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# *Scedosporium prolificans* Osteomyelitis in an Immunocompetent Child Treated with Voriconazole and Caspofungin, as Well as Locally Applied Polyhexamethylene Biguanide

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***Scedosporium*** **species are increasingly isolated from immunocompromised and immunocompetent patients. Unfortunately, *Scedosporium* infections are generally resistant to amphotericin B, and *Scedosporium prolificans* strains are particularly resistant to the antifungal agents now in use. We report here on an immunocompetent child with *S. prolificans*-associated osteomyelitis successfully treated with debridement, local irrigation with polyhexamethylene biguanide, and the systemic administration of voriconazole and caspofungin despite poor in vitro activity of voriconazole alone against the isolate. We also review the treatments and outcomes of 28 reported cases of osteomyelitis or septic arthritis caused by *Scedosporium* species in immunocompetent patients.**

## CASE REPORT

An immunocompetent 5-year-old boy stepped on a nail in a chicken coop on 9 December 2001. The next day he developed swelling and bruising of his left foot and was given amoxicillin for cellulitis. On 31 December 2001 he was seen by a local orthopedic specialist, where a three-phase bone scan was negative and he was placed on trimethoprim-sulfamethoxazole therapy. Magnetic resonance (MR) imaging on 3 January 2002 revealed a tiny fluid collection over the cuneiform bone, as well as talar and tarsal navicular bone enhancement. On 4 January 2002 he underwent computed tomography (CT)-guided biopsy, and 3 days later a local infectious diseases consultant empirically placed him on fluconazole due to the suspicion of fungal disease.

On 9 January 2002 the patient underwent surgical debridement, with pathology results showing granulomatous reaction of the first metatarsal and acute osteomyelitis of the second metatarsal. On 9 January 2002, his antifungal therapy was changed to intravenous itraconazole to expand mold coverage. The biopsy culture finally revealed *Scedosporium prolificans* on 28 January 2002, and 2 days later the patient's therapy was changed to voriconazole (4 mg/kg/dose) on a compassionate use protocol. Antifungal susceptibilities were performed according to the NCCLS M38-P protocol (53) (Specialty Laboratories, Santa Monica, Calif.), which revealed an amphotericin B MIC of 2.0 μg/ml, and an itraconazole MIC of >1 μg/ml. On 11 February 2002, further antifungal susceptibility to voriconazole performed by the Fungus Testing Laboratory at the University of Texas Health Sciences Center at San Antonio revealed a 48-h voriconazole MIC of 32 μg/ml.

A second foot MR image obtained on 1 March 2002 showed marked disease progression with near absence of the tarsal navicular bone, and the talus, calcaneous, cuboid, and two cuneiforms appeared to be involved. Voriconazole treatment was stopped on 7 March 2002, and the patient was transferred to our medical center on 10 March 2002 after three separate local orthopedic opinions concluded amputation was the only alternative. On 14 March 2002 the child arrived at our medical center, and we placed him on voriconazole at the standard dose and then increased the dosage (to 6 mg/kg/dose) after 2 days. We also added caspofungin (load, 1 mg/kg, followed by maintenance at 0.75 mg/kg/day). An MR image obtained at this time showed that disease was localized to the submalleolar region, but there was clear progression compared to the initial imaging studies. The patient underwent surgical debridement on 15 March and 18 March 2002, which included local irrigation and soaking of the operative site for approximately 4 min with a 0.2% solution of polyhexamethylene biguanide (PHMB).

Repeat MR imaging on 9 April 2002 revealed minimal improvement, and plain radiographs revealed stability. The patient's mother stopped the voriconazole after ca. 6 weeks of therapy due to unrelenting voriconazole side effects (hallucinatory visual changes), and the caspofungin was also stopped because of a central line infection. Another MR image obtained on 15 May 2002 showed that the disease was stable.

At follow-up more than 11 months after the patient first presented to our medical center, the child can run around the examination room with no noticeable limp, and recent MR imaging shows mild soft tissue changes that indicate swelling, but no active osteomyelitis or necrotic bone is seen. He has been off all antifungals since completing the 6-week course of voriconazole and caspofungin.

At our institution the *S. prolificans* isolate underwent in vitro testing according to a modification of the NCCLS M38-P guidelines (53) by using macrodilution checkerboard testing with an inocula of $10^3$ CFU/ml, with serial dilutions made in RPMI media and samples incubated at 30°C. At 48 h, the MIC

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for voriconazole was 8 μg/ml, and the MIC for caspofungin was >4 μg/ml. A microdilution checkerboard test was performed to assess drug interactions against the strain, and we observed a voriconazole fractional inhibitory concentration (FIC) of 0.25 and a caspofungin FIC of 0.00195. An in vitro synergistic interaction was noted between voriconazole and caspofungin, with an FIC index of 0.25 with these two agents at both 48 h and 72 h of incubation (33).

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*Scedosporium* species are ubiquitous fungi recovered from soil, sewage, and animal manure. Two species are medically important: *Scedosporium apiospermum* (formerly *Monosporium apiospermum*) is the predominant asexual stage (anamorph) of *Pseudallescheria boydii* (formerly *Petriellidium boydii*, formerly *Allescheria boydii*), and *S. prolificans* (formerly *Scedosporium inflatum*) has no known teleomorph (58). In immunocompromised patients, these organisms can parallel the clinical manifestations of aspergillosis or fusariosis and lead to pulmonary or disseminated infection (40, 44). In normal hosts, these hyaline molds often produce localized disease, such as septic arthritis or osteomyelitis after penetrating trauma, or can lead to pneumonia or meningitis after aspiration of polluted water. There have been few antifungal agents to effectively treat *Scedosporium* infections since the polyenes (e.g., amphotericin B) demonstrate poor activity. Recently, however, the newer triazoles such as voriconazole have shown some success against *S. apiospermum* infections, and in vitro the echinocandins show activity against this species. However, *S. prolificans* shows a poor response to all available antifungals in vitro, and infections with this fungal species remain extremely difficult to treat. Therefore, we detail here a case of *S. prolificans*-associated osteomyelitis in an immunocompetent child whose strain was resistant to all conventional antifungals tested, including voriconazole. We report success with surgical debridement with PHMB irrigation, coupled with the combination of voriconazole and caspofungin. We also review the literature on *Scedosporium*-associated osteomyelitis and septic arthritis infections and treatments for comparison with the case presented here.

**Discussion.** Soft tissue infection with *Scedosporium* species was originally termed "Madura foot" after the clinical description of patients with pedal mycetoma near Madura, India. While there are several reviews of disseminated *Scedosporium* infections in immunocompromised hosts (3, 26, 35, 55), we are aware of only 27 previous reports in the English language of *Scedosporium* species septic arthritis or osteomyelitis infections in immunocompetent patients (Table 1), not including two in a horse (54) and a dog (52). This list excludes a review of 13 cases from 1921 to 1959 by Green and Adams (19), which often led to amputation due to the lack of available antifungals at the time. There have also been some reports of *Scedosporium*-associated osteomyelitis in immunocompromised patients (2, 16, 31). Most cases in immunocompetent patients resulted from penetrating trauma, and treatment often included surgery and amphotericin B (systemic or intra-articular), miconazole, itraconazole, or ketoconazole. The only fatal case was a German man with *Scedosporium apiospermum*-associated foot osteomyelitis who later developed a cerebral lesion and died (23).

Although amphotericin B is generally considered the "gold standard" for treatment of fungal infections, in vitro studies have shown amphotericin B and its lipid formulations to have little effect on either *S. apiospermum* or *S. prolificans* (7). Recent in vitro studies including voriconazole and other conventional antifungals have clearly shown that voriconazole might have potential for treatment of *Scedosporium* species (8, 13, 28, 38, 50). In one in vitro study voriconazole showed superior activity over the other newer triazoles, posaconazole and ravuconazole, against both *Scedosporium* species. The difference was smaller against *S. apiospermum*, but voriconazole was clearly more active against the more-difficult-to-treat *S. prolificans* (6). However, in several studies a new triazole UR-9825 (Uriach Laboratories, Barcelona, Spain) showed the best activity against *S. prolificans* (6, 39, 40, 49), offering a potential agent for a very recalcitrant species. Caspofungin has shown in vitro activity against *S. apiospermum* only (10) but did have marginal activity against *S. prolificans* (12). In vitro combination studies may give hints for future therapy of *Scedosporium* species infections (Table 2), including reports of synergy using drug levels attainable in the blood (42) or synergy where there was poor in vitro activity with amphotericin B alone (1).

*S. prolificans* is more resistant to treatment compared to *S. apiospermum* both in vitro, in a murine model (5), and as confirmed by clinical experience. Furthermore, a murine model of natural infection showed that an *S. prolificans* strain possessed increased virulence over a *S. apiospermum* strain (47). Few animal models have been studied for this infection, but one murine model of systemic *P. boydii* infection showed that itraconazole was ineffective, whereas posaconazole was slightly more effective than fluconazole in survival and fungal burden reduction (G. Gonzalez, R. Tijerina, L. Najvar, R. Bocanegra, M. Rinaldi, D. Loebenberg, and J. Graybill, 41st Intersci. Conf. Antimicrob. Agents Chemother. [ICAAC], abstr. J-1615, 2001). Two recent reports of systemic murine scedosporiosis models showed that liposomal amphotericin B (10 mg/kg/day) with granulocyte colony-stimulating factor improved survival, highlighting both the need for an intact immune system to combat systemic disease and the potential role for increased polyene dose through use of liposomal amphotericin B (46) (M. Ortoneda, J. Capilla, F. Pastor, I. Pujol, and J. Guarro, 42nd ICAAC, abstr. M-191, 2002).

There is no proven effective therapy for *S. prolificans* disease, and most neutropenic patients with disseminated disease succumb to their infection regardless of the antifungal used (3). The therapeutic approach to *Scedosporium* infections generally involves complete surgical resection when possible, with the role of antifungals being unclear, including a notable lack of response to amphotericin B (51). It appears that few antifungal agents have consistent activity against *S. prolificans* but, due to general amphotericin B resistance, the extended-spectrum triazoles such as voriconazole or posaconazole may become the agents of choice for *S. prolificans* infections. There are a growing number of anecdotal successes with newer agents against disseminated scedosporiosis (18, 27, 41, 43–45, 57). However, some case reports are confounded by adjunctive surgical management and varying recovery of host defenses (40). Nevertheless, the anecdotal evidence with newer triazole

TABLE 1. *Scedosporium* osteomyelitis and septic arthritis infections in immunocompetent patients

| Age (yr)/sex | Risk factor | *Scedosporium* spp. | Infected site | Treatment | Outcome | Reference |
|---|---|---|---|---|---|---|
| 46/M | Cortisone injections | *Allescheria boydii* | Foot osteomyelitis | Surgery, miconazole | Cure | 21 |
| 6/M | Nail puncture | *Monosporium apiospermum* | Knee osteomyelitis | Intra-articular amphotericin B | Cure | 11 |
| 31/M | NA[a] | *Monosporium apiospermum* | Foot osteomyelitis | Direct instillation of amphotericin B through local catheters | No fungi isolated, amputation due to bacterial infection | 4 |
| 6/M | Nail puncture | *Monosporium apiospermum* | Knee osteomyelitis | Intra-articular amphotericin B | Cure | 22 |
| 50/M | Deep laceration | *Petriellidium boydii* | Knee osteomyelitis | Surgery, amphotericin B irrigation | Cure | 34 |
| 6/M | Penetrating wound | *Scedosporium inflatum* | Foot osteomyelitis | Surgery, amphotericin B + ketoconazole; miconazole; amphotericin B + ketoconazole; then ketoconazole | Cure | 36 |
| 53/M | Thorn puncture | *Pseudallescheria boydii* | Knee osteomyelitis | Surgery, ketoconazole | Improvement | 9 |
| 6/M | Penetrating wound | *Scedosporium apiospermum* | Knee osteomyelitis | Surgery, miconazole, then itraconazole | Improvement | 48 |
| 52/M | None | *Scedosporium apiospermum* | Vertebral osteomyelitis | Surgery, itraconazole | Expired due to pneumonia | 32 |
| 32/M | Penetrating injury | *Scedosporium apiospermum* | Knee osteomyelitis | Itraconazole | Improvement | 56 |
| 23/M | Open wound | *Pseudallescheria boydii* | Knee arthritis | Miconazole + itraconazole, then itraconazole | Improvement | 17 |
| 5/F | Nail puncture | *Allescheria boydii* | Knee arthritis | Surgery, miconazole, then intra-articular amphotericin B | Improvement | 37 |
| 69/M | None | *Pseudallescheria boydii* | Vertebral | Surgery, amphotericin B | Left against medical advice | 24 |
| 46/M | None | *Petriellidium boydii* | Vertebral osteomyelitis | Surgery, miconazole, then amphotericin B | Improvement | 15 |
| 32/M | Laceration | *Pseudallescheria boydii* | Knee osteomyelitis | Amputation, ketoconazole | Improvement after amputation | 25 |
| 7/M | Pitchfork laceration | *Petriellidium boydii* | Knee osteomyelitis | Surgery only | Improvement | 29 |
| 46/M | Blunt injury | *Pseudallescheria boydii* | Cranial osteomyelitis | Surgery only | Improvement | 14 |
| 10/M | Nail puncture | *Monosporium apiospermum* | Foot osteomyelitis | Chlortrimazole, surgery | Improvement after amputation | 30 |
| 6/M | Bicycle accident | *Petriellidium boydii* | Knee arthritis | Surgery, amphotericin B; ketoconazole | Improvement | 20 |
| 11/M | Laceration | *S. inflatum* | Ankle arthritis | Surgery, amphotericin B; itraconazole | Improvement | 62 |
| 3/M | Trauma to knee | *S. inflatum* | Knee arthritis | Surgery, ketoconazole, amphotericin B and ketoconazole; intra-articular amphotericin B; intra-articular miconazole | Amputation | 61 |
| 5/M | Penetrating trauma to knee | *S. inflatum* | Knee arthritis | Surgery, amphotericin B + 5-FC[b]; intra-articular amphotericin B; miconazole; ketoconazole | Improvement | 61 |
| 11/M | Sever epiphyseal fracture | *S. inflatum* | Knee arthritis | Surgery, amphotericin B; intra-articular amphotericin B | Improvement | 61 |
| 54/M | Trauma to knee | *S. inflatum* | Knee arthritis | Surgery, amphotericin B; ketoconazole; miconazole | Improvement | 61 |
| 6/M | Nail puncture | *S. inflatum* | Foot osteomyelitis | Surgery alone | Improvement | 61 |
| 6/M | Nail puncture | *S. inflatum* | Foot osteomyelitis | Surgery, amphotericin B + ketoconazole | Improvement | 61 |
| 25/F | Multiple fractures from trauma | *S. inflatum* | Knee osteomyelitis | Surgery, amphotericin B, ketoconazole | Improvement | 61 |
| 35/M | Intravenous drug abuse | *S. inflatum* | Hip arthritis | Amphotericin B + 5-FC | Improvement | 61 |

[a] NA, not applicable.
[b] 5-FC, 5-fluorocytosine.

TABLE 2. *In vitro* combination antifungal studies against *Scedosporium* species

| Antifungal agent 1 | Antifungal agent 2 | *Scedosporium* spp. (no. of isolates tested) | Results | Reference |
|---|---|---|---|---|
| Itraconazole | Terbinafine | *S. prolificans* (20) | Synergy in 19 of 20 isolates | 42 |
| Voriconazole | Terbinafine | *S. prolificans* (5) | Synergy | Meletiades et al.[a] |
| Voriconazole | Terbinafine | *S. prolificans* (38) | Synergy in most isolates | Perrie and Ellis[b] |
| Voriconazole | Itraconazole | *S. prolificans* (38) | Synergy in most isolates | Perrie and Ellis[b] |
| Amphotericin B | Fluconazole | *P. boydii* (8) | 67% synergy or additivity; no antagonism | 60 |
| Amphotericin B | Miconazole | *P. boydii* (8) | 67% synergy or additivity; no antagonism | 60 |
| Amphotericin B | Itraconazole | *P. boydii* (8) | 67% synergy or additivity; no antagonism | 60 |
| Amphotericin B | Pentamidine | *S. prolificans* (30) | Synergy | 1 |

[a] J. Meletiades, J. W. Mouton, J. F. G. Meis, and P. E. Verweij, 41st ICAAC, abstr. J-126, 2001.
[b] R. C. Perrie and D. H. Ellis, 42nd ICAAC, abstr. M-862, 2002.

success is increasing. A series of 36 *Scedosporium* species infections treated with voriconazole reported that >60% of patients with *S. apiospermum* infections had a positive clinical response but that those with *S. prolificans* infections had a <30% positive clinical response (J. Torre-Cisneros, A. Gonzalez-Ruiz, M. R. Hodges, and I. Lutsar, Abstr. 38th Infect. Dis. Soc. Am. Meet., abstr. 305, 2000). Another study with voriconazole analyzed eight cases of scedosporiosis, with a success rate of 83% in the six cases of *S. apiospermum* disease, while both cases of *S. prolificans* were refractory to voriconazole monotherapy (59).

Treatment for *Scedosporium*-associated osteomyelitis is generally believed to include surgical debridement with antifungal therapy, but the outcome can result in radical excision or amputation (37). The patient described here was infected with the more antifungal-resistant *S. prolificans*, and even the newest available antifungal, voriconazole, possessed poor in vitro activity against the strain. The child demonstrated a clear clinical worsening on voriconazole monotherapy even with previous surgical adjunctive therapy. We therefore chose a unique antifungal regimen of a combination of voriconazole and caspofungin and included PHMB for topical use as an irrigant during his orthopedic debridement operations. PHMB is a synthetic biocide that was developed for use as a presurgery antimicrobial scrub and was patented in 1977 for use as a sanitizer for swimming pools. In vitro testing has shown excellent fungicidal activity against a variety of molds and yeasts, and there has been clinical success with its topical treatment against fungal keratitis (S. Yi, C. E. Hayes, N. V. Myers, W. A. Schell, J. E. Arena, J. R. Perfect, B. C. Roberts, and W. C. Fowler, 40th ICAAC, abstr. 207, 2000; N. V. Myers, W. A. Schell, J. R. Perfect, D. Chang, and W. C. Fowler, 38th ICAAC, abstr. J-125, 1998).

*S. apiospermum* and *S. prolificans* are developing as emerging fungal pathogens as the number of immunocompromised patients increases. Additionally, the molds affect immunocompetent patients, most often leading to arthritis or osteomyelitis. Conventional antifungal agents have had little success, especially in the setting of immunosuppression, so new regimens are desperately needed. We report clinical success with the combination voriconazole and caspofungin, as well as with surgical debridement and PHMB irrigation for a case of *S. prolificans*-associated foot osteomyelitis. In vitro testing of our isolate revealed synergy with voriconazole and caspofungin. Our patient responded well to combination antifungal therapy and surgery. It is difficult to accurately assess which modality was most responsible for this success, but the case demonstrates how these difficult-to-treat fungi benefit from a coordinated in vitro and in vivo approach.

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