Update on the Therapy for Sporotrichosis

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Sporotrichosis is a fungal infection that typically results in cutaneous or lymphocutaneous disease, although other, more severe, life-threatening manifestations do occur. This article reviews updated treatment guidelines, which state that itraconazole has become the preferred therapy for most forms of infection. Amphotericin B remains the mainstay of treatment for severe cases, but lipid formulations are now preferred because of their more favorable toxicity profile. Also, fluconazole has been shown to be less effective than itraconazole and is no longer recommended except as an alternative for cutaneous and lymphocutaneous disease. [Drug Benefit Trends. 2010;22:49-52]

Sporotrichosis is a fungal infection caused by the dimorphic fungus Sporothrix schenckii (Figure). It has a worldwide distribution and is associated with soil, vegetation, and wood.

Disease most commonly results from traumatic inoculation, which leads to infection of the skin and adjacent lymphatics. Pulmonary disease is presumed to occur via inhalation. Dissemination to or inoculation at other sites, including bones, joints, and the CNS, also occurs, although rarely.¹ While person-to-person spread does not occur, zoonotic transmission involving cats as well as digging animals, such as armadillos, has been documented.² Risk factors for serious disease include alcoholism and immunosuppression, such as that seen in patients with AIDS.³-⁶

Although it most often manifests as a cutaneous infection that is not life-threatening, sporotrichosis usually requires treatment to resolve. The Infectious Diseases Society of America first published treatment guidelines for this disease in 2000.⁷ Because few randomized controlled treatment trials have been done, the guidelines committee put the most emphasis on multicenter trials of specific treatments. Several changes were made when these guidelines were updated in 2007 (Table).⁸
Available Agents for Treatment

There are several agents available for treatment of sporotrichosis. They include itraconazole, fluconazole, amphotericin B (AmB), saturated solution of potassium iodide (SSKI), and terbinafine. In addition, local application of heat has been used for cutaneous disease.

Itraconazole. This has become the preferred agent to treat many forms of sporotrichosis because of its effectiveness and tolerability. Several studies and many small series now support its use for the various manifestations of sporotrichosis. Itraconazole is available in 2 oral formulations, solution and capsule. Obtaining drug levels is recommended when treating more severe disease and when treatment failure is suspected. A random level of 1 mg/mL or greater indicates adequate absorption.

Other azoles. Fluconazole and ketoconazole are other azoles that have been clinically evaluated. Fluconazole has a more favorable toxicity profile and does not have the same issues of absorption that itraconazole does, but it is less effective. Kauffman and colleagues reported cure rates with fluconazole of 71% for lymphocutaneous disease and 31% for osteoarticular or visceral disease. This finding is reflected in the updated guidelines, and fluconazole is no longer specifically recommended, except as an alternative treatment for cutaneous and lymphocutaneous disease. Ketoconazole is no longer recommended because of its inferior effectiveness and less favorable toxicity profile.

Several studies have examined the newer azoles, posaconazole and voriconazole. Posaconazole has been shown to have in vitro activity comparable to that of AmB and itraconazole, and therefore is a promising alternative treatment. Susceptibility to voriconazole, however, varies. The correlation between in vitro data and clinical response has not been demonstrated, and there is insufficient clinical evidence to recommend either agent for use at this time.

AmB. This agent remains the treatment of choice for severe or life-threatening sporotrichosis. It is indicated for disseminated, meningeal, and severe pulmonary infections. In addition, it can be used for severe infection during pregnancy when other agents cannot be used. It should be noted that both clinical response and in vitro susceptibility to AmB can vary depending on the strain. Several formulations of AmB are available. Lipid formulations of AmB at a dosage of 3 to 5 mg/kg/d are recommended in the guidelines because of their more favorable toxicity profile. AmB deoxycholate at a dosage of 0.7 to 1 mg/kg/d is now listed as an alternative treatment.

SSKI. The classic treatment for cutaneous and lymphocutaneous sporotrichosis is SSKI. It is clinically effective and has a low cost. Typically, treatment is started at 5 drops 3 times daily, and this is increased to 40 to 50 drops 3 times daily as tolerated. Multiple daily dosing and mild but frequent adverse effects, including headache, GI disturbance, and taste disturbance, probably contribute to decreased adherence. It is
still used commonly in developing nations, where cost prohibits the use of more expensive treatments. Terbinafine. Clinical experience with terbinafine is limited, but a randomized controlled trial showed this treatment to be both effective and well-tolerated in patients with cutaneous and lymphocutaneous sporotrichosis. Recommended dosing for sporotrichosis is 500 mg twice daily. 

**Treatment Recommendations**

**Cutaneous and lymphocutaneous sporotrichosis.** Patients with cutaneous and lymphocutaneous sporotrichosis should be treated with itraconazole 200 mg daily until 2 to 4 weeks after lesions have resolved. Several series have demonstrated response rates greater than 90% with this regimen. Sharkey-Mathis and colleagues reported on a series 27 patients with various forms of sporotrichosis. All 9 patients with lymphocutaneous disease in their series responded to itraconazole. For patients who do not respond to itraconazole 200 mg daily, alternative treatments include itraconazole 200 mg twice daily, terbinafine, or SSKI. Fluconazole should be used only when these other agents cannot be tolerated. 

Terbinafine has been the focus of one of the few randomized controlled trials for sporotrichosis treatment. In a multicenter, randomized, double-blind trial in 2004, Chapman and colleagues compared patients with cutaneous or lymphocutaneous sporotrichosis treated with terbinafine 500 or 1000 mg daily. Treatment response was dose-dependent; there was a significantly higher clinical cure rate with the 1000-mg dose (87% vs 52%; \( P = .004 \)). No relapses were noted after 24 weeks of follow-up in the 1000-mg daily group.

Another study examined the effects of SSKI in the treatment of cutaneous sporotrichosis. Cabezas and colleagues performed a randomized nonblind study in Peruvian children to compare a once-daily dose of SSKI with the traditional 3-times-daily dosing. Clinical response was 89% in both groups with no relapses at 45 days. Adverse effects were common but did not result in treatment discontinuation. This study was too small to recommend a once-daily dosing regimen but highlights the likely niche that the drug currently fills. Other studies also support its use for cutaneous disease, particularly in developing nations.

Local application of heat is also an alternative treatment for pregnant patients with cutaneous sporotrichosis, although this treatment does require further study. AmB is not usually used as a treatment, given the low morbidity of this form of disease and the adverse effects of this medication.

**Osteoarticular sporotrichosis.** This form of the disease requires higher doses of itraconazole for a longer duration. Itraconazole 200 mg twice daily is recommended for at least 12 months. AmB can be used initially; when a favorable response is noted, itraconazole can then be substituted. In the series published by Sharkey-Mathis and colleagues, 11 of 15 patients with osteoarticular sporotrichosis responded to treatment with itraconazole. Four of these patients then relapsed within 6 months, and they had only received treatment for 6 months or less.

Winn and colleagues also published a study demonstrating efficacy of itraconazole for osteoarticular disease. Among 6 patients, 1 patient did not respond to treatment with itraconazole 100 mg daily. The data from this study highlight the need for higher dosing for an extended period. AmB is a treatment alternative for patients with severe disease or treatment failure. Other agents are not recommended.

**Pulmonary sporotrichosis.** In patients with pulmonary sporotrichosis, initial treatment with AmB is recommended. Again, when a favorable response is noted, itraconazole can then be substituted to complete at least 12 months of therapy. Itraconazole can be used initially in patients with less severe disease. Surgery can also be considered in combination with AmB for localized pulmonary disease, although this is now considered an alternative treatment.

Recommendations for treatment of pulmonary sporotrichosis are based on very limited clinical data. These data include a relatively small retrospective review done by Pluss and Opal in 1986. Before the advent of azoles, surgery combined with antifungal treatment, such as AmB, was the preferred option. The current guidelines no longer recommend AmB for the full course of treatment. In the retrospective study by Sharkey-Mathis and colleagues, pulmonary sporotrichosis resolved in 3 patients treated with itraconazole.

**Meningeal sporotrichosis.** AmB is recommended for the initial treatment of meningeal disease on the basis of a number of case reports. The expert panel that wrote the 2007 guidelines
recommended use of a lipid formulation at a dosage of 5 mg/kg/d. The optimal duration of treatment with AmB is unclear, but treatment should be continued for 4 to 6 weeks.

Combination antifungal therapy with itraconazole, fluconazole, or flucytosine does not seem to provide any substantial advantage. Once the patient improves, he or she may be treated with twice-daily itraconazole to complete 12 months of therapy.

Data supporting this recommendation are lacking. Suppressive therapy with itraconazole 200 mg daily is recommended for patients who have AIDS and other patients with immunosuppression.

**Disseminated sporotrichosis.** Patients with disseminated sporotrichosis should also be treated with AmB. As with meningeal disease, treatment can be switched to itraconazole 200 mg twice daily after initial improvement. This should be continued for at least 12 months. Suppressive therapy may be required.

Recommendations for disseminated sporotrichosis are based primarily on case reports, and most involve the use of AmB deoxycholate. However, a case report published in 2003 documents the successful treatment of disseminated sporotrichosis in an immunosuppressed patient who received AmB lipid complex. Lipid formulations of AmB are recommended because of the more favorable toxicity profile.

It may be possible to discontinue suppression therapy if immunosuppression can be reversed. Some experts feel that discontinuation of suppressive therapy in patients with AIDS who have sporotrichosis can be considered if the CD4+ cell counts remain greater than 200/µL for 1 year or more.

**Sporotrichosis in pregnant women and children.** Treatment recommendations for pregnant women and children are based on small series and expert opinion. AmB should be used for severe disease in pregnant women. Treatment of cutaneous disease can be deferred until after delivery. Infection may also be treated with local application of heat. Other agents should not be used: azoles are teratogenic; SSKI affects the fetal thyroid; and terbinafine can be passed in breast milk.

Children with disseminated or severe disease should be treated with AmB deoxycholate followed by itraconazole. Itraconazole and SSKI are treatment options for children with cutaneous or lymphocutaneous disease. Itraconazole 5 to 10 mg/kg/d divided into 2 doses can be used.

Cabezas and colleagues used SSKI at an initial dosage of 1 drop 3 times daily, which was titrated up by 3 drops daily until clinical response or signs of toxicity developed. A maximum of 1 drop/kg or 40 to 50 drops 3 times daily was used.

**References:**


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