2007 multi
dl 67/2020

adult dosing

pediatric dosing

Clinical Practice Guidelines for the Management of Sporotrichosis: 2007 Update by the Infectious Diseases Society of America

Carol A. Kauffman,[1] Beatriz Bustamante,[4] Stanley W. Chapman,[2] and Peter G. Pappas[3]

[1]Infectious Diseases Section, Veterans Affairs Medical Center, University of Michigan Medical School, Ann Arbor; [2]Division of Infectious Diseases, University of Mississippi Medical Center, Jackson; [3]Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham; and [4]Department of Infectious Diseases, Universidad Peruana Cayetano Heredia, Lima, Peru

Guidelines for the management of patients with sporotrichosis were prepared by an Expert Panel of the Infectious Diseases Society of America and replace the guidelines published in 2000. The guidelines are intended for use by internists, pediatricians, family practitioners, and dermatologists. They include evidence-based recommendations for the management of patients with lymphocutaneous, cutaneous, pulmonary, osteoarticular, meningeal, and disseminated sporotrichosis. Recommendations are also provided for the treatment of sporotrichosis in pregnant women and in children.

EXECUTIVE SUMMARY

Background

Guidelines for the management of patients with sporotrichosis were prepared by an Expert Panel of the Infectious Diseases Society of America and replace the guidelines published in 2000 [1]. Sporotrichosis is caused by the dimorphic fungus *Sporothrix schenckii*, which is found throughout the world in decaying vegetation, sphagnum moss, and soil [2]. 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 are 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 [3, 4]. Outbreaks have been well described and often are traced back to activities that involved contaminated sphagnum moss, hay, or wood [5–8].

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 among patients who have a history of alcohol abuse or immunosuppression, especially patients with 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 [9].

Lymphocutaneous and Cutaneous Sporotrichosis

1. For cutaneous and lymphocutaneous sporotrichosis, itraconazole 200 mg orally daily is recommended to be given for 2–4 weeks after all lesions have resolved, usually for a total of 3–6 months (A-II).
2. Patients who do not respond should be given

Received 20 August 2007; accepted 21 August 2007; electronically published 8 October 2007.

These guidelines were developed and issued on behalf of the Infectious Diseases Society of America.

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The Infectious Diseases Society of America considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

Reprints or correspondence: Dr. Carol A. Kauffman, Infectious Diseases Section, VA Medical Center (111-I), 2215 Fuller Rd., University of Michigan Medical School, Ann Arbor, MI 48105 (ckauff@umich.edu).

Clinical Infectious Diseases 2007; 45:1255–65

1058-4838/2007/4510-0001$15.00
DOI: 10.1086/522765

5 drops SSKI contains ~250 mg I-; tid = 750 mg/day
50 drops 3x/day = 7.5 gm I- per day!

multiple studies, good results

a higher dosage of itraconazole (200 mg twice daily; A-II); terbinafine, administered at a dosage of 500 mg orally twice daily (A-II); or saturated solution of potassium iodide (SSKI), initiated at a dosage of 5 drops (using a standard eye-dropper) 3 times daily and increasing, as tolerated, to 40–50 drops 3 times daily (A-II).

3. Fluconazole (400–800 mg daily) should be used only if the patient cannot tolerate these other agents (B-II).

4. Local hyperthermia can be used for treating patients, such as pregnant and nursing women, who have fixed cutaneous sporotrichosis and who cannot safely receive any of the previous regimens (B-III).

Osteoarticular Sporotrichosis

5. Itraconazole, administered at 200 mg orally twice daily for at least 12 months, is recommended (A-II).

6. Amphotericin B, given as a lipid formulation at a dosage of 3–5 mg/kg daily, or amphotericin B deoxycholate, administered at a dosage of 0.7–1.0 mg/kg daily, can be used for initial therapy (B-III). After the patient has shown a favorable response, therapy can be changed to itraconazole administered at a dosage of 200 mg orally twice daily to complete a total of at least 12 months of therapy (B-III).

7. Serum levels of itraconazole should be determined after the patient has been receiving this agent for at least 2 weeks to ensure adequate drug exposure (A-III).

Pulmonary Sporotrichosis

8. For severe or life-threatening pulmonary sporotrichosis, amphotericin B, given as a lipid formulation at 3–5 mg/kg daily, is recommended (B-III). Amphotericin B deoxycholate, administered at a dosage of 0.7–1.0 mg/kg daily, could also be used (B-III).

9. After the patient has shown a favorable response to amphotericin B, therapy can be changed to itraconazole (200 mg orally twice daily) to complete a total of at least 12 months of therapy (B-III).

10. For less severe disease, itraconazole administered at 200 mg orally twice daily for at least 12 months is recommended (A-III).

11. Serum levels of itraconazole should be determined after the patient has been receiving this agent for at least 2 weeks to ensure adequate drug exposure (A-III).

12. Surgery combined with amphotericin B therapy is recommended for localized pulmonary disease (B-III).

Meningeal Sporotrichosis

13. Amphotericin B, given as a lipid formulation at a dosage of 5 mg/kg daily for 4–6 weeks, is recommended for the initial treatment of meningeal sporotrichosis (B-III). Amphotericin B deoxycholate, administered at a dosage of 0.7–1.0 mg/kg daily, could also be used but was not preferred by the panel (B-III).

14. Itraconazole (200 mg twice daily) is recommended as step-down therapy after the patient responds to initial treatment with amphotericin B and should be given to complete a total of at least 12 months of therapy (B-III).

15. Serum levels of itraconazole should be determined after the patient has been receiving this agent for at least 2 weeks to ensure adequate drug exposure (A-III).

16. For patients with AIDS and other immunosuppressed patients, suppressive therapy with itraconazole at a dosage of 200 mg daily is recommended to prevent relapse (B-III).

Disseminated (Systemic) Sporotrichosis

17. Amphotericin B, given as a lipid formulation at a dosage of 3–5 mg/kg daily, is recommended for disseminated sporotrichosis (B-III). Amphotericin B deoxycholate (0.7–1.0 mg/kg daily) could also be used but was not preferred by the panel (B-III).

18. Itraconazole (200 mg twice daily) is recommended as step-down therapy after the patient responds to initial treatment with amphotericin B and should be given to complete a total of at least 12 months of therapy (B-III).

19. Serum levels of itraconazole should be determined after the patient has been receiving this agent for at least 2 weeks to ensure adequate drug exposure (A-III).

20. Lifelong suppressive therapy with itraconazole (200 mg daily) may be required for patients with AIDS and other immunosuppressed patients if immunosuppression cannot be reversed (B-III).

Sporotrichosis in Pregnant Women and in Children

21. Amphotericin B, given as a lipid formulation at a dosage of 3–5 mg/kg daily, or amphotericin B deoxycholate, given at a dosage of 0.7–1 mg/kg daily, is recommended for severe sporotrichosis that must be treated during pregnancy (B-III); azoles should be avoided.

22. Local hyperthermia can be used for the treatment of cutaneous sporotrichosis in pregnant women (B-III).

23. Itraconazole, administered at a dosage of 6–10 mg/kg to a maximum of 400 mg orally daily, is recommended for children with cutaneous or lymphocutaneous sporotrichosis (B-III).

24. An alternative for children is SSKI initiated at a dosage of 1 drop (using a standard eye-dropper) 3 times daily, increasing, as tolerated, up to a maximum of 1 drop per kg of body weight or 40–50 drops 3 times daily, whichever is lowest (B-III).

1 drop ~= 50 mg

25. For children with disseminated sporotrichosis, amphotericin B (0.7 mg/kg daily) should be the initial therapy, followed by itraconazole (6–10 mg/kg, up to a maximum of 400 mg daily) as step-down therapy (B-III).

INTRODUCTION

Sporotrichosis is caused by the dimorphic fungus *S. schenckii,* which is found in decaying vegetation, sphagnum moss, soil, and other environmental niches throughout the world. The usual mode of infection is by cutaneous inoculation of the organism. Pulmonary and disseminated forms of infection, although uncommon, occur when *S. schenckii* conidia are inhaled. Infections are most often sporadic and usually associated with trauma sustained during the course of outdoor activities. Infection can also be related to zoonotic spread from infected cats, which tend to have a high burden of organisms in ulcerated lesions [3, 10]. Scratches sustained from digging animals, such as armadillos, can also be infected with *S. schenckii* [4]. Outbreaks have been traced to activities involving contaminated sphagnum moss, hay, and wood [5–7].

Most cases of sporotrichosis remain localized to the skin only or to the skin and subcutaneous tissues, with spread occurring proximally along the lymphatic circulation. Strains of *S. schenckii* that cause fixed cutaneous lesions tend to be heat intolerant, compared with strains that spread through the lymphatics and cause lymphocutaneous sporotrichosis [11]. Some patients have lesions at multiple sites; these lesions are related to trauma to these different sites during exposure to *S. schenckii.* Lymphocutaneous and cutaneous forms of sporotrichosis are not life-threatening, but they generally will not resolve without antifungal treatment [12].

Osteoarticular sporotrichosis is an uncommon manifestation of sporotrichosis, occurring most often among patients with underlying alcoholism [13–15]. This disorder can involve single or multiple joints, and it is also a cause of granulomatous tenosynovitis and bursitis [16, 17]. Osteoarticular structures become infected secondary to hematogenous spread or through local inoculation. In general, the outcome is poor with regard to joint function, partly because of the delay in diagnosis and partly because of poor host response. The disease is usually chronic, and systemic symptoms are uncommon [18].

Pulmonary sporotrichosis, acquired by inhalation of conidia of *S. schenckii,* is a rare manifestation of sporotrichosis, usually manifesting as chronic cavitary fibronodular disease in middle-aged men who have underlying risk factors of alcoholism and chronic obstructive pulmonary disease [19]. The outcome of this condition is usually poor, often because of delay in diagnosis and severe underlying pulmonary disease [18–20]. Laryngeal sporotrichosis has been described rarely, and individual case reports describe the response to treatment with amphotericin B or itraconazole [21–23].

Disseminated infection with *S. schenckii* is unusual and is most likely to occur in immunosuppressed patients, including patients with AIDS who have low $CD4^+$ cell counts, transplant recipients, and those who are receiving chemotherapy, corticosteroids, or TNF antagonists [24–28]. In immunosuppressed patients, sporotrichosis is an opportunistic mycosis and may present with a variety of clinical forms, including disseminated cutaneous disease, fungemia, and disseminated visceral disease. Patients who have AIDS have an especially high risk for dissemination if they develop sporotrichosis [26, 28]. The diagnosis of cutaneous or lymphocutaneous sporotrichosis in a patient with AIDS should spark a search for dissemination to other sites, including the CNS. The treatment outcome for patients with AIDS and disseminated sporotrichosis remains poor despite antifungal therapy.

Meningitis occurs rarely as an isolated chronic infection in nonimmunosuppressed patients, but it occurs more often during the course of disseminated infection in immunosuppressed patients [29]. Most of the recently described patients with meningeal disease have had AIDS as an underlying risk factor. The diagnosis of meningeal sporotrichosis is difficult to establish, treatment options are limited, and the outcome is poor.

The Panel addressed the following clinical questions.

1. What is the treatment for lymphocutaneous and cutaneous sporotrichosis?
2. What is the treatment for osteoarticular sporotrichosis??
3. What is the treatment for pulmonary sporotrichosis?
4. What is the treatment for meningeal sporotrichosis?
5. What is the treatment for disseminated (systemic) sporotrichosis?
6. What is the treatment for sporotrichosis in pregnant women and in children?

PRACTICE GUIDELINES

Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances [30]. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation [30].

UPDATE METHODOLOGY

Panel composition. A panel of experts composed of infectious diseases specialists from North and South America who were experts in sporotrichosis was convened. The panelists had both clinical and laboratory experience with sporotrichosis. Panel participants are listed in Appendix A.

Literature review and analysis. For the 2007 update, the Expert Panel reviewed and analyzed the literature on the treatment of sporotrichosis published since 2000, as well as literature noted in the 2000 Guidelines. Computerized literature searches of the PubMed database from January 2000 through July 2006 using both the English and Spanish languages were performed.

Searches were limited to human-only studies. The search yielded 93 articles: 72 case reports, 17 reviews, 1 clinical practice guideline, and 2 multicenter, randomized, controlled treatment trials.

Process overview. In evaluating the evidence regarding the management of sporotrichosis, the Expert Panel followed a process used in the development of other Infectious Diseases Society of America guidelines. The process included a systematic weighting of the quality of the evidence and the grade of recommendation (table 1) [31]. Recommendations for the treatment of sporotrichosis were derived primarily from case reports and nonrandomized treatment trials (table 2).

Consensus development based on evidence. The Expert Panel met via teleconference on 3 occasions to complete the work of the guideline. The purpose of the teleconferences was to discuss the questions to be addressed, make writing assignments, and discuss recommendations. All members of the panel participated in the preparation and review of the draft guideline. Feedback from external peer reviews was obtained. The guideline was reviewed and approved by the Standards and Practice Guidelines Committee and the Board of Directors prior to dissemination.

Guidelines and conflicts of interest. All members of the Expert Panel complied with the Infectious Diseases Society of America policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel were provided with the Infectious Diseases Society of America conflict of interest disclosure statement and were asked to identify ties to companies developing products that might be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. No limiting conflicts were identified.

Revision dates. At annual intervals, the Expert Panel Chair, the Standards and Practice Guideline Committee liaison advisor, and the Chair of the Standards and Practice Guideline Committee will determine the need for revisions to the guideline on the basis of an examination of current literature. If necessary, the entire Expert Panel will be reconvened to discuss potential changes. When appropriate, the Expert Panel will recommend revision of the guideline to the Standards and Practice Guideline Committee and the Infectious Diseases Society of America Board for review and approval.

RESULTS

Diagnostic issues. Even though the lymphocutaneous lesions have a classic presentation in many cases, other diseases, including atypical mycobacterial infections, nocardiosis, and leishmaniasis, can produce lesions similar to those seen with sporotrichosis [32]. Because of its rarity and the similarity of clinical manifestations with those of other fungi and mycobacteria, the diagnosis of visceral infection with *S. schenckii* is often delayed.

Culture of *S. schenckii* remains the gold standard for establishing the diagnosis of sporotrichosis. Material from cutaneous lesions should be aspirated or scraped with a scalpel blade, or a biopsy should be performed. Sputum, synovial fluid, or CSF specimens should be obtained, when appropriate, for smear and culture. The material that is cultured is incubated at room temperature to allow growth of the mold phase of *S. schenckii;* conversion to the yeast phase is required to definitively identify *S. schenckii,* although a tentative identification can be made if the characteristic conidia formation is noted in the mold phase [2]. In 89% of cases, isolation of *S. schenckii* occurs within 8 days, but in some cases, it may take 4 weeks for growth to occur [12].

Table 1. Strength of recommendation and quality of evidence.

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use.
B	Moderate evidence to support a recommendation for use.
C	Poor evidence to support a recommendation.
Quality of evidence	
I	Evidence from ⩾1 properly randomized, controlled trial.
II	Evidence from ⩾1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

NOTE. Adapted from Canadian Task Force on the Periodic Health Examination [31].

Table 2. Summary of recommendations.

Manifestation	Preferred treatment	Alternative treatment	Comments
Lymphocutaneous/cutaneous	Itr 200 mg/day (A-II)	Itr 200 mg b.i.d. (A-II); or terbinafine 500 mg b.i.d. (A-II); or SSKI with increasing doses (A-II); or fluconazole 400–800 mg/day (B-II); or local hyperthermia (B-III)	Treat for 2–4 weeks after lesions resolved.
Osteoarticular	Itr 200 mg b.i.d. (A-II)	Lipid AmB 3–5 mg/kg/day (B-III); or deoxycholate AmB 0.7–1 mg/kg/day (B-III)	Switch to Itr after favorable response if AmB used; treat for a total of at least 12 months.
Pulmonary	Lipid AmB 3–5 mg/kg/day, then Itr 200 mg b.i.d. (B-III); or Itr 200 mg b.i.d. (A-III)	Deoxycholate AmB 0.7–1 mg/kg/d, then Itr 200 mg b.i.d. (B-III); surgical removal (B-III)	Treat severe disease with an AmB formulation followed by Itr; treat less severe disease with Itr; treat for a total of at least 12 months.
Meningitis	Lipid AmB 5 mg/kg/day, then Itr 200 mg b.i.d. (B-III)	Deoxycholate AmB 0.7–1 mg/kg/day, then Itr 200 mg b.i.d. (B-III)	Length of therapy with AmB not established, but therapy for at least 4–6 weeks is recommended; treat for a total of at least 12 months; may require long-term suppression with Itr.
Disseminated	Lipid AmB 3–5 mg/kg/day, then Itr 200 mg b.i.d. (B-III)	Deoxycholate AmB 0.7–1 mg/kg/day, then Itr 200 mg b.i.d. (B-III)	Therapy with AmB should be continued until the patient shows objective evidence of improvement; treat for a total of at least 12 months; may require long-term suppression with Itr.
Pregnant women	Lipid AmB 3–5 mg/kg/day or deoxycholate AmB 0.7–1.0 mg/kg/day for severe sporotrichosis (B-III); local hyperthermia for cutaneous disease (B-III)	…	It is preferable to wait until after delivery to treat non–life-threatening forms of sporotrichosis.
Children	Itr 6–10 mg/kg/day (400 mg/day maximum) for mild disease (B-III); deoxycholate AmB 0.7 mg/kg/day for severe disease (B-III)	SSKI with increasing doses for mild disease (B-III)	Treat severe disease with an AmB formulation followed by Itr.

NOTE. AmB, amphotericin B; b.i.d., twice per day; Itr, itraconazole; SSKI, saturated solution potassium iodide.

Histopathologic review of tissue samples reveals a mixed granulomatous and pyogenic inflammatory process. The organisms, oval to cigar-shaped yeasts that are 3–5 mm in diameter, are often difficult to visualize because of the small number of organisms that are present. Serological testing has not proved to be very useful for the diagnosis of sporotrichosis and is not readily available.

Treatment options. Treatment options for sporotrichosis include local measures (hyperthermia), SSKI, azoles (ketoconazole, itraconazole, and fluconazole), amphotericin B, and the allylamine, terbinafine [1, 9]. For decades, it has been known that hyperthermia decreases the size of the lesions of cutaneous sporotrichosis. Use of specific devices that heat tissues to 42°C–43°C using infrared and far infrared wave lengths has been recommended [33, 34].

SSKI has been used for more than a century, but only recently has there been a randomized treatment trial investigating different dosing regimens [35]. The mechanism of action is not known [36]. This agent is effective only for cutaneous and lymphocutaneous sporotrichosis.

Azoles have become the preferred agents for treatment of several forms of sporotrichosis. Ketoconazole was the initial azole used for sporotrichosis; however, it was not very effective, was associated with many adverse effects, and should no longer be used [37, 38]. Itraconazole supplanted ketoconazole for the treatment of the endemic mycoses and has become the agent of choice for sporotrichosis.

For cutaneous and lymphocutaneous infections, response rates of 90%–100% were noted with itraconazole therapy [18, 39, 40], compared with a 63%–71% response rate associated with fluconazole therapy [20, 41]. Osteoarticular infections respond less well. Sharkey-Mathis et al. [18] reported that 11 (73%) of 15 patients responded to itraconazole therapy, and Winn et al. [42] described 6 patients with osteoarticular sporotrichosis, all of whom responded to treatment with itraconazole. Fluconazole therapy was ineffective, with only 3 (23%) of 13 patients with osteoarticular infection responding [20]. A small number of patients with pulmonary and disseminated sporotrichosis have been treated with itraconazole therapy, with mixed results [18].

Itraconazole comes in 2 oral dosage forms: a 100-mg capsule and a solution of 100 mg per 10 mL. It is recommended that doses >200 mg/day be given in 2 divided doses. Therapy should be initiated with a loading dose of 200 mg 3 times daily for 3 days. The capsule formulation of itraconazole is best absorbed when taken with food, and agents that decrease stomach acidity should be avoided. In contrast, itraconazole solution is best absorbed when taken on an empty stomach. If the patient tolerates the oral solution, it is the preferred formulation because of its improved absorption characteristics. However, some patients experience gastrointestinal adverse effects with the solution and will have to use the capsule formulation. For patients with visceral involvement with sporotrichosis and for those who have lymphocutaneous disease but are experiencing failure of therapy, serum levels of itraconazole should be determined to be certain that the patient has adequate absorption of drug. Because the half-life of the drug is long, there is little variation over a 24-h period; blood samples can be obtained at any time point, and the level should be ≥ 1 μg/mL.

There are no published data regarding the new azoles, voriconazole and posaconazole. Voriconazole is not active in vitro against *S. schenckii* [43], whereas posaconazole does have activity in vitro [44].

Amphotericin B remains the treatment of choice for patients with serious or life-threatening sporotrichosis. The experience in the literature is almost entirely with amphotericin B deoxycholate, but many clinicians, including the panel members, now prefer to use lipid formulations of amphotericin B, because such formulations have fewer adverse effects. There is no firm basis for picking one lipid formulation over another for the treatment of sporotrichosis, with the possible exception that the liposomal formulation might be preferred for treating meningitis. There are animal data (but no human data) noting that higher concentrations are achieved in brain tissue with liposomal amphotericin B, compared with amphotericin B lipid complex and amphotericin B deoxycholate [45]. However, the relevance of this finding to the treatment of meningeal sporotrichosis is unknown.

There is little clinical experience using terbinafine for the treatment of sporotrichosis. However, 1 of only 2 randomized, controlled treatment trials for sporotrichosis involved this agent. The study assessed 2 different dosages of terbinafine (500 mg daily vs. 1000 mg daily) for the treatment of cutaneous and lymphocutaneous sporotrichosis and showed treatment superiority of the higher dosage [46].

GUIDELINE RECOMMENDATIONS FOR THE TREATMENT OF SPOROTRICHOSIS

What Is the Treatment for Lymphocutaneous and Cutaneous Sporotrichosis?

Recommendations

1. For cutaneous and lymphocutaneous sporotrichosis, itraconazole (200 mg orally daily) is recommended to be given for 2–4 weeks after all lesions have resolved, usually a total of 3–6 months (A-II).

2. Patients who do not respond to treatment should be given a higher dosage of itraconazole (200 mg twice daily; A-II), terbinafine at a dosage of 500 mg orally twice daily (A-II), or SSKI initiated at a dosage of 5 drops (using a standard eyedropper) 3 times daily, increasing as tolerated to 40–50 drops 3 times daily (A-II).

3. Fluconazole at a dosage of 400–800 mg daily should be used only if the patient cannot tolerate other agents (B-II).

4. Local hyperthermia can be used for treating patients, such as pregnant and nursing women, who have fixed cutaneous sporotrichosis and who cannot safely take any of the previous regimens (B-III).

Evidence summary. Open treatment trials of itraconazole administered at a dosage of 100–200 mg orally daily for 2–9 months have shown success rates of 90%–100% without significant adverse events [18, 39, 40]. Clinical improvement is often manifested within 4 weeks after starting therapy, and only a small number of patients need higher dosages of itraconazole or therapy with other antifungals. Although some of these studies reported on the use of a 100-mg daily dose, the panel felt that the success rate was too low with this dosage, and 200 mg administered daily should be the minimum dosage used.

Terbinafine, administered to 5 patients at a dosage of 500 mg orally daily, resulted in a 100% cure rate [47], but results from a randomized, blinded treatment trial found only a 52% cure rate and a 21% relapse rate at 6 months after treatment among 28 patients receiving this dosage [46]. The same study showed an 87% cure rate and no relapses among 35 patients who received 1000 mg daily. Although adverse events were frequent, the majority were mild or moderate in severity and required stopping the drug for only 2 of 35 patients, both of whom were treated with the higher dosage.

SSKI has been used since the early 1900s; this agent was the standard treatment for cutaneous and lymphocutaneous sporotrichosis until the 1990s. One randomized treatment trial, several open, noncontrolled clinical trials, and several large case series have reported cure rates ranging from 80% to 100% [35, 48–50]. SSKI is much less costly than other agents, but it is inconvenient to take, and adverse effects, including metallic taste, nausea, abdominal pain, salivary gland enlargement, and rash, are common.

An open-label, multicenter trial of fluconazole administered at a dosage of 200–400 mg daily in 19 patients showed a 63% cure rate [41]. Only 3 of 12 patients who were cured received 200 mg daily, and the other patients were given different initial dosages but finished the course of therapy at a dosage of 400 mg daily. A randomized, open-label trial of fluconazole (200 mg vs. 400 mg daily) showed a poor response at the lower dosage, and the dosage was increased to 400 mg versus 800 mg daily. Among 14 enrolled patients, 9 were definitely or probably cured (64%), and another patient improved [20].

Efficacy of local hyperthermia has not been satisfactorily evaluated. A descriptive study reported a cure rate of 71% among 14 patients [33, 34]. This therapy entails weeks of daily applications of heat 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.

Although effective, treatment with amphotericin B is not recommended because of toxicity and the inconvenience of administration, and because cutaneous and lymphocutaneous sporotrichosis is a localized non–life-threatening infection. There are no studies reported with use of the newer azoles, voriconazole and posaconazole.

What Is the Treatment for Osteoarticular Sporotrichosis?

Recommendations

1. Itraconazole administered at a dosage of 200 mg orally twice daily for at least 12 months is recommended (A-II).

2. Amphotericin B, given as a lipid formulation at 3–5 mg/kg daily, or amphotericin B deoxycholate, administered at a dosage of 0.7–1.0 mg/kg daily, can be used for initial therapy (B-III). After the patient has shown a favorable response, therapy can be changed to itraconazole administered at a dosage of 200 mg orally twice daily to complete a total of at least 12 months of therapy (B-III).

3. Serum levels of itraconazole should be determined after the patient has been receiving this agent for at least 2 weeks to ensure adequate drug exposure (A-III).

Evidence summary. The bulk of data supports the use of itraconazole for the initial treatment of osteoarticular sporotrichosis [18, 42]. Sharkey-Mathis et al. [18] described 15 patients with osteoarticular disease, of whom 11 had an initial response to therapy. Among the 11 responders, 4 experienced relapse when no longer receiving therapy, but all 4 had received ⩽6 months of therapy.

Amphotericin B is indicated for treating patients with extensive involvement or disease unresponsive to itraconazole. Success with amphotericin B therapy is similar to that with itraconazole therapy, although the drug is less well tolerated [13]. There have been reports of using intra-articular amphotericin B injections, but this form of therapy is rarely indicated [51].

The clinical experience with fluconazole is limited. In 1 open-label treatment trial, 13 patients were treated, of whom 3 had a favorable response and 10 had persistent or progressive disease [20]. Thus, fluconazole cannot be recommended; SSKI and terbinafine are not effective for the treatment of osteoarticular sporotrichosis and are not recommended.

Surgical debridement for osteoarticular sporotrichosis is not commonly needed, but there are patients for whom drainage of a septic joint or removal of a sequestrum will prove to be beneficial. Surgical debridement as sole therapy for osteoarticular sporotrichosis is not effective. [13]. More often, the clinical scenario is that a surgical procedure, such as a synovectomy or carpal tunnel release, has been performed for diagnostic

purposes and is instrumental in establishing the diagnosis of unsuspected sporotrichosis.

What Is the Treatment for Pulmonary Sporotrichosis?

Recommendations

1. For severe or life-threatening pulmonary sporotrichosis, amphotericin B, given as a lipid formulation at 3–5 mg/kg daily, is recommended (B-III). Amphotericin B deoxycholate, administered at a dosage of 0.7–1.0 mg/kg daily, could also be used (B-III).
2. After the patient has shown a favorable response to amphotericin B treatment, therapy can be changed to itraconazole administered at a dosage of 200 mg orally twice daily to complete a total of at least 12 months of therapy (B-III).
3. For less severe disease, itraconazole administered at a dosage of 200 mg orally twice daily for at least 12 months is recommended (A-III).
4. Serum levels of itraconazole should be determined after the patient has been receiving this agent for at least 2 weeks to ensure adequate drug exposure (A-III).
5. Surgery combined with amphotericin B therapy is recommended for localized pulmonary disease (B-III).

Evidence summary. Data on treatment of pulmonary sporotrichosis are derived from 1 retrospective review, an open-label treatment trial, and case reports. Pluss and Opal [19] described 55 cases that were treated before azoles became available; in this review, antifungal therapy alone often resulted in treatment failure. The authors concluded that the combination of amphotericin B therapy and surgical resection of the involved lung offered the best hope for long-term cure. Although most reported experience is with amphotericin B deoxycholate [52], the Expert Panel preferred to use lipid formulations of amphotericin B to decrease toxicity. Currently, amphotericin B, no matter which formulation is used, is rarely given for the entire course of therapy, as previously recommended in the 2000 guidelines. This agent is used initially until the patient has shown a favorable response, and then itraconazole can be given for the remainder of the treatment course. In a prospective study of itraconazole for the treatment of all forms of sporotrichosis, successful outcomes were noted in 2 of 3 individuals with pulmonary involvement [18]. SSKI, fluconazole, and terbinafine are ineffective in the treatment of this manifestation of sporotrichosis. There are even fewer reports of treating focal disease involving the respiratory tract, such as laryngeal infection. Amphotericin B and/or itraconazole therapy have been used with variable success [21–23]; the Expert Panel could make no recommendations.

What Is the Treatment for Meningeal Sporotrichosis?

Recommendations

1. Amphotericin B, given as a lipid formulation at a dosage of 5 mg/kg daily for 4–6 weeks, is recommended for initial treatment of meningeal sporotrichosis (B-III). Amphotericin B deoxycholate, administered at a dosage of 0.7–1.0 mg/kg daily, could also be used but was not preferred by the panel (B-III).
2. Itraconazole administered at a dosage of 200 mg twice daily is recommended as step-down therapy after the patient responds to initial treatment with amphotericin B and should be given to complete a total of at least 12 months of therapy (B-III).
3. Serum levels of itraconazole should be determined after the patient has been receiving this agent for at least 2 weeks to ensure adequate drug exposure (A-III).
4. For patients with AIDS and other immunosuppressed patients, suppressive therapy with itraconazole administered at a dosage of 200 mg daily is recommended to prevent relapse (B-III).

Evidence summary. On the basis of a small number of case reports, amphotericin B is the preferred treatment for meningeal sporotrichosis. There are no studies that specifically address the efficacy of lipid formulations for meningitis due to *S. schenckii.* The total amount of amphotericin B that should be administered depends on the patient's response to therapy. At a minimum, therapy should continue for 4–6 weeks at the dosages noted above for this life-threatening manifestation of sporotrichosis. A limited number of patients have been treated with amphotericin B in combination with itraconazole, fluconazole, or flucytosine. No improvement in survival was associated with combination treatment, and this is not recommended [28].

Itraconazole may have a role in the treatment of patients who survive after completion of initial therapy with amphotericin B, although there are no data that specifically address this issue. Similar to other opportunistic fungal infections in patients with AIDS, the risk of relapse of meningeal sporotrichosis is high, and lifelong suppressive therapy seems prudent. Itraconazole, because of its potent antifungal activity against *S. schenckii,* may prove to be useful in this situation.

Fluconazole, terbinafine, and SSKI should not be used for the treatment of meningeal sporotrichosis. Voriconazole has less antifungal activity against *S. schenckii* than does itraconazole and has no role in the treatment of sporotrichosis. Posaconazole has documented antifungal activity against *S. schenckii* isolates [44], but no treatment results have been published.

What Is the Treatment for Disseminated (Systemic) Sporotrichosis?

Recommendations

1. Amphotericin B, given as a lipid formulation at a dosage of 3–5 mg/kg daily, is recommended for treatment of disseminated sporotrichosis (B-III). Amphotericin B deoxycholate, administered at a dosage of 0.7–1.0 mg/kg daily, could also be used but was not preferred by the panel (B-III).
2. Itraconazole administered at a dosage of 200 mg twice daily is recommended as step-down therapy after the patient responds to initial treatment with amphotericin B and should be given to complete a total of at least 12 months of therapy (B-III).
3. Serum levels of itraconazole should be determined after the patient has been receiving this agent for at least 2 weeks to ensure adequate drug exposure (A-III).
4. Life-long suppressive therapy with itraconazole administered at a dosage of 200 mg daily may be required in patients with AIDS and other immunosuppressed patients if immunosuppression cannot be reversed (B-III).

Evidence summary. There are no clinical trials to guide therapy for disseminated sporotrichosis. On the basis of anecdotal case reports, amphotericin B remains the drug of choice for patients with disseminated disease [25, 26, 28, 53, 54]. The use of lipid formulations of amphotericin B has been reported infrequently [25], but these better-tolerated formulations should be as effective as amphotericin B deoxycholate, for which there is more anecdotal experience. Step-down therapy with itraconazole should be based on the physician's judgment of the patient's response to amphotericin B. Life-long maintenance therapy with itraconazole for patients with AIDS after completion of an initial course of amphotericin B has been recommended on the basis of only a few cases [55, 56]. There are no studies that have addressed discontinuation of therapy, but on the basis of evidence from other fungal infections, the Expert Panel thought that it was reasonable to discontinue therapy for those patients with AIDS who have been treated with itraconazole for at least 1 year and whose $CD4^+$ cell counts have remained >200 cells/μL for $\geq$1 year. There are no data supporting the use of any other drugs for treating disseminated sporotrichosis.

What Is the Treatment for Sporotrichosis in Pregnant Women and in Children?

Recommendations

1. Amphotericin B, given as a lipid formulation at a dosage of 3–5 mg/kg daily, or amphotericin B deoxycholate, given at a dosage of 0.7–1 mg/kg daily, is recommended for severe sporotrichosis that must be treated during pregnancy (B-III); azoles should be avoided.
2. Local hyperthermia can be used for the treatment of cutaneous sporotrichosis in pregnant women (B-III).
3. Itraconazole, administered at a dosage of 6–10 mg/kg up to a maximum of 400 mg orally daily, is recommended for children with cutaneous or lymphocutaneous sporotrichosis (B-III).
4. An alternative for children is SSKI therapy, which should be initiated at a dosage of 1 drop (using a standard eyedropper) 3 times daily and increased as tolerated up to a maximum of 1 drop/kg or 40–50 drops 3 times daily, whichever is lowest (B-III).
5. For children with disseminated sporotrichosis, amphotericin B, administered at a dosage of 0.7 mg/kg daily, should be the initial therapy, followed by itraconazole, administered at a dosage of 6–10 mg/kg up to a maximum of 400 mg daily, as step-down therapy (B-III).

Evidence summary. Pregnant women with sporotrichosis should not receive azole therapy because of the teratogenetic potential of this class of drugs [57], nor should they be treated with SSKI because of its toxicity for the fetal thyroid. Terbinafine is classified by the US Food and Drug Administration (FDA) as a pregnancy category B drug that it is not expected to harm an unborn baby. Terbinafine passes into breast milk, and this could have an effect on a nursing baby. Pregnant patients and nursing mothers should discuss with their physicians the risks and benefits of taking terbinafine for the treatment of cutaneous or lymphocutaneous sporotrichosis. Local hyperthermia is another option. It may be prudent 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. Life-threatening infection should be treated with amphotericin B, which can be safely administered during pregnancy.

Children with cutaneous and lymphocutaneous sporotrichosis should be treated with itraconazole. Dosages of either 100 mg daily or 6–10 mg/kg daily (to a maximum of 400 mg daily) have been used for the small number of children who have been treated with itraconazole [58]. SSKI has also been used as treatment in children who have cutaneous sporotrichosis at dosages of 1 drop administered 3 times daily, up to a maximum of 1 drop/kg or 40–50 drops administered 3 times daily [35]. However, adverse effects are quite common among children treated with SSKI. Although a single child with pulmonary sporotrichosis and HIV infection was reported to have been successfully treated with fluconazole [59], amphotericin B is recommended as the initial therapy for visceral or disseminated sporotrichosis in children. Itraconazole, as noted for adult patients, may prove to be effective for step-down therapy

following amphotericin B therapy and as chronic suppressive therapy in children with HIV infection.

PERFORMANCE MEASURES

1. Lymphocutaneous sporotrichosis should be treated with itraconazole or SSKI in countries in which the latter is the standard of care. When other azole agents are used, the medical record should document the specific reasons that they were chosen over itraconazole or SSKI.

2. Patients with disseminated or severe pulmonary sporotrichosis should be treated with an amphotericin B formulation initially. When amphotericin B is used, the patient's electrolyte levels, renal function, and complete blood cell counts should be monitored several times per week and documented in the medical record.

Acknowledgments

We thank Drs. William E. Dismukes and Ronald A. Greenfield for their thoughtful reviews of earlier drafts of the guideline. We also thank Dr. Stanley Deresinski for his guidance throughout the guideline development process.

Financial support. The Infectious Diseases Society of America.

Potential conflicts of interest. C.A.K. has received research grants from Merck, Astellas, and Schering-Plough and is on the Speaker's Bureau for Merck, Pfizer, Astellas, and Schering-Plough. B.B. has received a research grant from Schering-Plough. P.G.P. has received research grants from Merck, Astellas, Pfizer, and Schering-Plough and is on the speaker's bureau of Merck, Pfizer, Astellas, and Schering-Plough. S.W.C.: no conflicts.

APPENDIX A.

EXPERT PANEL

Carol A. Kauffman (University of Michigan, Veterans Affairs Medical Center, Ann Arbor), Beatriz Bustamante (Universidad Peruana Cayetano Heredia, Lima, Peru), Stanley W. Chapman (University of Mississippi Medical Center, Jackson), and Peter G. Pappas (University of Alabama at Birmingham, Birmingham).

References

1. Kauffman CA, Hajjeh R, Chapman SW. Practice guidelines for the management of patients with sporotrichosis. For the Mycoses Study Group. Infectious Diseases Society of America. Clin Infect Dis **2000**; 30:684–7.
2. Kwon-Chung KJ, Bennett JE. Sporotrichosis: medical mycology. Philadelphia: Lea & Febiger, **1992**:707–29.
3. Reed KD, Moore FM, Geiger GE, Stemper ME. Zoonotic transmission of sporotrichosis: case report and review. Clin Infect Dis **1993**; 16: 384–7.
4. Conti Diaz IA. Epidemiology of sporotrichosis in Latin America. Mycopathologia **1989**; 108:113–6.
5. Dixon DM, Salkin IF, Duncan RA, et al. Isolation and characterization of *Sporothrix schenckii* from clinical and environmental sources associated with the largest US epidemic of sporotrichosis. J Clin Microbiol **1991**; 29:1106–13.
6. Hajjeh R, McDonnell S, Reef S, et al. Outbreak of sporotrichosis among tree nursery workers. J Infect Dis **1997**; 176:499–504.
7. Dooley DP, Bostic PS, Beckius ML. Spook house sporotrichosis: a point-source outbreak of sporotrichosis associated with hay bale props in a Halloween haunted-house. Arch Intern Med **1997**; 157:1885–7.
8. Lurie HI. Five unusual cases of sporotrichosis from South Africa showing lesions in muscles, bones, and viscera. Br J Surg **1963**; 50:585–91.
9. Kauffman CA. Old and new therapies for sporotrichosis. Clin Infect Dis **1995**; 21:981–5.
10. Barros MB, Schubach Ade O, do Valle AC, et al. Cat-transmitted sporotrichosis epidemic in Rio de Janeiro, Brazil: description of a series of cases. Clin Infect Dis **2004**; 38:529–35.
11. Kwon-Chung KJ. Comparison of isolates of *Sporothrix schenckii* obtained from fixed cutaneous lesions with isolates from other types of lesions. J Infect Dis **1979**; 139:424–31.
12. Pappas PG, Tellez I, Deep AE, Nolasco D, Holgado W, Bustamante B. Sporotrichosis in Peru: description of an area of hyperendemicity. Clin Infect Dis **2000**; 30:65–70.
13. Bayer AS, Scott VJ, Guze LB. Fungal arthritis. III. Sporotrichal arthritis. Semin Arthritis Rheum **1979**; 9:66–74.
14. Crout JE, Brewer NS, Tompkins RB. Sporotrichosis arthritis: clinical features in seven patients. Ann Intern Med **1977**; 86:294–7.
15. Howell SJ, Toohey JS. Sporotrichal arthritis in south central Kansas. Clin Orthop Relat Res **1998**; 346:207–14.
16. Stratton CW, Lichtenstein KA, Lowenstein SR, Phelps DB, Reller LB. Granulomatous tenosynovitis and carpal tunnel syndrome caused by *Sporothrix schenckii.* Am J Med **1981**; 71:161–4.
17. Schwartz DA. Sporothrix tenosynovitis—differential diagnosis of granulomatous inflammatory disease of the joints. J Rheumatol **1989**; 16: 550–3.
18. Sharkey-Mathis PK, Kauffman CA, Graybill JR, et al. Treatment of sporotrichosis with itraconazole. NIAID Mycoses Study Group. Am J Med **1993**; 95:279–85.
19. Pluss JL, Opal SM. Pulmonary sporotrichosis: review of treatment and outcome. Medicine (Baltimore) **1986**; 65:143–53.
20. Kauffman CA, Pappas PG, McKinsey DS, et al. Treatment of lymphocutaneous and visceral sporotrichosis with fluconazole. Clin Infect Dis **1996**; 22:46–50.
21. Khabie N, Boyce TG, Roberts GD, Thompson DM. Laryngeal sporotrichosis causing stridor in a young child. Int J Pediatr Otorhinolaryngol **2003**; 67:819–23.
22. Henry LR, Danaher PJ, Boseley ME. Laryngeal sporotrichosis mimicking merkel cell carcinoma recurrence. Otolaryngol Head Neck Surg **2005**; 132:336–8.
23. Torrealba JR, Carvalho J, Corliss R, England D. Laryngeal granulomatous infection by *Sporothrix schenckii.* Otolaryngol Head Neck Surg **2005**; 132:339–40.
24. Gullberg RM, Quintanilla A, Levin ML, Williams J, Phair JP. Sporotrichosis: recurrent cutaneous, articular, and central nervous system infection in a renal transplant recipient. Rev Infect Dis **1987**; 9:369–75.
25. Gottlieb GS, Lesser CF, Holmes KK, Wald A. Disseminated sporotrichosis associated with treatment with immunosuppressants and tumor necrosis factor–α antagonists. Clin Infect Dis **2003**; 37:838–40.
26. Rotz LD, Slater LN, Wack MF, Boyd AL, Scott EN, Greenfield RA. Disseminated sporotrichosis with meningitis in a patient with AIDS. Infect Dis Clin Prac **1996**; 5:566–8.
27. Wroblewska M, Swoboda-Kopec E, Kawecki D, Sawicka-Grzelak A, Stelmach E, Luczak M. Infection by a dimorphic fungus *Sporothrix schenckii* in an immunocompromised patient. Infection **2005**; 33: 289–91.
28. Silva-Vergara ML, Maneira FR, De Oliveira RM, Santos CT, Etchebehere RM, Adad SJ. Multifocal sporotrichosis with meningeal involvement in a patient with AIDS. Med Mycol **2005**; 43:187–90.

29. Scott EN, Kaufman L, Brown AC, Muchmore HG. Serologic studies in the diagnosis and management of meningitis due to *Sporothrix schenckii.* N Engl J Med **1987**; 317:935–40.
30. Field MJ, Lohr KN. Institute of Medicine Committee to Advise the Public Health Service on Clinical Practice Guidelines. Clinical practice guidelines: directions for a new program. Washington, DC: National Academy Press, **1990**:52–77.
31. Canadian Task Force on the Periodic Health Examination. The periodic health examination. Can Med Assoc J **1979**; 121:1193–254.
32. Smego RA Jr, Castiglia M, Asperilla MO. Lymphocutaneous syndrome: a review of non-sporothrix causes. Medicine (Baltimore) **1999**; 78: 38–63.
33. Hiruma M, Katoh T, Yamamoto I, Kagawa S. Local hyperthermia in the treatment of sporotrichosis. Mykosen **1987**; 30:315–21.
34. Hiruma M, Kawada A, Noguchi H, Ishibashi A, Conti Diaz IA. Hyperthermic treatment of sporotrichosis: experimental use of infrared and far infrared rays. Mycoses **1992**; 35:293–9.
35. Cabezas C, Bustamante B, Holgado W, Begue RE. Treatment of cutaneous sporotrichosis with one daily dose of potassium iodide. Pediatr Infect Dis J **1996**; 15:352–4.
36. Rex JH, Bennett JE. Administration of potassium iodide to normal volunteers does not increase killing of *Sporothrix schenckii* by their neutrophils or monocytes. J Med Vet Mycol **1990**; 28:185–9.
37. Dismukes WE, Stamm AM, Graybill JR, et al. Treatment of systemic mycoses with ketoconazole: emphasis on toxicity and clinical response in 52 patients. National Institute of Allergy and Infectious Diseases collaborative antifungal study. Ann Intern Med **1983**; 98:13–20.
38. Calhoun DL, Waskin H, White MP, et al. Treatment of systemic sporotrichosis with ketoconazole. Rev Infect Dis **1991**; 13:47–51.
39. Restrepo A, Robledo J, Gomez I, Tabares AM, Gutierrez R. Itraconazole therapy in lymphangitic and cutaneous sporotrichosis. Arch Dermatol **1986**; 122:413–7.
40. Conti Diaz IA, Civila E, Gezuele E, et al. Treatment of human cutaneous sporotrichosis with itraconazole. Mycoses **1992**; 35:153–6.
41. Diaz M, Negroni R, Montero-Gei F, et al. A Pan-American 5-year study of fluconazole therapy for deep mycoses in the immunocompetent host. Pan-American Study Group. Clin Infect Dis **1992**; 14(Suppl 1): S68–76.
42. Winn RE, Anderson J, Piper J, Aronson NE, Pluss J. Systemic sporotrichosis treated with itraconazole. Clin Infect Dis **1993**; 17:210–7.
43. McGinnis MR, Nordoff N, Li RK, Pasarell L, Warnock DW. *Sporothrix schenckii* sensitivity to voriconazole, itraconazole and amphotericin B. Med Mycol **2001**; 39:369–71.
44. Espinel-Ingroff A. Comparison of in vitro activities of the new triazole SCH56592 and the echinocandins MK-0991 (L-743,872) and LY303366 against opportunistic filamentous and dimorphic fungi and yeasts. J Clin Microbiol **1998**; 36:2950–6.
45. Groll AH, Giri N, Petraitis V, et al. Comparative efficacy and distribution of lipid formulations of amphotericin B in experimental *Candida albicans* infection of the central nervous system. J Infect Dis **2000**; 182:274–82.
46. Chapman SW, Pappas P, Kauffman C, et al. Comparative evaluation of the efficacy and safety of two doses of terbinafine (500 and 1000 mg day(−1)) in the treatment of cutaneous or lymphocutaneous sporotrichosis. Mycoses **2004**; 47:62–8.
47. Hull PR, Vismer HF. Treatment of cutaneous sporotrichosis with terbinafine. Br J Dermatol **1992**; 126(Suppl 39):51–5.
48. da Rosa AC, Scroferneker ML, Vettorato R, Gervini RL, Vettorato G, Weber A. Epidemiology of sporotrichosis: a study of 304 cases in Brazil. J Am Acad Dermatol **2005**; 52:451–9.
49. Mahajan VK, Sharma NL, Sharma RC, Gupta ML, Garg G, Kanga AK. Cutaneous sporotrichosis in Himachal Pradesh, India. Mycoses **2005**; 48:25–31.
50. Itoh M, Okamoto S, Kariya H. Survey of 200 cases of sporotrichosis. Dermatologica **1986**; 172:209–13.
51. Downs NJ, Hinthorn DR, Mhatre VR, Liu C. Intra-articular amphotericin B treatment of *Sporothrix schenckii* arthritis. Arch Intern Med **1989**; 149:954–5.
52. Gerding DN. Sporotrichosis. In: Sarosi GA, Davies SF, eds. Fungal diseases of the lung. New York: Raven Press, **1993**:113–23.
53. al-Tawfiq JA, Wools KK. Disseminated sporotrichosis and *Sporothrix schenckii* fungemia as the initial presentation of human immunodeficiency virus infection. Clin Infect Dis **1998**; 26:1403–6.
54. Bolao F, Podzamczer D, Ventin M, Gudiol F. Efficacy of acute phase and maintenance therapy with itraconazole in an AIDS patient with sporotrichosis. Eur J Clin Microbiol Infect Dis **1994**; 13:609–12.
55. Bonifaz A, Peniche A, Mercadillo P, Saul A. Successful treatment of AIDS-related disseminated cutaneous sporotrichosis with itraconazole. AIDS Patient Care STDS **2001**; 15:603–6.
56. Oscherwitz SL, Rinaldi MG. Disseminated sporotrichosis in a patient infected with human immunodeficiency virus. Clin Infect Dis **1992**; 15:568–9.
57. Pursley TJ, Blomquist IK, Abraham J, Andersen HF, Bartley JA. Fluconazole-induced congenital anomalies in three infants. Clin Infect Dis **1996**; 22:336–40.
58. Recommended doses of parenteral and oral antifungal drugs. Redbook **2003**; 2003:722–4.
59. Callens SF, Kitetele F, Lukun P, et al. Pulmonary *Sporothrix schenckii* infection in a HIV positive child. J Trop Pediatr **2006**; 52:144–6.