oral suspension | 5ml four times daily for 7–14 days | May cause stomach upset | Swish around mouth before swallowing |
| SYSTEMIC THERAPIES | | | |
| ketoconazole (Nizoral) tablet | 200mg a day, 7–14 days; 400mg day, 14–21 days* | Nausea, vomiting, stomach pain; liver toxicity | Monitor liver function while on this drug; take with food |
| itraconazole (Sporanox) | 100 mg a day, 7–14 days; 200mg a day, 14–21 days* | Nausea, vomiting, stomach pain; liver toxicity | Monitor liver function while on this drug |
| fluconazole (Diflucan) | 200mg a day, 7–14 days; 200mg a day, 14–21 days* | Nausea, vomiting, stomach pain; liver toxicity | Monitor liver function while on this drug |
| amphotericin B (Fungizone) amphotericin B lipid complex (Abelcet) | 100mg a day four times daily (oral suspension); 0.5mg/kg a day, 14–21 days (intravenous)* | For intravenous form: kidney toxicity, electrolyte losses, fever, chills, sweats | For oral suspension, swish around mouth before swallowing; monitor kidney function |
| OTHER THERAPY | | | |
| gentian violet (1% solution in water) | Applied to affected areas twice a day for three days | May cause swelling | Available over the counter; may be useful for recurrent infections when applied every 7 days for 1 month; messy application |

* Esophageal candidiasis

Side effects and drug interactions

Common side effects of oral *azole* drugs (ketoconazole, fluconazole and itraconazole) are nausea, vomiting and belly pain. Others include headaches, dizziness, drowsiness, fever, diarrhea, rash and changes in the sense of taste. The most serious problem is liver toxicity, but this is rare and usually reverses after treatment when the drug is stopped. Nevertheless, liver function should be monitored closely, particularly with ketoconazole.

Intravenous amphotericin B may pose serious side effects, including kidney toxicity. The most common side effects are fever, shaking, chills, altered blood pressure, nausea, vomiting and headache. These reactions are usually severe after the first few doses and lessen with subsequent treatment. Liposomal versions of the drug (like Abelcet) are generally less toxic and as effective than its earlier formula. Intravenous amphotericin B should only be used in cases where there is a direct threat to life or all other treatments have failed.

Oral *azole* drugs have similar drug interactions:

- Anyone taking the antihistamines terfenadine (Seldane) or astemizole (Hismanal) or the anti-reflux drug cisapride (Propulsid) SHOULD NOT take ketoconazole or itraconazole and should probably avoid fluconazole. These drugs can interact to cause serious heart problems.
- *Azole* drugs should not be taken with the sedatives triazolam (Halcion) or midazolam (Versed) as this could lead to dangerous levels of sedation.
- When taken with warfarin (Coumadin), *azoles* can make the blood clot more slowly, so clotting time should be monitored.
- Taking *azoles* with oral hypoglycemic drugs may result in severe low blood sugar (*hypoglycemia*), so blood glucose levels should be checked carefully.

Amphotericin B has several drug interactions:

- Risk of kidney damage increases when amphotericin B is used with pentamidine (Nebupent), cidofovir (Vistide), adefovir (Preveon), cyclosporine (Neoral) or foscarnet (Foscavir).
- Taking amphotericin B with zidovudine (AZT, Retrovir), flucytosine (Ancobon) or ganciclovir (Cytovene) may result in increased bone marrow damage.

Other drug interactions may occur. More details can be found in Project Inform's publication, *Drug Interactions*, and from your pharmacist.

Antifungal drugs and pregnancy

The Guidelines for the Prevention of Opportunistic Infections include recommendations regarding the use of antifungal drugs during pregnancy. In short, the Guidelines recommend that the oral *azole* antifungals (including fluconazole, itraconazole and ketoconazole) not be started during pregnancy because of concerns to the developing child. The Guidelines further state that these drugs be stopped in HIV-positive women who become pregnant and that women receiving these drugs take effective birth control.

For treating or preventing oral candidiasis, topical antifungal therapies such as nystatin may be preferable for pregnant women. Amphotericin B is also approved for the treatment of oral candidiasis. Although no formal studies have been performed, amphotericin B has been used by pregnant women without apparent harm to their unborn children. While amphotericin B may be preferable to *azole* therapy in pregnant women, it is not without potentially severe side effects, including kidney toxicity and anemia.



Kids and candidiasis

Recurrent fungal infections are very common in children living with HIV. In particular, oral candidiasis is extremely prevalent. Esophageal candidiasis may occur with advanced HIV disease and cause discomfort, swallowing difficulties and weight loss. Symptoms and diagnosis of these infections are similar to those seen in adults.

Oral candidiasis may be treated with topical clotrimazole (five 10mg trouches a day). Usually nystatin (four 2–6mL doses every 6 hours) is ineffective in children who have recurrent oral thrush. Some parents have found gentian violet applied 2–3 times daily on affected areas a useful topical treatment, though studies have not been conducted to confirm these reports in children with HIV. (NOTE: Gentian violet should never be swallowed.)

When topical treatment fails, using fluconazole, itraconazole or ketoconazole is recommended. Doses are determined by weight of the child. As in adults, long-term preventive treatment may lead to development of resistance, therefore it is best to treat each occurrence of infection individually.

Prevention

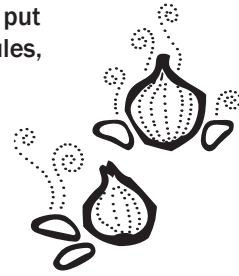
Recurrent oral candidiasis in people living with HIV is common, especially as CD4+ cell counts decline. Thus, the most important method of preventing oral candidiasis may be strengthening the immune system by stopping or slowing the course of HIV infection. Other preventive methods include use of antifungals, smoking cessation, good oral hygiene, avoidance of unnecessary antibiotics, alcohol, sugars and steroids. Topical therapy and gentian violet may also be useful as a preventive measure.

The benefits of preventive antifungal therapy are unclear. This is partly because of the risk it poses in the development of drug resistance, drug interactions and drug side effects. In general, long-term use of antifungals should be reserved for people with frequent or severe recurrences of candidiasis, particularly as the CD4+ cell count declines. People who experience occasional or infrequent recurrences of oral candidiasis (no more than three episodes per year) can be treated for each episode.

If recurrences are more frequent or severe, or if there is a history of esophageal candidiasis, preventive therapy with fluconazole may be recommended. According to the need, daily, three times weekly or weekly fluconazole at a dose of 100–200mg is recommended. Again, the potential risk of developing *azole* resistance must be taken into account when considering long-term use of systemic therapy for preventive purposes.

help from food and diet changes

- Decrease or avoid sugars (corn and maple syrup, glucose, fructose and sucrose). Sugars are food for *Candida* and help it to grow.
- Decrease or avoid alcohol. Alcohol converts to sugar and promotes the growth of *Candida*.
- Some nutritionist and complementary therapy advocates suggest that ingesting large quantities of garlic might be helpful as an antifungal. According to garlic advocates, fresh garlic is considered best (mince and put into empty gelatin capsules, up to six cloves a day). Garlic is believed to have some natural antifungal properties and may help prevent candidiasis.
- Drink milk or eat yogurt that contains acidophilus bacteria. Acidophilus is “friendly” bacteria which helps keep our bodies in balance and able to fight off “unfriendly” bacteria and fungus, like *Candida*.



good oral health helps!



- Maintain good oral health: brush teeth daily (at least twice) and floss.
- Gargle with antiseptic mouthwash (like Listerine or Verdesol).
- Gargle with 3% hydrogen peroxide diluted with equal amounts of water after brushing.

A final thought on oral candidiasis

Candidiasis is among the most common conditions in people with HIV. While candidiasis is a relatively common condition in the general population, it is often the first illness and signal that HIV disease is progressing to a more severe stage, particularly infections that are recurrent or less responsive to treatment. Candidiasis outbreaks can be frequent, can cause great discomfort and can add to the decline in health seen in AIDS.

Preventing and treating oral candidiasis, like other forms of the infection, is important not only because it decreases discomfort caused by the condition, but it also prevents further damage to the immune system.

For information on vaginal or systemic candidiasis, read Project Inform's publications, *Vaginal Candidiasis* and *Systemic Candidiasis*, available at 1-800-822-7422 or www.projectingform.org.

treating and preventing fungal infections naturally

There is a strong connection between what you eat and the health of your immune system. Nevertheless, nutritional approaches to prevent and treat conditions like candidiasis are complicated and controversial. While there isn't a magic recipe that prevents or treats yeast infections in everyone, following some basic guidelines may lower the risk of yeast becoming a problem.

Most nutritionists agree that sugar, yeast, dairy, wheat, caffeine, nicotine and alcohol are the main culprits in *Candida* diseases because they help yeast to grow. To prevent this, nutritionists recommend ingesting as little as possible of these substances that contribute to the excess production of yeast.

Another approach is to eat larger amounts of foods that may suppress the growth of yeast. For example, garlic is believed by some nutritionists to have natural antifungal properties and may help prevent candidiasis. Fresh garlic is considered best, although commercial garlic "pills" offer the advantage of reduced odors. Fresh garlic can be mixed into other foods, eaten raw after removing the dry outer skin, or minced and put into empty gelatin capsules, up to six cloves a day. (NOTE: It is unknown if large amounts of garlic interfere with anti-HIV therapies, but some evidence exist that it may increase the risk of side effects associated with ritonavir [Norvir].)

Another factor that can contribute to uncontrolled yeast growth is the use of antibiotics. "Friendly" bacteria are found naturally in the body and establish a healthy balance while eliminating unfriendly yeasts. These bacteria are similar to *Lactobacilli*, the bacteria that turn milk into yogurt. Many common antibiotics (like tetracycline and penicillin) kill these bacteria—which then promotes yeast growth.

In order to lessen this effect from antibiotics and promote healthy bacteria in general, many nutritionists recommend adding *Lactobacilli acidophilus* bacteria to your diet. It can be found in yogurts and certain milks (look for *Lactobacilli acidophilus* on

the label). You can also take it in pill form, available at many health food stores. (NOTE: There is not a great deal known about the effect vitamins, herbs and supplements on HIV disease. It is further not known if there are interactions between commonly used anti-HIV therapies and complementary medicine. To minimize risk, discuss these issues with your doctor and pharmacist. Also, read Project Inform's publication, *Herbs, Supplements and HIV Disease*.)

Oral candidiasis can change how you taste and enjoy foods. It can also make eating and swallowing difficult. Avoiding acidic, spicy or hot foods as well as cigarettes, alcohol and carbonated drinks may lessen this effect. All of these can irritate the insides of your mouth. Soft, cool and bland foods (like oatmeal, mashed beans, apple sauce, etc.) are recommended.

Many people use liquid food supplements to ease painful mouth infections and to keep or add on weight. Unfortunately, many of these supplements are high in sugars, which can promote yeast growth. If you use liquid supplements, make sure they contain mainly complex carbohydrates, are high in protein and have low-to-moderate sugar levels. It's important to remember that these products are intended to be supplements and should not replace solid food.

There are some reports that gargling with Tea Tree oil diluted with water can help treat oral candidiasis. Generally these gargles (two drops of oil in a tablespoon of water) are used in the morning, night and after meals. They are sometimes swabbed directly on mouth sores (one drop of oil to one drop of water). Grapefruit seed extract and 1% hydrogen peroxide may also be used in a similar way, but must be more heavily diluted and should NEVER be swallowed. However, these approaches (especially grapefruit seed extract) may irritate the mouth and promote infection. Moreover, they only address the local symptoms of yeast growth and not the underlying causes.