

Practice Guidelines for the Management of Patients with Sporotrichosis

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Executive Summary

The recommendations for the treatment of sporotrichosis were derived primarily from multicenter, nonrandomized treatment trials, small retrospective series, and case reports; no randomized, comparative treatment trials have been reported. Most cases of sporotrichosis are non-life-threatening localized infections of the skin and subcutaneous tissues that can be treated with oral antifungal agents. The treatment of choice for fixed cutaneous or lymphocutaneous sporotrichosis is itraconazole for 3–6 months. The preferred treatment for osteoarticular sporotrichosis also is itraconazole, but therapy must be continued for at least 12 months. Pulmonary sporotrichosis responds poorly to treatment. Severe infection requires treatment with amphotericin B; mild to moderate infection can be treated with itraconazole. Meningeal and disseminated forms of sporotrichosis are rare and usually require treatment with amphotericin B. AIDS patients most often have disseminated infection and require life-long suppressive therapy with itraconazole after initial use of amphotericin B.

Overview. Sporotrichosis is caused by the dimorphic fungus *Sporothrix schenckii*, which is found throughout the world in decaying vegetation, sphagnum moss, and soil [1]. The usual mode of infection is by cutaneous inoculation of the organism. Pulmonary and disseminated forms of infection, although uncommon, can occur when *S. schenckii* conidia are inhaled. Infections are most often sporadic and usually associated with trauma during the course of outdoor work. Infection can also be related to zoonotic spread from infected cats or scratches from digging animals, such as armadillos [2, 3]. Outbreaks have been well-described and often are traced back to activities that involved contaminated sphagnum moss, hay, or wood [4–7].

Most cases of sporotrichosis are localized to the skin and subcutaneous tissues. Dissemination to osteoarticular structures and viscera is uncommon and appears to occur more often

in patients who have a history of alcohol abuse or immunosuppression, especially AIDS. Spontaneous resolution of sporotrichosis is rare, and treatment is required for most patients. Although sporotrichosis localized to skin and subcutaneous tissues is readily treated, management of osteoarticular, other localized visceral, and disseminated forms of sporotrichosis is difficult [8].

Objective. The objective of these guidelines is to provide recommendations for the treatment of various forms of sporotrichosis.

Outcomes. The desired outcomes of treatment include eradication of *S. schenckii* from tissues, resolution of symptoms and signs of active infection, and return of function of involved organs. In persons with AIDS, eradication of the organism may not be possible, but clinical resolution should be attained and subsequently maintained with suppressive antifungal therapy.

Evidence. The English-language literature on the treatment of sporotrichosis was reviewed. Although randomized, blinded, controlled treatment trials were sought, none were found to have been performed for the treatment of sporotrichosis. Therefore, most weight was placed on those reports that were derived from multicenter trials of specific treatment modalities for sporotrichosis. Small series from a single institution and individual case reports were accorded less importance.

Values. The highest value was placed on clinical efficacy and the ability of the antifungal regimen to eradicate the organism, but safety, tolerability, and cost of therapy were also valued.

Benefits and costs. The benefits of successfully treating sporotrichosis accrue primarily for the patient. Because this infection is not spread from person-to-person, public health aspects of treatment are of minor importance. Most forms of sporotrichosis are not life-threatening; thus, therapy is aimed at decreasing morbidity, improving quality of life, and allowing the patient to return to occupational and familial pursuits.

Treatment options. Treatment options for sporotrichosis include local measures (hyperthermia), saturated solution of potassium iodide (SSKI), azoles (ketoconazole, itraconazole, and fluconazole), polyenes (amphotericin B), and allylamines (terbinafine).

SSKI and amphotericin B clearly are effective, but these agents have not been subjected to specific treatment trials. The studies that have been reported included triazole agents. Two trials showed a 100% response rate, and another study showed

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a 90% response rate for lymphocutaneous infection treated with itraconazole [9–11] compared with a 71% response rate for treatment with fluconazole [12]. For osteoarticular disease, the response is modest with itraconazole and poor with fluconazole. Sharkey-Mathis et al. [9] reported a 73% rate of response to itraconazole, although 4 of 11 patients later relapsed and required further therapy. Winn et al. [13] described 6 patients with osteoarticular sporotrichosis, all of whom responded to itraconazole. The rate of response to fluconazole was poor; only 3 of 13 patients with osteoarticular infection responded favorably [12]. Too few patients with other forms of sporotrichosis have been studied to establish response rates, but it appears that itraconazole is superior to other azoles [8].

Specific Treatment Recommendations

Lymphocutaneous and Cutaneous Sporotrichosis

Cutaneous sporotrichosis remains localized to the skin (fixed cutaneous or plaque sporotrichosis) and lymphocutaneous sporotrichosis involves skin, subcutaneous tissues, and regional lymphatics. Although the usual host is healthy, the infection rarely resolves spontaneously, and treatment is necessary. Several systemic antifungals and, sometimes, local hyperthermia are beneficial as treatment of this form of sporotrichosis (table 1).

Itraconazole has become the drug of choice for treatment of lymphocutaneous sporotrichosis, with an expected success rate of 90%–100% (these findings are based on open treatment trials of 100–200 mg daily [8, 9–11]) (AII; see article by Sobel [14] for definitions of categories reflecting the strength of each recommendation for or against its use and grades reflecting the quality of evidence on which recommendations are based). Fluconazole is second-line treatment for sporotrichosis [12, 15]. It is less effective than itraconazole and should be used at a dose

of 400 mg only if the patient cannot tolerate itraconazole (BII). Ketoconazole is less effective than fluconazole and should not be used to treat sporotrichosis [16] (CIII).

SSKI has been used since the early 1900s. Although the mechanism of action is unknown [17], this agent was the standard treatment for lymphocutaneous sporotrichosis up until the last few years. It is inconvenient to take, and side effects, including metallic taste, salivary gland enlargement, and rash, are common. However, because SSKI is much less costly than other agents, it is still recommended. Treatment is usually initiated with 5 drops 3 times daily and is increased as tolerated to 40–50 drops 3 times daily (BIII).

Terbinafine has been used as treatment for a few patients and appears to be effective [18]. However, too few data are available to recommend its use until ongoing clinical trials are completed.

Although effective, treatment with amphotericin B is not recommended because of toxicity and inconvenience of administration and because lymphocutaneous sporotrichosis is a localized non-life-threatening infection.

Local hyperthermia may be effective for treating fixed cutaneous lesions [19, 20]. This therapy entails weeks of daily applications to the lesions and requires that the patient faithfully apply heat generated by a pocket warmer, infrared or far-infrared heater, or similar device that will warm the tissue to ~42°C–43°C. This form of therapy should be used only rarely, such as in the case of sporotrichosis in a pregnant women who cannot safely take any other antifungal (BIII).

Pulmonary Sporotrichosis

Most often, pulmonary sporotrichosis, an uncommon form of sporotrichosis, manifests as chronic cavitory fibronodular disease. Pulmonary sporotrichosis is most common in middle-

Table 1. Guidelines for the treatment of various forms of sporotrichosis.

Type of disease	Preferred treatment (rating) ^a	Alternative treatment (rating) ^a
Lymphocutaneous, cutaneous	Itr, 100–200 mg q.d. for 3–6 mo (AII)	SSKI, increasing from 5 to 40–50 drops t.i.d. as tolerated for 3–6 mo (BIII) Flu, 400 mg q.d. for 6 mo (BII) Local hyperthermia for 2–3 mo (BIII)
Pulmonary	AmB, total dose, 1–2 g (BIII); or Itr, 200 mg b.i.d. (BIII); or Surgical resection combined with antifungals when feasible (BIII)	Begin with AmB and switch to Itr after the patient's condition has stabilized (BIII)
Osteoarticular	Itr, 200 mg b.i.d. for 12 mo (AII)	AmB, total dose, 1–2 g (AIII) Flu, 800 mg q.d. for 12 mo (BII)
Meningeal	AmB, total dose, 1–2 g (BIII)	Itr, 200 mg b.i.d. after AmB for suppression (CIII) Flu, ≥800 mg q.d. after AmB for suppression (CIII)
Disseminated	AmB, total dose, 1–2 g (AIII)	Itr, 200 mg b.i.d. if AmB not tolerated and for suppression (BIII)
Special circumstance		
AIDS	AmB, total dose, 1–2 g (AIII), then Itr, 200 mg b.i.d. for life (BIII)	
Pregnancy	Local hyperthermia for lymphocutaneous infection (BIII); AmB for serious infection (AIII)	

NOTE. AmB, amphotericin B; Flu, fluconazole; Itr, itraconazole; SSKI, saturated solution of potassium iodide.

^a See article by Sobel [14] for rating definitions of categories reflecting the strength of each recommendation for or against its use and grades reflecting the quality of evidence on which recommendations are based.

aged men who have underlying risk factors of alcoholism and chronic obstructive pulmonary disease [9, 12, 21]. The outcome is poor, and patients often die of their infection, most likely because of delay in the diagnosis and the severity of the underlying pulmonary disease [21]. Treatment options include amphotericin B and itraconazole; the choice is dependent on the severity of the infection (table 1).

Amphotericin B is indicated for patients with life-threatening or extensive pulmonary sporotrichosis [21] (BIII). The most effective therapy appears to be a combination of amphotericin B and subsequent surgical resection [21] (BIII). However, many patients are unable to tolerate such a procedure because of severe underlying pulmonary disease.

Itraconazole at a dosage of 200 mg twice daily can be used as initial therapy for patients who have non-life-threatening pulmonary sporotrichosis [9] (BIII).

SSKI, ketoconazole, and fluconazole have not proved to be effective and should not be used for treating pulmonary sporotrichosis [12, 21] (EIII).

Osteoarticular Sporotrichosis

Osteoarticular sporotrichosis is an uncommon manifestation of sporotrichosis and occurs most often in patients with underlying alcoholism [22]. Osteoarticular sporotrichosis may involve a single joint or multiple joints or bones; isolated tenosynovitis and bursitis also occur. Osteoarticular structures are infected secondary to either local inoculation or from hematogenous spread. The outcome is poor in regard to joint function, partly because of the frequent delay in diagnosis and also because of poor host response [9, 12, 13]. Systemic symptoms are uncommon, and the infection is usually chronic. Therapeutic options include itraconazole and amphotericin B (table 1).

Itraconazole at a dosage of 200 mg twice daily should be used as initial therapy for most patients, because this form of sporotrichosis is rarely accompanied by systemic illness. The rate of success of this therapy approaches 60%–80% [9, 13] (AII).

Amphotericin B may be indicated for treating patients with extensive involvement or for those patients for whom itraconazole therapy fails. Success rates appear to be similar to those for itraconazole, but the drug is less well tolerated (AIII). Intra-articular injection of amphotericin B has been used rarely [23], but there is little justification to recommend this form of therapy (DIII).

Fluconazole has been used with only very modest success in treating this form of sporotrichosis [12]. It should be reserved for treating those patients who do not tolerate itraconazole or amphotericin B, and the minimum dosage should be 800 mg daily (BII).

Although there is 1 report to the contrary [24], ketoconazole has little role in the treatment of osteoarticular sporotrichosis

[9] (DIII). SSKI is not effective and should not be used for treating osteoarticular sporotrichosis (EIII).

Meningeal Sporotrichosis

Meningeal sporotrichosis is one of the worst complications of infection with *S. schenckii*. Meningitis may be a manifestation of disseminated sporotrichosis or may occur as an isolated event. Many of the recently described patients had AIDS as an underlying risk factor [25, 26]. The diagnosis is difficult to establish [27], treatment options are limited, and the outcome is poor.

On the basis of a small number of anecdotal case reports, amphotericin B is the preferred treatment for meningeal sporotrichosis [8] (BIII) (table 1).

Itraconazole may have a role, after initial therapy with amphotericin B is completed. In patients with AIDS, it is expected that meningitis will require lifelong suppressive therapy, which could be attempted with itraconazole [28] (CIII). It is also possible that fluconazole, which achieves high CSF concentrations, might be useful in circumstances in which itraconazole is not tolerated, but the antifungal activity of fluconazole against *S. schenckii* is less than that of itraconazole (CIII).

Disseminated Sporotrichosis and Sporotrichosis in Patients with AIDS

Disseminated infection with *S. schenckii* is quite unusual. Patients with AIDS appear to have an increased risk for dissemination if they develop sporotrichosis [25, 26, 28]. The diagnosis of lymphocutaneous sporotrichosis in a patient with AIDS should spark a search for dissemination to other sites, including the CNS. The outcome for patients with AIDS is usually dismal, despite antifungal therapy, although a few cases of sustained remission, if not cure, have been reported [28].

On the basis of anecdotal case reports, amphotericin B is the drug of choice for treatment [28] (AIII) (table 1).

Itraconazole may prove beneficial for lifelong maintenance therapy for patients with AIDS after a course of amphotericin B and can be tried as initial therapy for non-life-threatening disease in those patients who cannot tolerate amphotericin B [28] (BIII).

There are no data supporting the use of other drugs for treating disseminated sporotrichosis.

Special Circumstances

Pregnant women with sporotrichosis should not receive azole therapy because of the teratogenic potential of this class of drugs, nor can they be treated with SSKI because of its toxicity for the fetal thyroid [29] (EIII). Terbinafine has not been approved for use in pregnancy. Amphotericin B can be used safely during pregnancy but should be used only for treating dissem-

inated or pulmonary sporotrichosis. One option for cutaneous disease is local hyperthermia; another option is to wait until the pregnancy is completed and then initiate itraconazole therapy. There is no risk of the infection disseminating to the fetus, nor is sporotrichosis worsened with pregnancy; thus, there is little risk involved with delaying treatment of cutaneous or lymphocutaneous sporotrichosis.

Children with sporotrichosis can be safely treated with itraconazole. Dosages of either 100 mg daily or 5 mg/kg daily have been used for the small number of children who have been treated with itraconazole. SSKI has also been used as treatment of children at dosages of 50 mg or 1 drop 3 times daily, up to a maximum of 500 mg or 10 drops 3 times daily.

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