Mycetoma Medical Therapy

Oliverio Welsh1*, Hail Mater Al-Abdely2*, Mario Cesar Salinas-Carmona3*, Ahmed Hassan Fahal4*

1 Department of Dermatology, Dr. Jose E. Gonzalez University Hospital, Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, Mexico, 2 Section of Infectious Diseases, Department of Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, 3 Department of Immunology, Faculty of Medicine, Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, Mexico, 4 The Mycetoma Research Centre, University of Khartoum, Khartoum, Sudan

Abstract: Medical treatment of mycetoma depends on its fungal or bacterial etiology. Clinically, these entities share similar features that can confuse diagnosis, causing a lack of therapeutic response due to inappropriate treatment. This review evaluates the response to available antimicrobial agents in actinomycetoma and the current status of antifungal drugs for treatment of eumycetoma.

Introduction

Mycetoma is a potentially serious, devastating, chronic, inflammatory disease caused by aerobic actinomycetic bacteria (actinomycetoma) or fungi (eumycetoma). The worldwide incidence of actinomycetoma and eumycetoma varies from country to country and region to region, but this infection is predominant in countries that are located between 30°N and 15°S. Most cases of mycetoma occur in Sudan, Venezuela, Mexico, and India. Sudan has the highest incidence of eumycetoma (up to 70%). In Mexico, actinomycetoma predominates in about 97% of cases [1]. The clinical picture of both infections is quite similar. To achieve cure, it is important to define the fungal or bacterial etiology because treatment for each is completely different. Actinomycetoma is currently treated with antibiotics, which can be used alone or in different combinations depending on the severity, dissemination, and location of the disease. Medical cure is generally achieved if the patient is properly treated [2]. In contrast, treatment of eumycetoma consists of antifungals and surgical excision [3]. Medical cure is more difficult to obtain and the extension and location of the disease may lead to chronic progressive lesions that often lead to amputation [4]. However, in both forms of mycetoma, prolonged treatment is needed. Our objective is to present the current status of medical therapy of mycetoma and the best antibiotic and antifungal options available for its management.

Methods

Most of the literature we reviewed related to treatment was based on case reports and in vitro and in vivo studies of drug susceptibilities. We assessed and collected leading articles on drugs and locations of the disease. Medical cure is more difficult to obtain and the extension and location of the disease. Medical cure is generally achieved if the patient is properly treated [2]. In contrast, treatment of eumycetoma consists of antifungals and surgical excision [3]. Medical cure is more difficult to obtain and the extension and location of the disease may lead to chronic progressive lesions that often lead to amputation [4]. However, in both forms of mycetoma, prolonged treatment is needed. Our objective is to present the current status of medical therapy of mycetoma and the best antibiotic and antifungal options available for its management.

Actinomycetoma

Causative agents

Three genera (Nocardia, Streptomyces, and Actinomadura) comprise the most frequent causative agents of actinomycetoma. Etiological agents of actinomycetoma include Nocardia brasiliensis, N. asteroides, N. caviae, N. farcinica, N. transvalensis, N. dassonvillei, N. mexicana, N. veterana, Actinomadura madurae, A. pelletieri, A. laitana, Streptomyces somaliensis, and S. sudanensis. New species of Nocardia that have been reported to cause actinomycetoma are N. harenae and N. takedensis [5,6].

In vitro susceptibility data

Studies of sensitivity of N. brasiliensis to different antimicrobials and antibiotics have been reported in vitro and in vivo [7–10]. A study by Gomez et al. demonstrated that the best inhibitory effect occurs with aminoglycosides (100% susceptibility to amikacin, gentamicin, isepamicin, netilmicin, and tobramycin); however, all strains were resistant to streptomycin and kanamycin. Nocardia strains were also susceptible to linezolid in 100% of cases and to sulfonamides (trimethoprim-sulfamethoxazole) in 83% [10]. Amoxicillin-clavulanate showed an inhibitory effect of 97%. Other oxazolidinones have been evaluated in the laboratory and found effective for future treatment in cases that could be resistant to other antimicrobials [11].

The susceptibility of 30 strains of N. brasiliensis isolated from patients with actinomycetoma was determined using econazole, imipenem, and meropenem, both alone and combined with clavulanic acid. MIC50 and MIC90 values for econazole were 2 and 4 µg/ml, respectively. For imipenem, values were 64 and 64 µg/ml, respectively. Only seven isolates had a minimum inhibitory concentration (MIC) of 2 µg/ml. Regarding meropenem, MIC values were 2 and 8 µg/ml with 16 out of 30 isolates exhibiting an MIC of 2 µg/ml. The addition of clavulanic acid to the carbapenems did not significantly change MIC values [8]. Because of the cost of carbapenems, it is necessary to determine if the isolated strain is susceptible to these antibiotics.

Molecular studies have also been useful to identify the species of the infecting organism with greater specificity [7,9].

Animal models

Animal models have been successfully used to study the pathogenic mechanism of actinomycetoma and the therapeutic efficacy of diverse antimicrobials. Experimental N. brasiliensis...
actinomycetoma infection was induced by inoculation in the footpad of immunocompetent and athymic nude homozgyous and heterozygous Lewis rats. Classic actinomycetoma lesions occurred in the infected foot of the immunocompetent rats. After 20–25 days, the lesions began to heal. A more active infection was found in homozygous athymic rats, and some animals died because of dissemination of the infection with organ involvement. Histopathological examination showed an infiltrate mainly of polymorphonuclear cells; after 20 days, the infiltrate was composed mostly of histiocytes, lymphocytes, fibroblasts, and Langhans cells. The presence of grains was observed after 15 days in heterozygote Lewis rats, but not in homozygous nude rats [12].

Studies in BALB/c mice have allowed analysis of the inflammatory mechanisms and therapeutic effect of diverse antimicrobials [13]. Since combination therapy seems to work better for actinomycetoma, amikacin, SXT, amoxicillin-clavulanic acid, and linezolid were analyzed to determine the effect of drug combinations on *N. brasiliensis* [10]. Some of the combinations tested, particularly amoxicillin-clavulanic acid in combination with linezolid, showed synergistic activity.

Because of the ethical and patient selection difficulties in carrying out prospective clinical trials in endemic areas, the animal model becomes a useful alternative to determine which antimicrobials could be therapeutically effective in human infection.

**Clinical data**

Actinomycetoma frequently affects the feet and legs; in Mexico, the back is the second most frequent location affected, but different body parts may also be affected. The infection involves subcutaneous tissues and can disseminate to underlying structures, such as bone and organs. It is characterized by a painless, firm mass with nodules, abscesses, fistulae, and draining sinuses discharging a syrup-like filamentous exudate that contains aerobie grains of the causative organism. The differential diagnosis includes other bacterial infections causing osteomyelitis, tuberculosis, other mycobacterial infections, subcutaneous and systemic mycoses, and neoplasia [2].

In contrast to eumycetoma, in actinomycetoma, surgery is seldom used. Most cases respond to medical therapy, although some require prolonged administration of antimicrobial combinations (for weeks or months) (Table 1) [2].

**Current treatment of actinomycetoma**

Effective medical treatment of actinomycetoma began in the early 1940s and 1950s with the use of sulfonamides and dianmio diphenyl sulphone (DDS), achieving cure in some cases. In the 1960s, trimethoprim-sulfamethoxazole (TS) became standard treatment for actinomycetoma. This drug was given for 3–4 months, and in some cases, for longer periods. Other antibiotics, such as streptomycin, isoniazid, rifampin, and minocycline, have been added in isolated cases that did not respond to TS [14,15]. There are no comparative studies of the efficacy of these drugs in combination with TS.

Treatment with TS continued in the 1970s [16]. In 1982, a case of severe actinomycetoma successfully treated with a combination of amikacin sulphate and TS was reported [17]. The patient was a 19-year-old man with multiple lesions and ulcers on his chest wall and with pulmonary involvement accompanied with malaise. The causative organism was identified as *N. brasiliensis* and was isolated from skin lesions, pleural effusion fluid, and blood. Skin biopsy from the affected site revealed multiple granulomas and *Nocardia* grains. The colony was sent to the American Type Culture Collection (ATCC) reference database for characterization and further study. The strain was named HUJEG-1 (*N. brasiliensis* ATCC 700358). The complete sequence of this strain was achieved in 2012 [18].

Because of the infection severity and its dissemination, the authors sought treatment alternatives and selected amikacin sulphate because of its in vitro inhibitory activity against *N. asteroides*. This drug was combined with TS and given as follows: amikacin 15 mg/kg/day intramuscularly (IM) divided into two daily doses for 3 weeks simultaneously with TS 8/40 mg/kg/day orally for 5 weeks. At the end of this time, the patient obtained an improvement of 90% and all pulmonary lesions disappeared. He was released from the hospital and did not return for evaluation, nor did he continue any treatment. About a year later, the patient was seen, and he was completely cured.

The results obtained in this patient led to a prospective study with this combination scheme in severe cases of actinomyecytic mycetoma that did not respond to TS alone [19]. Up to 1989, a total of 25 patients unresponsive to previous therapy or with extensive involvement and/or risk of dissemination to underlying organs were treated. Depending on the severity and extension of disease, some patients were treated as inpatients and others as outpatients. The combination was administered in 5-week cycles (3 weeks of amikacin sulphate intramuscularly together with 5 weeks of oral TS). Audiometry and creatinine clearance were performed before and after each cycle of amikacin sulphate. Depending on the clinical response, this cycle of treatment was consecutively repeated for up to four cycles. All patients in this group were cured except for one who after 3 months developed a recurrence that required further treatment [20].

To date, the response to this combination has been encouraging (see Figure 1) [2], achieving a cure rate of about 90% [36 patients]. Twenty percent of these patients developed minimal or moderate auditory changes detected by audiometry. In one patient, it was severe and detected clinically. In three patients, the medication was stopped; in one because of drug allergy, another due to development of bacterial resistance, and in a third because of recurrence 2 years after remission. Treatment in this patient was continued with a combination of TS, moxifloxacin, netilmicin, and imipenem, and he was cured.

Different antibiotics have been assayed in vitro, ex vivo, and in experimental *N. brasiliensis* actinomycetomas to find treatment alternatives. Among these are TS, amikacin, other aminoglycosides, amoxicillin-clavulanic acid, minocycline, moxifloxacin, linezolid, and carbapenems [7,10,11,21–25]. Most of the recalcitrant cases in patients have responded well to amikacin/TS and only a few had further treatment with imipenem and/or carbapenem [2].

**Eumycetoma treatment in Mexico**

Eumycetoma occurs in Mexico in 3.48% of cases [1]. Treatment is based on prolonged administration of imidazoles such as itraconazole, alone or combined with terbinafine [24]. Posaconazole and voriconazole are available but are expensive, and their therapeutic efficacy has not been assayed. Amphotericin B is rarely used. The combination of medical and surgical treatment is the usual management of this fungal infection.

**Adverse effects**

Amikacin sulphate or the administration of any aminoglycoside requires close clinical observation with audiometry and renal function tests every 3 to 5 weeks to detect auditory and nephrotoxicity and adjust dosing accordingly. Loop diuretics should be avoided with amikacin sulphate because of potential cochlear damage [25]. Cephalothin may increase the risk of aminoglycoside nephrotoxicity [26].
reactions, usually due to hypersensitivity, such as rash, pruritis, peripheral and optic neuropathy, can develop [28,29]. Must be performed weekly. Neurological symptoms, such as nausea. An important adverse effect, myelosuppression, has been reported with high and prolonged doses. Blood parameters return to normal after discontinuing the drug and a complete blood count must be adjusted for renal function and for haemofiltration.

| Antibiotics                  | In vitro | Human infection | Dose                |
|------------------------------|----------|-----------------|---------------------|
| Sulfonamides DDS (4,4        | No data  | Effective       | 100-200 mg/day single dose |
| diaminodiphenyl-sulfone)     |          |                 |                     |
| Trimethoprim-Sulfamethoxazole (T5) | Active   | Effective       | 8 mg/40 mg          |
| Amikacin sulphate-T5         | Active   | Effective       | Amikacin: 15 mg kg/day IM or IV in two daily doses; T5 as above |
| Netilmicin-T5                | Active   | Effective       | Netilmicin 300 mg/day IM single dose; T5 as above |
| Minocycline                  | Active   | Effective in 70%| 200 mg/day PO in divided dose |
| Amoxicillin-clavulanate      | Active   | Effective       | 500 mg/125 mg PO; tid for 3 to 6 months |
| Linezolid                    | Active   | Effective       | 600 mg PO twice daily |
| Fosfomycin                   | Active   | Effective       | 100-200 mg/kg/day q6-8 h IV or PO in 21-day cycles. |
| Imipenem                     | Active depending on the strain | Effective depending on the strain | 500 mg IV q8 hours; not to exceed 50 mg/kg/day or 4 g/day |
| Meropenem                    | Active   | Effective       | 500 mg IV q8 hr; not to exceed 2 g IV daily |
| Rifampicin                   | Active depending on the strain | Effective depending on the strain | 10 mg/kg/day PO |
| Moxifloxacin                 | Active   | Effective       | 400 mg/day IV or PO |

**Antifungal agents**

| Antibiotics | In vitro | Human infection | Dose |
|-------------|----------|-----------------|------|
| Amphotericin B | Moderate activity | Not effective |      |
| Fluconazole  | Limited activity | Not effective |      |
| Ketoconazole | Active    | Variable efficacy | 400-800 mg |
| Itraconazole | Active    | Variable efficacy | 200-400 mg |
| Voriconazole | Active    | Effective in few case reports | 200 mg |
| Posaconazole | Active    | Effective in few cases |      |
| Isavuconazole | Active    | No data |      |
| Echinocandins | Not active | No data |      |
| Terbinafine  | Moderate activity | No data |      |

Possible drug interactions, history of drug allergies, and co-morbidities should be analyzed in all drugs. IM, intramuscularly; IV, intravenous; PO, orally; tid, three times daily. 

**Eumycetoma**

**Causative agents**

Causative agents of eumycetoma are classified into those that produce black grains and those that produce white or grayish grains: *Acremonium falcesforme*, *Acr. kiliense*, *Acr. recifei*, *Aspergillus flavus*, *Asp. nidulans*, *Cladophialophora bantiana*, *Cochliobolus spieiher*, *Corynespora cassicola*, *Curvularia geniculata*, *Cur. lunata*, *Cylindrocarpon cyaneusens*, *Cyl. destructans*, *Drechslera rostrata*, *Exophiala jeaneslani*, *Exserohilum rostratum*, *Fusarium spp.*, *Fusarium moniliforme*, *F. oxysporum*, *F. solani*, *Leptosphaeria senegalensis*, *L. tompkinsii*, *Madurella mycetomatis*, *M. grisea*, *M. fahalii*, *Neotestudina rosati*, *Phaeoaeromonas kajde- nii*, *Phialophora cyanescens*, *Plenodomus avani*, *Polycystella hominis*, *Pseudallescheria boydii*, *Pseudochaetosphaerena lar- ense*, *Pyrenochaeta mackinnoni*, *P. romeroi*, and *Scedosporium apiospermum*. Four etiological agents cause more than 90% of the eumycetomas worldwide. These are *M. mycetomatis*, *M. grisea*, *Pseudosporum boydii*, and *L. senegalensis* [31,32].

**In vitro susceptibility data**

Several in vitro studies have been conducted on fungal organisms that commonly cause eumycetoma. Most of the studies were of *M. mycetomatis* and *Scedosporium boydii complex* (*Sc. apiospermum*, *Sc. boydii*, *Sc. aurantiacum*) and a few agents of...
phaeohyphomycosis that can cause mycetoma such as *Exophiala jeanselmei* [33–40]. Almost no data have been reported for *Falciformispora senegalensis* (synonym: *L. senegalensis*) and *Medicopsis romeroi* (synonym: *P. romeroi*) [41]. van de Sande and colleagues have conducted several studies on *M. mycetomatis* susceptibility to many of the currently available antifungals. In vitro testing was done by known methods for filamentous fungi. These methods included the CLSI broth dilution method and the colorimetric Sensititre YeastOne test, as well as the viability-based XTT test. The three methods were compared by testing 36 isolates of *M. mycetomatis* against six antifungals: amphotericin B, ketoconazole, fluconazole, itraconazole, voriconazole, and 5-flucytosine [34]. The Sensititre test was comparable to the CLSI method but produced lower MICs when compared to the viability-based XTT test. This was more obvious with the azoles. The most active antifungals, in vitro, were ketoconazole and the extended-spectrum triazoles, itraconazole and voriconazole. Amphotericin B had a median MIC of 1 μg/mL, while fluconazole had limited activity, and 5-flucytosine had no activity against *M. mycetomatis*. The echinocandins, caspofungin, micafungin, and anidulafungin showed no activity in vitro against 17 isolates of *M. mycetomatis* utilizing the XTT method [35]. However, another study of three isolates of *M. mycetomatis* against anidulafungin using the CLSI method had an MIC of 1 μg/mL [42].

The role of melanin in fungal resistance to antifungals in *M. mycetomatis* is not clear. One study has shown a several-fold increase in MICs to ketoconazole and itraconazole with the addition of melanin to the culture media [43]. Posaconazole and isavuconazole have good activity against *M. mycetomatis*, *Sc. apiospermum* and *E. jeanselmei*. MICs against *M. mycetomatis* were in the range of 0.016 to 0.25 μg/mL [36,44].

The allylamine antifungal, terbinafine, showed moderate activity against *M. mycetomatis* and variable activity against *Sc. apiospermum* [36,45–47]. Several in vitro studies have indicated low MICs for itraconazole and voriconazole to several strains of *Sc. apiospermum* [37,39,45,48]. Several agents of phaeohyphomycosis, including *E. jeanselmei*, are susceptible in vitro to itraconazole, voriconazole, and posaconazole [39,40,49,50].

The extended spectrum triazoles and ketoconazole have the best activity against *M. mycetomatis*, while ketoconazole has limited or variable activity against *Sc. boydii* complex and phaeohyphomycetes.

Animal models

Few experimental animal models on the development of *M. mycetomatis* cutaneous mycetoma infection have been published. Data regarding experimental fungal infections that can cause mycetoma
come from a few successful models (athymic mice, BALB/c mice and goat); however, none of these have evaluated the therapeutic effect of antifungals on *M. mycetomatis* infection [32,33]. Animal models for therapy of infections due to *S. boydii* complex and agents of phaeohyphomycosis are several, including murine, rat, and guinea pig [34,35]. *Sc. apiospermum* experimental infection in mouse and guinea pig has shown the efficacy of voriconazole and posaconazole [56–58]. A high dose of posaconazole was required for efficacy in a murine model of disseminated *Sc. apiospermum* infection, while itraconazole was not effective [57]. Higher MIC to voriconazole correlated with failure of experimental therapy in one study [34]. Several phaeohyphomycetes, including *Exophiala* species, were responsive to itraconazole and posaconazole in an experimental murine infection [59]. Posaconazole demonstrated the best activity in these animal studies [60,61].

**Clinical data**

Published studies indicate the need for combined medical and surgical therapy to achieve success in fungal mycetoma. Factors that determine therapy outcome include extent of tissue and bone involvement, site of the disease, and antifungal therapy. It is not yet clear if the extent of surgical debridement and the type and duration of antifungal therapy alter outcome [4]. However, near complete surgical excision and prolonged antifungal therapy is more likely to succeed. Timing of surgery in relation to antifungal therapy is not well established. One prospective study indicates that medical therapy may limit the disease and make complete excision of the lesions more feasible [3].

**Current treatment of eumycetoma**

As neglected diseases, mycetoma in general and fungal mycetoma in particular have received little attention in the development of specific therapeutics. All currently used drugs against causative agents of eumycetoma were developed and studied with other, more common fungi [62]. For several decades, systemic antifungal therapy has been limited to a few drugs that are potentially toxic and delivered parenterally. Amphotericin B deoxycholate was widely used despite its toxicity. However, a wide range of antifungal agents have been approved and marketed for various fungal infections [62]. These include less toxic lipid formulations of amphotericin B, second and third generation azoles, terbinafine and echinocandins. The newer azoles are broad-spectrum and oral, with good bioavailability and low toxicity [63]. These agents are particularly attractive for prolonged outpatient therapy, which is typically needed in a chronic fungal infection such as eumycetoma; however, there are limited in vitro and in vivo studies. Clinical data are almost exclusively from case reports and a small number of case series. Prospective clinical studies are needed to evaluate the therapeutic potential of these antifungals.

Amphotericin B was the only systemic antifungal available for almost three decades. It was not widely used for eumycetoma because of significant toxicity and the need to be given parenterally for prolonged periods. Lipid-associated amphotericin B was tried at the Mycetoma Research Centre in Sudan in four patients, but the results were disappointing. One patient had acute renal failure; treatment was stopped and he recovered. The other three patients had courses of 6 weeks duration with no dramatic response, and viable organisms were cultured from the lesions.

The imidazole ketoconazole, introduced in the early 1980s, was a breakthrough in systemic antifungal therapy. It is active against *Candida* and several other fungi and can be administered orally. Mahgoub and Gumaa published their experience with ketoconazole therapy in 13 patients with mycetoma due to *M. mycetomatis* from Saudi Arabia and the Sudan. Doses ranged from 200 to 400 mg daily, and the therapeutic response was variable: ten patients had a good response and three did not [64]. The follow-up period was short in half the patients; therefore, the frequency of relapse could not be determined. Afterwards, reports of variable responses with ketoconazole in different parts of the world were published [65,66]. In a report from India, six out of ten patients were reported cured of fungal mycetoma after prolonged therapy with ketoconazole (8 to 24 months) [66]. However, recently, the use of ketoconazole has been limited by the United States Food and Drug Administration and the European Medicines Agency (EMA) due to its hepatic and adrenal toxicity. Ketoconazole should not be used as first-line treatment. It is recommended only for the treatment of certain life-threatening fungal infections (endemic mycoses) when alternative antifungal therapies are not available or tolerated [67]. Fluconazole is not an effective therapy for eumycetoma and is currently not used for treatment [68].

Itraconazole was released in the early 1990s and became the most commonly used drug for the treatment of eumycetoma in places where it was affordable. The bioavailability of itraconazole is variable, and absorption is related to stomach acidity and food. Reports indicate a clinical response to itraconazole in patients with eumycetoma [3,69–71]. These are mostly retrospective case series or case reports that suggest a variable response. In one prospective non-comparative study of medical therapy with itraconazole for 12 months followed by surgical excision in 13 subjects, most patients had a favorable outcome [3].

Limited data is available on the new classes of antifungals (Table 1). Few case reports show a good response to voriconazole [72,73]. Treatment with posaconazole was successful in one case and stable in another due to *M. mycetomatis*, three cases due to *M. grisea* were successful, and one case due to *Sc. apiospermum* had a partial improvement [74]. Duration of therapy and extent of surgical debridement was variable among these cases. Terbinafine given in a high dose was successful in a few cases of eumycetoma and in two cases of disseminated *E. jeanesimei* infection [75–76]. In a study of 23 patients, terbinafine at a high dose of 500 mg twice daily for 24–48 weeks resulted in 25% cure and 55% improvement of patients [77]. Terbinafine was not effective in deep-seated infections due to *Sc. apiospermum* [78,79]. Both voriconazole and posaconazole were reported to be efficacious in disseminated infections due to *Sc. apiospermum* [80–83]. There are no clinical data on the efficacy of echinocandins or the investigational triazole isavuconazole.

**Adverse effects**

It is important to evaluate possible drug interactions of azoles. Antacids may reduce their absorption, and azoles may cause edema when calcium channel inhibitors are used. Hypoglycemia may occur with concomitant use of sultobunolurates. Azoles may increase plasma concentrations of tacrolimus and cyclosporine at high doses and they can also increase digoxin levels and plasma levels of midazolam and triazolam. Rhabdomyolysis has been reported with cholesterol-lowering drugs (lovastatin and simvastatin) and severe cardiac arrhythmias and possible sudden death with cisapride. Co-administration with phenytoin, rifampin, and H2 receptor antagonists causes a reduction in azole plasma levels. Imidazoles can increase the antiocoagulant effect of warfarin. Simultaneous treatment with warfarin and imidazoles should be carefully monitored. The patient must avoid alcohol consumption, and liver function should be periodically monitored [24].

Notable adverse effects of ketoconazole are hepatotoxicity, gynecomastia, lip dryness and ulceration, skin hyperpigmentation, and decreased libido. Itraconazole is contraindicated in patients
with evidence of ventricular dysfunction such as congestive heart failure or a history of congestive heart failure [86].

Posaconazole can cause fever, diarrhea, nausea, vomiting, and headache. Other adverse events include hypokalemia, rash, thrombocytopenia, and abdominal pain. Liver function tests should be performed at baseline and throughout therapy to monitor possible liver damage. Treatment should be discontinued if serious liver abnormalities occur. Rare serious adverse events are hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, pulmonary embolus, adrenal insufficiency, and allergic and/or hypersensitivity reactions. Prolongation of the QT interval may be seen [87].

Common side effects of voriconazole are visual alterations, fever, rash, vomiting, nausea and diarrhea, headache, sepsis, purpura, pulmonary embolus, abdominal pain, and respiratory disorders [24].

Conclusion

The therapeutic outcome of mycetoma depends on the bacterial or fungal etiology of the infection; factors such as the infecting agent; and the patient’s social and economic status, cultural background, nutrition, therapeutic compliance, and resistance to previous therapies; and the extension and location of the disease are important.

Actinomycetoma must be treated with TS alone or in combination with other available antibiotics. Amikacin has been proven effective in disseminated infections or cases resistant to previous therapy. Renal and auditory evaluations are essential. Carbapenems are useful in some disseminated infections. Amoxicillin-clavulinate can be used in some cases and during pregnancy. Most patients with eumycetoma are treated with either ketoconazole or itraconazole. Itraconazole 200–400 mg daily for 6 months is used to create a good fibrous capsule around the lesion, followed by wide local excision, continuing itraconazole 200–400 mg daily until cure is achieved. Cure is defined by the disappearance of the mass and all sinuses, normal ultrasound, and negative mycology findings. The decision to stop therapy is determined by complete sinus healing, disappearance of the eumycetoma lesion clinically and radiologically by CT scan or MRI, and absence of the infecting agent. Other antifungal agents that can be used as second-line treatment include voriconazole and posaconazole.

Looking Forward

Actinomycetoma requires prompt diagnostic procedures to define the etiological agent. Precise identification of species by molecular techniques can achieve this goal and provide knowledge for testing the antimicrobial susceptibility patterns of each species of aerobic actinomycetes to determine the best drug regimen for clinical use. Future universal availability of these techniques in endemic areas with actinomycetoma will facilitate this objective.

There are currently no treatment guidelines for eumycetoma. Treatment is based on personal experience and a few case reports or case series. There is a pressing need to develop guidelines. The lack of prospective randomized clinical trials on fungal therapeutics makes the choice and duration of treatment of eumycetoma with antifungal agents difficult. Multicenter clinical trials to develop novel antifungals are required as current drugs are of limited efficacy, have adverse effects, and are expensive. Drug choice in eumycetoma is largely determined by availability and cost.

The International Mycetoma Center in Sudan and centers in other countries such as the Netherlands, England, Switzerland, and Mexico are joining efforts to design clinical studies to select and evaluate the best therapeutic regimes for mycetoma.

In February 2013, a meeting was convened in Geneva, supported by the Drugs for Neglected Diseases initiative (DNDi), to highlight disease awareness and propose inclusion of this infection in the list of neglected tropical diseases (NTDs) of the World Health Organization. Experts from Sudan, United Kingdom, the Netherlands, Mexico, and Switzerland participated in that event, and the Mycetoma Consortium was established. In May 2013, the proposal led by Professors Ahmed Fahal and El Sheikh Mahgoub and other researchers had a safe landing at the WHO, and by July 2013 mycetoma was included in the WHO NTDs list. This action will increase awareness and facilitate and promote international studies on new effective antifungal and antibacterial agents for the treatment of mycetoma.

Acknowledgments

The authors thank Sergio Lozano-Rodriguez, MD for his help in editing the manuscript.

Box 2. Top Five Papers

1. Welsh O, Vera-Cabrera L, Welsh E, Salinas MC (2012) Actinomycetoma and advances in its treatment. Clin Dermatol 30: 372–381
2. Fahal AH, Rahman IA, El-Hassan AM, Rahman ME, Zijlstra EE (2011) The safety and efficacy of itraconazole for the treatment of patients with eumycetoma due to Madurella mycetomatis. Trans R Soc Trop Med Hyg 105: 127–132.
3. Brown-Elliott BA, Brown JM, Conville PS, Wallace RJ Jr (2006) Clinical and laboratory features of the Nocardia spp. based on current molecular taxonomy. Clin Microbiol Rev 19: 259–282.
4. van de Sande WW, Luijendijk A, Ahmed AO, Bakker-Woudenberg IA, van Belkum A (2005) Testing of the in vitro susceptibilities of Madurella mycetomatis to six antifungal agents by using the Sensititre system in comparison with a viability-based 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-5-[(phenylamino)carbonyl]-2H-tetrazolium hydroxide (XTT) assay and a modified NCCLS method. Antimicrob Agents Chemother 49: 1364–1368.
5. De Sarro A, La Camera E, Fera MT (2008) New and investigational triazole agents for the treatment of invasive fungal infections. J Chemother 20: 661–671.
References

1. Lopez-Martinez R, Mendez-Tovar IJ, Bonifaz A, Arenas R, Mayorga J, et al. (2013) Update on the epidemiology of mycetoma in Mexico. A review of 3933 cases. J Med Microbiol 62: 1086-1094.

2. Welsh O, Vera-Cabrera L, Welsh E, Salinas MC (2012) Actinomycetoma and advances in its treatment. Clin Dermatol 30: 372-381.

3. Fahal AH, Rahman IA, El-Hassan AM, Rahman ME, Zijlstra EE (2011) The safety and efficacy of itraconazole for the treatment of patients with eumycetoma due to Madurella mycetomatis. Trans R Soc Trop Med Hyg 105: 127–132.

4. Zein HA, Fahal AH, Mahgoub E, S, El Hassan TA, Abdel-Rahman ME (2012) Predictors of cure, amputation and follow-up dropout among patients with mycetoma seen at the Mycetoma Research Centre, University of Khartoum, Sudan. Trans R Soc Trop Med Hyg 106: 639-644.

5. Kresch-Tronik NS, Carrillo-Casas EM, Arenas R, Atoche C, Ochoa-Carrera IL, et al. (2012) Nocardia harenae, an uncommon causative organism of mycetoma: report on two patients. J Med Microbiol 61: 1153-1155.

6. Welsh O, Vera-Cabrera L, Welsh E, Salinas-Carmona MC, Ocampo-Candiani J, et al. (2012) Nocardia harenae, an uncommon causative organism of mycetoma: report on two patients. J Med Microbiol 61: 1153-1155.

7. Welsh O, Vera-Cabrera L, Carrillo-Casas EM, Arenas R, Atoche C, Del Rio-Avila C, et al. (2013) First case of mycetoma associated with Nocardia takedensis. J Dermatol 40: 135–136.

8. Brown-Elliott BA, Brown JM, Cornille PS, Wallace RJ Jr (2006) Clinical and laboratory features of the Nocardia spp. based on current molecular taxonomy. Clin Microbiol Rev 19: 259–282.

9. Vera-Cabrera L, Campos-Riveros MP, Escalante-Fuentes WG, Pucci MJ, Ocampo-Candiani J, et al. (2010) In vitro activity of ACH-702, a new isoxazolquinolone, against Nocardia brasiliensis compared with cefazolin and the carbapenems imipenem and meropenem alone or in combination with clavulanic acid. Antimicrob Agents Chemother 54: 2191–2193.

10. Larrauain J, Idígoras P, Martín JM, Pérez-Trallero E (2011) Susceptibility of 186 Nocardia sp. isolates to 20 antimicrobial agents. Antimicrob Agents Chemother 55: 2995-2998.

11. Gomez-Flores A, Welsh O, Said-Fernandez S, Lozano-Garza G, Tavarez-Aguilera RE, et al. (2004) In vitro and in vivo activities of antimicrobials against Nocardia brasiliensis. Antimicrob Agents Chemother 48: 832-837.

12. Espinoza-Gonzalez NA, Welsh O, de Torres NW, Cavazos-Rocha N, Ocampo-Candiani J, et al. (2008) Efficacy of DA-7216, a new oxazolidinodione produrg, in the treatment of experimental actinomycetoma produced by Nocardia brasiliensis. Molecules 13: 31-40.

13. Vera-Cabrera L, Rodriguez-Quintanilla MA, Boiron P, Salinas-Carmona MC, Welsh O (1998) Experimental mycetoma by Nocardia brasiliensis in rats. Journal of the Mexican Dermatological Society 3: 183–187.

14. Almaguer-Chávez JA, Welsh O, Lozano-Garza HG, Said-Fernández S, Romero-Díaz VJ, et al. (2011) Decrease of virulence for BALB/c mice produced by continuous subculturing of Nocardia brasiliensis. BMC Infect Dis 11: 290.

15. Gonzalez-Ochoa A, Shields J, Vázquez P (1952) Acción de la 4-4 diamino-12-

16. Mahgoub ES (1972) Treatment of actinomycetoma with sulphamethoxazole and neem oil. J Dermatol 186 (4): 179-181.

17. Black RE, Lau WK, Weinstein RJ, Young LS, Hewitt WL (1976) Ototoxicity of aminoglycosides in man. J Infect Dis 134: 173–179.

18. Escorcia-Ortiz G, Medina-Perez Y, Ponce de Leon J, et al. (2011) Decrease of virulence for BALB/c mice produced by continuous subculturing of Nocardia brasiliensis. BMC Infect Dis 11: 290.

19. Welsh O, Sauceda E, Gonzalez J, Ocampo J (1987) Amikacin alone and in combination with trimethoprim-sulfamethoxazole in the treatment of actinomycetoma. Bol Med Hosp Infant Mex 44: 109-113.

20. Welsh O (1989) Amikacina-Trimethoprim-Sulfamethoxazole en el tratamiento de actinomycetoma. VIII Congres International de Botanique; Paris, France.

21. Mahgoub ES (1972) Treatment of actinomycetoma with sulphamethoxazole and neem oil. J Dermatol 186 (4): 179-181.

22. Vera-Cabrera L, Gonzalez E, Rendon A, Ocampo-Candiani J, Welsh O, et al. (2011) Complete genome sequence of Nocardia brasiliensis ATCC 10898. J Bacteriol 193: 2761–2762.

23. Welsh O, Sauceda E, Gonzalez J, Ocampo J (1987) Amikacin alone and in combination with trimethoprim-sulfamethoxazole in the treatment of actino-

24. Estrada R, Cárdenas-Chávez G, López-Martínez R, Welsh O (2012) Eumycetoma. Clin Dermatol 30: 389–396.

25. de Hoog GS, van den Brink W, van Belkum A, de Hoog G (2008) Clinical and in vitro antifungal susceptibility of the species. Med Mycol 46: 318–332.

26. Badalí H, Najafzadeh MJ, van Erobek M, van den Enden E, Tarzabie BO, et al. (2010) The clinical spectrum of Exophiala jeansiemei, with a case report and in vitro antifungal susceptibility of the species. Med Mycol 48: 1318–1327.

27. Zeng J, Kamei K, Zheng Y, Nishimura K (2004) Susceptibility of Pseudal-

28. Estrada R, Salvatierra J, López-Martínez R, Welsh O, et al. (2011) Decrease of virulence for BALB/c mice produced by continuous subculturing of Nocardia brasiliensis. BMC Infect Dis 11: 290.

29. Verma R, Misra S, Samanta M, Aggarwal RK (2012) Eumycetoma. Clin Dermatol 30: 389–396.

30. Carrillo AJ, Guarro J (2001) In vitro activities of four novel triazoles against clinical Scedosporium isolates. Antimicrob Agents Chemother 45: 2456–2458.

31. Fothergill AW, Rinaldi MG, Sutton DA (2009) Antifungal susceptibility testing of agents of black grain eumycetoma. J Med Vet Mycol 47: 1011–1019.
52. Mahgoub ES (1978) Experimental infection of athymic nude New Zealand mice, nu nu strain with mycetoma agents. Sabouraudi 16: 211–216.
53. Ahmed AO, van Vianen W, ten Kate MT, van de Sande WW, van Belkum A, et al. (2003) A murine model of Madurella mycetomatis eumycetoma. FEMS Immunol Med Microbiol 37: 29–36.
54. Capilla J, Guarro J (2004) Correlation between in vitro susceptibility of Scedosporium apiospermum to voriconazole and in vivo outcome of scedosporiosis in guinea pigs. Antimicrob Agents Chemother 48: 4009–4011.
55. Capilla J, Serena G, Pastor FJ, Ortorena M, Guarro J (2003) Efficacy of voriconazole in treatment of systemic scedosporiosis in neutropenic mice. Antimicrob Agents Chemother 47: 3976–3978.
56. Gonzalez GM, Tijerina R, Najvar LK, Bocanegra R, Yeh IT, et al. (2002) Experimental murine model of disseminated Pseudallescheria infection. Med Mycol 40: 243–248.
57. Gonzalez GM, Tijerina R, Najvar LK, Bocanegra R, Rinaldi MG, et al. (2003) Activity of posaconazole against Pseudallescheria boydii in vitro and in vivo assays. Antimicrob Agents Chemother 47: 1436–1438.
58. Lelievre B, Legras P, Godon C, Franconi F, Saint-Andre JP, et al. (2013) Experimental models of disseminated scedosporiosis with cerebral involvement. J Pharmacol Exp Ther 345: 190–205.
59. Calvo E, Pastor FJ, Guarro J (2010) Antifungal therapies in murine disseminated phaeohyphomycoses caused by Exophiala species. J Antimicrob Chemother 65: 1455–1459.
60. Graybill JR, Najvar LK, Johnson E, Bocanegra R, Leebenberg D (2004) Posaconazole therapy of disseminated phaeohyphomycosis in a murine model. Antimicrob Agents Chemother 48: 2288–2291.
61. Al-Abdely HM, Najvar LK, Bocanegra R, Guarro J (2004) Correlation between in vitro susceptibility of Pseudallescheria boydii and in vivo outcome of scedosporiosis in a murine model. J Antimicrob Chemother 54: 1701–1707.
62. Pasqualotto AC, Denning DW (2008) New and emerging treatments for fungal infections. J Antimicrob Chemother 61, Suppl 1: i9–30.
63. De Sarro A, La Camera E, Fera MT (2008) New and investigational triazole agents for the treatment of invasive fungal infections. J Antimicrob Chemother 60: 661–671.
64. Mahgoub ES, Guama SA (1984) Ketoconazole in the treatment of eumycetoma due to Madurella mycetomatis. Trans R Soc Trop Med Hyg 78: 376–379.
65. Andreu JM (1986) [Value of ketoconazole in combination with the surgical treatment of fungal mycetoma]. Chirurgie; memoires de l’Academie de chirurgie 112: 163–169.
66. Venugopal PV, Venugopal TV (1993) Treatment of eumycetoma with ketoconazole. Australas J Dermatol 34: 27–29.
67. Food and Drug Administration (2013) Postmarket Drug Safety Information for Patients and Providers. Available: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm357101.htm. Accessed 15 July 2014.
68. Diaz M, Negroni R, Montero-Gri F, Castro LG, Sampaio SA, et al. (1992) A Pan-American 5-year study of flucytosine therapy for deep mycoses in the immunocompetent host. Pan-American Study Group. Clin Infect Dis 14 Suppl 1: S68–S76.
69. Resnik BI, Burdick AE (1995) Improvement of eumycetoma with itraconazole. J Am Acad Dermatol 33: 917–919.
70. Paugam A, Tourte-Schaefer C, Keita A, Chemla N, Chevrolet A (1997) Clinical cure of fungal madura foot with oral itraconazole. Carin 66: 191–193.
71. Smith EI, Kushi S (1997) Improvement of eumycetoma with iraconazole. J Am Acad Dermatol 36: 279–280.
72. Lacroix C, de Kerviler E, Morel P, Derouin F, Feuillade de Chavain M (2005) Madurella mycetomatis mycetoma treated successfully with oral voriconazole. Brit J Dermatol 152: 1067–1068.
73. Louderque P, Hot A, Dannahou E, Dallet A, Poiree S, et al. (2006) Successful treatment of black-grain mycetoma with voriconazole. Am J Trop Med Hyg 75: 1106–1107.
74. Negroni R, Tobon A, Bastamante R, Shikanai-Yasuda MA, Patino H, et al. (2005) Posaconazole treatment of refractory eumycetoma and chromoblastomycosis. Rev Inst Med Trop Sao Paulo 47: 339–346.
75. Agger WA, Andres D, Burgess JW (2004) Exophiala jeannelseii infection in a heart transplant recipient successfully treated with oral terbinafine. Clin Infect Dis 38: e112–115.
76. Rallis E, Frangoulis E (2006) Successful treatment of subcutaneous phaeohyphomycosis owing to Exophiala jeannelseii with oral terbinafine. Int J Dermatol 45: 1369–1370.
77. N’Diaye B, Dieng MT, Perea A, Stockmeyer M, Bakshi R (2006) Clinical efficacy and safety of oral terbinafine in fungal mycosis. Int J Dermatol 45: 154–157.
78. Lackner M, De Man FH, Eygendaal D, Wintemans RG, Kluytmans JA, Klaassen CH, et al. (2011) Severe prothetic joint infection in an immunocompetent male patient due to a therapy refractory Pseudallescheria apiosperma. Mycosis 54: 22–27.
79. Moro F, Horreaux-Langlard G, Gay-Andrieu F, Talarmin JP, Haloun A, et al. (2010) Disseminated Scedosporium/Pseudallescheria infection after double-lung transplantation in patients with cystic fibrosis. J Clin Microbiol 48: 1978–1982.
80. Matsumoto Y, Oh IT, Nagai A, Ohyama F, Ooshii T, et al. (2009) Case of cutaneous Scedosporium apiospermum infection successfully treated with voriconazole. J Dermatol 36: 98–102.
81. Rogasi PG, Zanazzi M, Nocentini J, Fantoni E, Trotta M, et al. (2007) Disseminated Scedosporium apiospermum infection in renal transplant recipient: long-term successful treatment with voriconazole: a case report. Transplantation proceedings 39: 2033–2035.
82. Nesky MA, McDougal EG, Peacock JE Jr (2000) Pseudallescheria boydii brain abscess successfully treated with voriconazole and surgical drainage: case report and literature review of central nervous system pseudallescheriasis. Clin Infect Dis 31: 673–677.
83. Porte L, Khantri S, Haji LE, Cassaing S, Berry A, et al. (2006) Scedosporium apiospermum mycetoma with bone involvement successfully treated with voriconazole. Trans R Soc Trop Med Hyg 100: 891–894.
84. Troke P, Aguirrebengoa K, Artega C, Ellis D, Heath CH, et al. (2008) Treatment of scedosporiosis with voriconazole: clinical experience with 107 patients. Antimicrob Agents Chemother 52: 1743–1750.
85. Mellinghoff IK, Winston DJ, Mukwaisa T, Schiller GJ (2002) Treatment of Scedosporium apiospermum brain abscesses with voriconazole and surgical drainage: case report. Antimicrob Agents Chemother 47: 3976–3978.
86. Food and Drug Administration (2012) Drugs at FDA. Itraconazole. Available: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020083s048s049s050sbl.pdf. Accessed 15 July 2014.
87. Greer ND (2007) Posaconazole (Novafill): a new triazole antifungal agent. Proc (Bayl Univ Med Cent) 20: 185–196.

---

Please note that the above text is a natural representation of the content, assuming it is in the context of a scientific discussion about the treatment of fungal infections with various antifungal agents. The text includes references to studies and clinical reports on the efficacy of different antifungal drugs in treating mycetoma and other fungal infections.