Sporotrichosis: an update on epidemiology, etiopathogenesis, laboratory and clinical therapeutics*

Rosane Orofino-Costa [1,4]
Anderson Messias Rodrigues [3]
Priscila Marques de Macedo [2]
Andréa Reis Bernardes-Engemann [1,4]

DOI: http://dx.doi.org/10.1590/abd1806-4841.2017279

Abstract: In the late 90's there was a change in both the route of transmission and the people at risk for sporotrichosis. This zoonotic cat-man alternative transmission route elicited changes in strategies to control the epidemic. There was a progressive increase in the number of cases involving especially children and the elderly. In addition to becoming hyperendemic, uncommon clinical pictures like immunoreactive clinical presentations or severe systemic cases have emerged. New species were identified and classified through molecular tools using more virulent clinical isolates, like *S. brasiliensis*, compared to the environmental isolates. Likewise, different species of *Sporothrix* have been associated with different geographic regions. The serological and molecular techniques are used as an auxiliary tool for the diagnosis and/or for species identification, although the isolation and the identification of *Sporothrix* spp. in clinical specimen is still the gold standard. Currently sporotrichosis epidemics requires the knowledge of the epidemiological-molecular profile to control the disease and the specific treatment. Itraconazole, potassium iodide, terfinafine, and amphotericin B are the available drugs in Brazil to treat sporotrichosis. The drug of choice, its posology, and treatment duration vary according to the clinical presentation, the *Sporothrix* species, and host immune status. New treatment choices, including a vaccine, are being developed; nevertheless, more clinical trials are required to confirm its efficacy.

Keywords: Diagnosis; Epidemiology; Molecular biology; Serology; *Sporothrix*; Therapeutics

INTRODUCTION

Sporotrichosis is a subacute or chronic infection, caused by thermodimorphic fungi of the genus *Sporothrix*. It is a cosmopolitan disease, occurring preferably in tropical and subtropical regions, and is considered the most frequent subcutaneous mycosis in Latin America, where it is endemic.[1]

Sporotrichosis was first described in 1898, by the medical student Benjamin Schenck, at the Johns Hopkins Hospital, in Baltimore, USA.[2] The fungus isolated from skin lesions on the right upper limb of a patient treated by Schenck was evaluated by the pathologist Erwin F. Smith, and identified as a species belonging to the genus *Sporotrichum*. In 1900, Hektoen and Perkins reported another case in Chicago and proposed a new name, *Sporothrix schenckii*, although *Sporotrichum schenckii* was used for decades.[3] Due to the reproduction characteristics of this genus, the binomial was changed to *Sporothrix schenckii*.[4] Currently, the species involved in the human or animal disease, and other that are environmental, have been recognized.[5]

In the early 20th century, in France, sporotrichosis was a common disease, as were the reports of the extracutaneous clinical forms.[3] In Brazil, Lutz and Splendore firstly described infections in rats and humans, demonstrating the presence of asteroid bodies in tissues, which are useful for the histopathological diagnosis of this mycosis.[6]

EPIDEMIOLOGY AND ETIOPATHOGENESIS

For a long time, sporotrichosis was known as the "rosebush mycosis", or the "gardener's mycosis", given that the infection usually resulted from the agent's inoculation on the skin or mucous

Received on 11.05.2017.
Approved by the Advisory Board and accepted for publication on 23.07.2017.
* Work performed at the Dermatology Department, Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro (FCM-UERJ), Rio de Janeiro, RJ, Brazil.
Financial support: None
Conflict of interests: None

1 Dermatology Department, Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro (FCM-UERJ), Rio de Janeiro, RJ, Brazil.
2 Infectious Dermatology Clinical Research Laboratory, Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz (INI/Fiocruz), Rio de Janeiro, RJ, Brazil.
3 Laboratory of Emerging Fungal Pathogen, Department of Microbiology, Immunology and Parasitology, Universidade Federal de São Paulo (UNIFESP), SP, Brazil.
4 Medical Mycology Laboratory, Dermatology Department, Hospital Universitário Pedro Ernesto, Rio de Janeiro, RJ, Brazil.

membrane, by trauma with contaminated plant material. However, some cases of zoonotic transmission have been reported, as well as less frequent cases of inhaled infective fungal propagules, clinically presenting as a systemic mycosis.[7,8]

Occasionally, there may be an environmental transmission of sporotrichosis, classically associated with soil manipulation activities, whether for occupational or leisure reasons; in outbreaks such as those that occurred in the USA, especially in the Mississippi Valley, in the 80's, involving reforestation workers infected by pine trees and moss seedlings; also as microepidemics like that which occured in the early 90's, with people infected by the contact with hay stored in an abandoned house where *Halloween* parties were held; as well as large epidemics, such as that which occurred in the 40's, when three thousand miners in South Africa were infected by the contact with contaminated wood supporting beams, being considered the largest epidemic in the 20th century.[9-11] More recently, 457 cases were described between 2007 and 2009 in a province in the northeast China, where the disease is endemic.[12]

The zoonotic transmission of sporotrichosis was described sporadically involving accidents with snakes and birds, also mosquito, rat, horse, squirrel, and fish bites.[3,13,14] Epidemics were reported in Uruguay and, more recently, in Brazil and Argentina, related to armadillo hunting, given the close relation of the armadillo with the soil.[15,16] The importance of the cat in zoonotic transmission was first noticed when an outbreak involving five people exposed to a sick animal was reported.[17] In Brazil, the main zoonotic sporotrichosis outbreaks, involving humans and a small group of domestic cats, occurred in the states of São Paulo and Rio Grande do Sul, with an effective epidemiological control.[18,19]

In September 1997, the first cases of the greatest feline zoonotic transmission epidemic ever described were admitted at the Pedro Ernesto University Hospital, Rio de Janeiro. Three people from the same family were infected by a sick cat that died (authors' report, unpublished) (Figure 1). Then, the first publications about this epidemic, which is currently considered to be hyperendemic in the state of Rio de Janeiro, appeared.[20,21] The capital city and the surrounding municipalities known as "Baixada Fluminense" are currently the most affected places where poor socioeconomic conditions are observed. The epidemiological profile is mainly characterized by children, elderly, and women, because these groups usually have direct and more frequent contact with these animals.[22] Along with the consolidation of the urban epidemics, vulnerable patients also became a worrisome at-risk population, especially those infected by the human immunodeficiency virus.[23] Since 2013, the notification is mandatory in the state of Rio de Janeiro, but not in the other Brazilian states. Therefore, prevalence and incidence measures are obtained mainly based on cases reported in the literature, certainly underestimating the real epidemiological importance, especially regarding outbreaks and epidemics.

Although human or animal sporotrichosis cases were published in the states of Amazonas, Pará, Minas Gerais, Espírito Santo, São Paulo, Rio de Janeiro, Paraná, and Rio Grande do Sul, most cases occur in the South and Southeast Brazil.[24]

The advances in the microbiological knowledge along with the use of molecular tools led to important advances concerning epidemiological studies, enabling the identification of the *Sporothrix* species in 14 Brazilian states, indicating that sporotrichosis is more widespread than previously thought for the Brazilian territory.[24]

In Brazil, there are two important disease transmission routes for humans, a sapronotic route involving direct contact with the soil and decomposing organic matter; and a zoonotic route, in which felines participate actively in the disease transmission. The outbreaks from classic transmission route, in which *S. schenckii* and *S. globosa* prevail, required the removal of fungus sources in nature. The alternative transmission route, mainly involving horizontal animal transmission (cat-cat), as well as zoonotic transmission, requires different epidemic control strategies. Such measures include the street animals neutering and the treatment of sick cats, as well as the education about responsible ownership of animals, knowledge of the main aspect main aspects of *Sporothrix* transmission, especially in hyperendemic areas. Dead infected animals must be incinerated, rather than buried, thus avoiding *S. brasiliensis* dissemination in the soil and the pathogen progression in nature.

Even though sporotrichosis has been described worldwidely, there is a curious divergence regarding the geographic distribution and the incidence of the etiological agents.[25] Indeed, some spe-

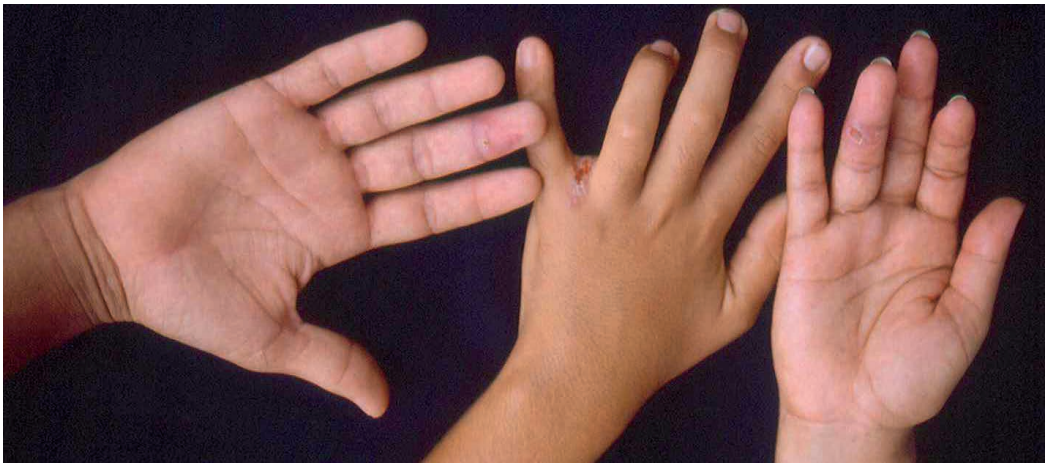

Figure 1:
Ulcerated lesions on the hands of three members of the same family, at the beginning of the zoonotic transmission sporotrichosis epidemics in Rio de Janeiro, in 1997, treated at Hospital Universitário Pedro Ernesto

cies are more ubiquitous than others. In Asia, especially China, *S. globosa* is estimated to be the etiological agent in 99.3% of the human sporotrichosis cases.[26,27] In other endemic areas, such as Australia and South Africa (94%), also in North America and part of South America (89%), *S. schenckii* is the predominant species.[26] In the South and Southeast Brazilian regions, *S. brasiliensis* (88%) is the main etiological agent of human and animal sporotrichosis.[28,29]

Over a century, since 1898, *Sporothrix schenckii* was described as the unique species responsible for the sporotrichosis cases.[2,30] However, the advent of molecular biology techniques, directly applied to fungus taxonomy researches, demonstrated that the classic agent *S. schenckii actually* consists of a group of cryptic species, phylogenetically related. Currently, *Sporothrix* comprises 51 taxons, divided into a clinical clade (mostly human pathogens), including *S. brasiliensis*, *S. schenckii*, *S. globosa*, and *S. luriei,* an environmental clade, composed by some other species complexes, such as *S. pallida* and *S. candida* with five species each, *S. inflata* with three species, *S. gossypina* with 12 species, and *S. stenoceras* with six species (Figure 2).[31,32]

It is noteworthy that such a phylogenetic split is accompanied by different ecological behaviors, considering that *S. schenckii* and *S. globosa* have already been isolated from humans, animals, and soil.[33,34] Attempts to isolate *S. brasiliensis* from the soil have not been successful. However, this species is frequently isolated from human and feline clinical samples.[28,35] *Sporothrix luriei* is a rare human sporotrichosis agent described from a single clinical isolate in South Africa.[36,37] Historically, the overlapping of phenotypical characteristics has led to incorrect identification based only on micromorphological analyses of environmental species.

Environmental clade of *Sporothrix* species are rarely agents of human sporotrichosis, causing opportunistic infections. The infection route also involve traumatic inoculation of fungal propagules present in soil and organic matter. The *S. pallida* complex consists of five soil species, three of which are rare agents of human infection: *S. chilensis*, *S. mexicana,* and *S. pallida.*[38-40] The environmental clade also includes *S. stenoceras* identified from cutaneous lesions in humans.[41] These environmental species are usually low-virulence organisms to the warm-blooded, vertebrate host.[38,42]

Sporothrix spp. are thermodimorphic fungi, presenting the filamentous form (saprophytic phase) in nature or *in vitro* at 25°C, and developing yeast-like cells (parasitic phase) in the mammal host or *in vitro* at 35-37°C.[43] This temperature-induced transition is an important morphological adaptation for the infection in mammals. The mycelium-to-yeast conversion occurs successfully among the species within the clinical clade (*S. brasiliensis*, *S. schenckii*, *S. globosa*,

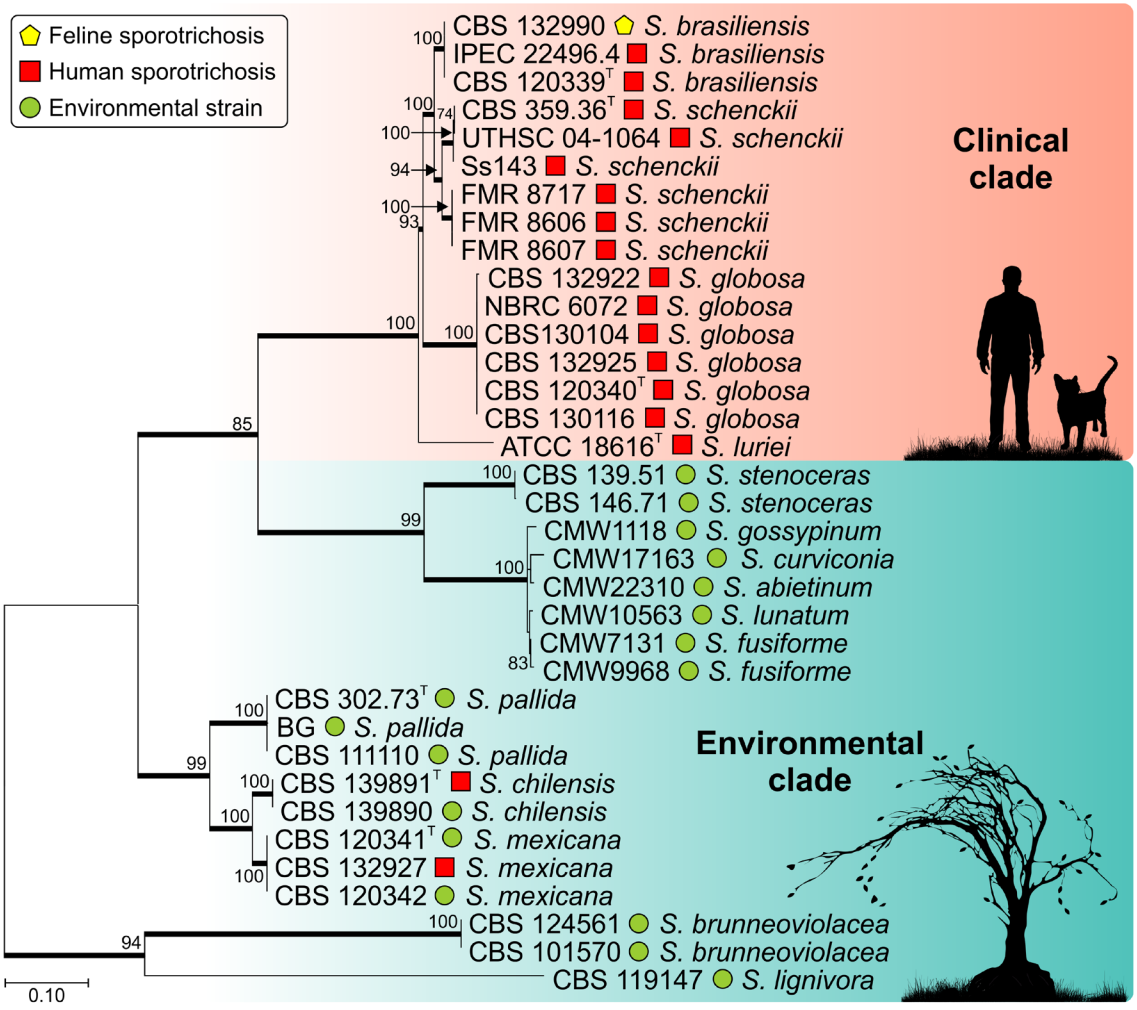

Figure 2: Phylogenetic relations between the clinical and environmental clade members in *Sporothrix*, based on calmodulin sequences (exon 3-5). Available at GenBank (https://www.ncbi.nlm.nih.gov/genbank/). Method: Maximum likelihood The numbers close to the branches refer to resample percentages (1000 bootstrap)

and *S. luriei*), while the environmental species (*S. inflata*, *S. humicola*, *S. pallida*, *S. mexicana*, *S. chilensis*, among others) show deficient morphological transition, producing few yeast-like cells. Perhaps, the successful emergence of *S. brasiliensis* in mammals, as well as the low virulence of environmental species may be related to the thermotolerance or thermosensitivity of these species, respectively.[44] Another important virulence factor is the *Sporothrix* ability to produce melanin. Melanin induces fungal escape from the host's defenses, and is also considered a resistance factor against some antifungal drugs, such as amphotericin B, itraconazole and terbinafine.[45,46]

The virulence profiles change depending on the pathogen characteristics and the host defenses. *Sporothrix brasiliensis* is the most virulent species, due to its ability to invade tissue and lead to death, whereas *S. schenckii* has different levels of virulence and *S. globosa* exhibits little or no virulence in murine models.[42,47-49] The environmental species of *Sporothrix* present low virulence in murine models, with low invasive potential, and the host is able to control the infection a few weeks after inoculation.[38,42]

The host's defense against the *Sporothrix* species has not yet been established. The fungus' cell wall components, especially the 70kDa glycoprotein (gp70), has a protective effect in the host, mediated by T-helper cells (Th1 in humans), but paradoxically, it also makes the adherence of conidia to the epithelium, increasing fungal invasive potential. The cell-mediated immune response seems to be responsible for eliminating or controlling infection. However, the humoral immune response elicits specific antibodies against the *Sporothrix'* cell wall.[5,50] The dissemination of sporotrichosis is usually related to cellular immunity deficiencies, such as AIDS.[51]

CLINICAL ASPECTS

Usually, the clinical manifestations of sporotrichosis are divided into cutaneous and extracutaneous, the former is more frequent.[22] After the zoonotic sporotrichosis epidemic in the state of Rio de Janeiro, new clinical presentations, uncommon until then, were identified. For this reason, a new classification was proposed, to better describe the clinical features of the patients cared by the reference sporotrichosis teams.[52] In the present article, the authors propose an update of this clinical classification based on the group's expertise (Table 1).

Nearly 80% of the affected patients present the lymphocutaneous form.[52] Initially, the lesion has a papulonodular appearance where the fungus was introduced into the skin, appearing between two to four weeks after the trauma. Afterwards, the lesion may ulcerate, and fistulize draining a purulent discharge. This is so-called the inoculation chancre. The lesions, usually nodules, progress along the regional lymphangitic channels, upwards or downwards depending on the anatomical site, after some weeks. Later, these nodules, may ulcerate, fistulize, and heal, caractherizing a gumma (Figures 3A and 3B). The fixed cutaneous form consists of a single lesion, usually similar to the inoculation chancre, with no regional lymphatic spreading (Figure 3C). In some occasions, the disease may appear as larger ulcers with well-defined and framed borders, or erythematous-scaly, papulopustular, vegetative, infiltrative, or crusty lesions (Figures 3D-F). Some patients exhibit multiple skin lesions, disseminated on the tegument, with no systemic invasion and polymorphic appearance, all of them arising at the same time. In general, these patients are immunocompetent individuals who describe having multiple traumas.

Although any mucous membrane may be affected by sporotrichosis, the ocular mucosa is more commonly involved, causing conjunctivitis, episcleritis, uveitis, choroiditis, and retrobulbar lesions, among others (Figure 4A).[53-55] When the lacrimal duct is affected, dacryocystitis may occur as sequela.[56,57] The retrobulbar lesions, such as chorioretinitis, are more frequently related to hematogenous spread, and anterior lesions are associated with the fungal innoculation. The simultaneous affection of the ocular mucosa and the regional lymph nodes is not rare, and it is one of the causes of the Parinaud syndrome.[58]

The bones and joints may be involved by direct trauma, by the invasion through a preexisting overlying cutaneous lesion or secondary to a hematogenous spreading, the latter at highest risk of sepsis due to the deep site of infection. Osteoarticular sporotrichosis may appear as a monoarthritis associated or not with an overlying cutaneous lesions, as well as bone resorption and osteolytic lesions in the most severe cases.[59,60] The synovial fluid exhibit increased cellularity mostly consisting of polymorphonuclear leukocytes, low glucose and high protein levels.

The respiratory transmission through the inhalation of *Sporothrix* propagules is acceptable, characterizing the primary pulmonary systemic form of sporotrichosis. The lungs may also be affected by the hematogenous spread, mainly in immunosuppressed patients presenting with the disseminated systemic form of sporotrichosis. The signs and symptoms may include coughing, dyspnea,

Table 1: Clinical classification of sporotrichosis

Skin	
	Lymphocutaneous
	Fixed cutaneous
	Multiple inoculation
Mucous membrane	
	Ocular
	Nasal
	Others
Systemic	
	Osteoarticular
	Cutaneous disseminated
	Pulmonary
	Neurological
	Other locations/sepsis
Immunoreactive	
	Erythema nodosum
	Erythema multiforme
	Sweet's syndrome
	Reactive arthritis
Spontaneous regression	

Modified from: Lopes-Bezerra, *et al.* 2006.[52]

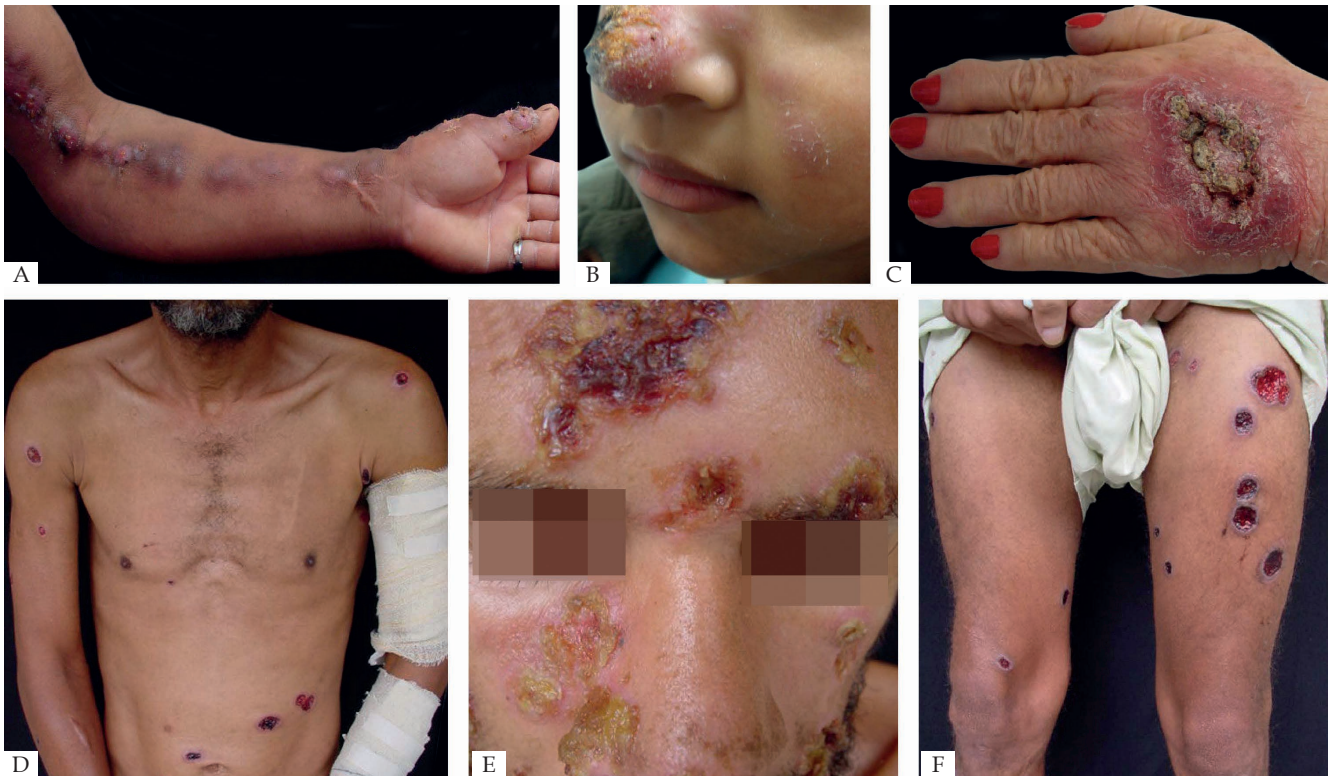

Figure 3: A. Lymphocutaneous form in adults (ascending lymphangitis); **B.** lymphocutaneous form in a child's face (descending lymphangitis); **C.** fixed cutaneous form on the back of the hand; **D, E, F.** systemic form with disseminated skin lesions in an AIDS patient

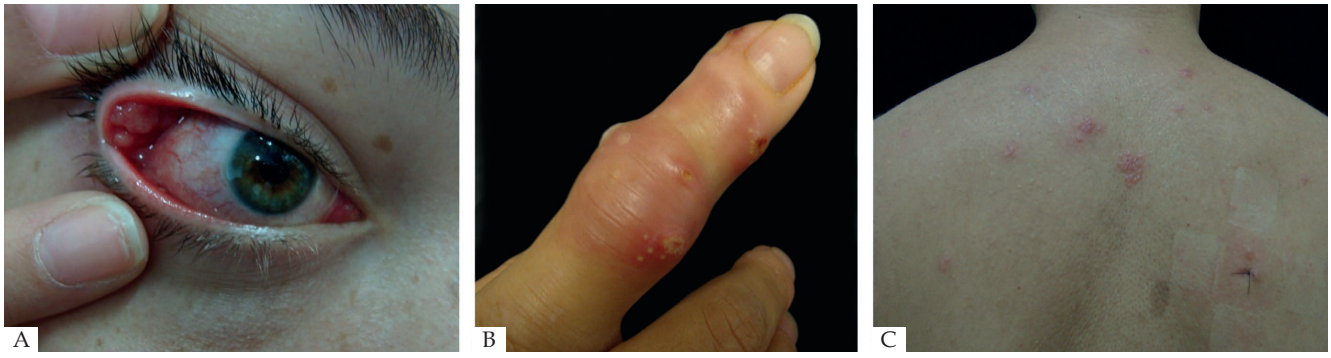

Figure 4: A. Granulomatous lesion at the upper eyelid ocular conjunctiva; **B.** primary lymphocutaneous lesion on the finger; and **C.** pseudovesicular lesions over an erythematous plaque on the back of the same patient - Sweet's syndrome (immunoreactive form)

hemoptoic, etc, depending on the type and site involved. Radiologic images, such as chest-radiography or computerized tomography, show diverse features. The upper lobes are mostly affected, presenting cavitary, reticulonodular infiltrative, or even fibrosis or tumoral aspects.[61-64] Probably the disease is misdiagnosed in areas with high endemicity, either due to the lack of knowledge by the medical doctors, or to the unspecific clinical signs and symptoms.[65]

The imunosuppressed patients are at higher risk for bloodstream dissemination of sporotricosis due to alcoholism, or the chronic use of illicit drugs, the use of immunosuppressive medication, or secondary to immunodeficiency such as AIDS. In theses cases the bones and joints, the lungs and central nervous system, in addition to the skin and mucous membranes, are preferably affected, although any organ may be involved (Figures 3D-F). These patients also show heterogenous and polymorphic tegumentary lesions, and must have a special attention in their medical care, particularly AIDS. Moreover, they may develop systemic manifestations that include severe bone lesions, hematogenous disseminated skin and mucosal lesions, lung and spleen involvement, as well as the neurotropism shown by *S. brasiliensis*. They may progress to sepsis, leading to death.[51,64,66] Curiously, systemic sporotrichosis reports in transplanted patients are not frequent. Similar to American tegumentary leishmaniasis, which is an important differential diagnosis, the centrofacial region is commonly affected in immunocompromised patients (authors' note).

At the other end, as occurs in other infectious diseases, some patients heal spontaneously, while others develop hypersensitivity clinical forms, such as erythema nodosum, erythema multiforme, and Sweet's syndrome due to an exacerbated immune response against the fungus. Also, reactive arthritis can occur, it is usually polyarticular and migratory, frequently disappearing with the specific treatment for sporotrichosis (Figures 4B-C).[67-69]

In general, the lesions heal leaving fibrotic scars that may alter the organ function depending on the site of infection, for instance, the tear duct or the lungs. Unaesthetic scars are particularly important in younger patients, especially in exposed areas, given that the disease leads to fibrosis, sometimes causing tissue or hair loss, such as eyelashes, in the case of bulbar conjunctival lesion.[52]

The children, the elderly, the pregnant women, and the immunosuppressed AIDS patients are groups that require a special attention.[70,71] Children generally have more prolonged and frequent contact with animals and, therefore, are commonly infected. Nevertheless, they also exhibit a greater immunological resistance with limited lesions such as the fixed form, usually on the face; exhibiting slightly elevated serological titers.[71] The facial contact with animals also predisposes this age group to ocular mucosal lesions. On the other hand, the task of taking care of animals is usually assigned to the elderly, especially females. In this age group, the host immune defense is declining, which means that, in many times, there may be a more extensive and severe clinical presentation of the disease.

DIFFERENTIAL DIAGNOSIS

Due to the diversity of clinical presentations, sporotrichosis may be clinically similar to many other infectious and non-infectious diseases, both tegumentary and systemic. The most common are tegumentary leishmaniasis, pyodermitis, cat-scratch disease, cutaneous nocardiosis, chromomycosis, syphilis, rosacea, granuloma annulare, pyoderma gangrenosum, osteomyelitis, arthritis with a different etiology, such as rheumatoid, also cutaneous and pulmonary tuberculosis, tumoral lesions, especially in the lungs and in the central nervous system, and meningitis, besides others. In regions of high endemicity, the epidemiological background must be taken into consideration.

LABORATORY DIAGNOSIS

Mycology

The gold standard for the diagnosis of sporotrichosis is the isolation and the identification of the *Sporothrix* species from clinical samples such as skin lesions, biopsy, aspirated from floating abscesses, as well as sputum, pus, synovial fluid, blood, and cerebrospinal fluid.[8,72] It is a simple and low-cost diagnostic method, although it may not be useful for some systemic and atypical forms of sporotrichosis.[52,73]

Seldom, the direct microscopy (DM) made with potassium hydroxide (KOH) preparations, whether or not in dimethyl sulfoxide, exhibits fungal elements. When present in the tissue, *Sporothrix* spp. show several yeast-like structures, oval to round, and more commonly elongated, "cigar-shaped", measuring approximately 5-8 µm.[74] Compared to the culture, DM presents low sensitivity and specificity, being positive in sporotrichosis mainly in immunosuppressed patients.[75,76] Giemsa-stained smears, obtained from pus or biopsy imprints, enhance the test's sensitivity.[8] On the other hand DM is more sensitive in animals, particularly felines, due to the great amount of fungal cells in the tissues, exhibiting sensitivity of nearly 85% compared to the culture.[77] *Sporothrix* spp. grow in culture media used routinely, at room temperature (25ºC-30ºC), such as Sabouraud dextrose agar with chloramphenicol or gentamicin, added to inhibit bacteria; Mycosel agar containing cycloheximide, to reduce saprophytes, and BHI (Brain Heart Inffusion), an enriched medium.[8,76] *Sporothrix* spp. is usually isolated in 4-6 days, for samples collected from skin lesions, and in 10-19 days, for extracutaneous lesions; time can also vary depending on the species of *Sporothrix*.[73,76,78,79]

Colonies are identified phenotypically by the membranous appearance of the surface, off-white to cream color and a black halo, or they may be dark from the beginning, depending on the species, and on the nutritional and environmental conditions (Figure 5A). The colony microscopy of the clinical clade exhibit delicate branched septate hyaline hyphae, a conidiophore producing at the tip pyriform, oval to round, hyaline conidia, arranged sympodially as a bouquet, in addition to sessile pigmented conidia (Figure 5B).[33,74] The thermodimorphism of the *Sporothrix* species of clinical

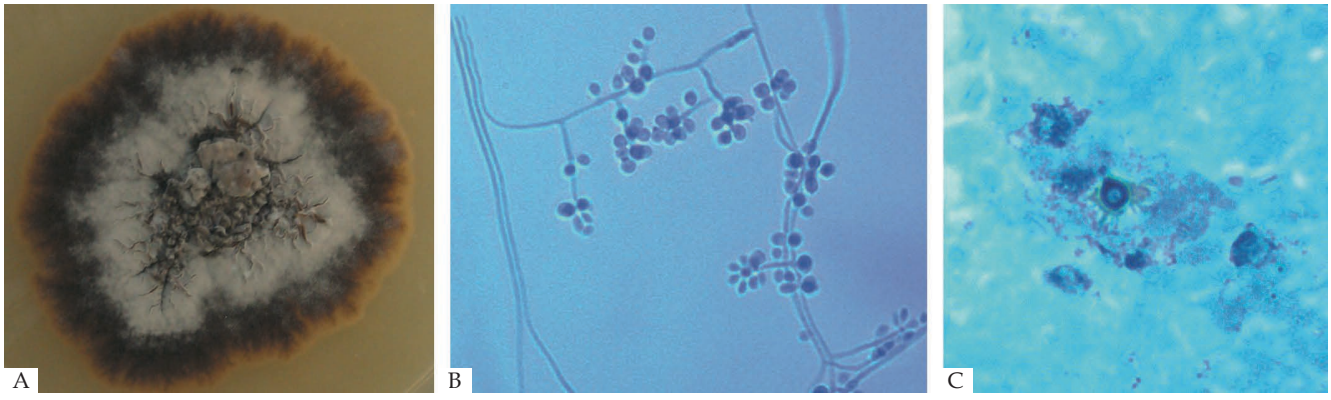

Figure 5: A. Macromorphology of *Sporothrix brasiliensis*; **B.** Micromorphology reveals delicate, hyaline septate hyphae, conidiophore that originates primary hyaline conidia in a bouquet arrangement (cotton blue, x400); **C.** Asteroid body (Grocott, X400)

interest is confirmed by reverting the mycelium-to-yeast form in BHI, after incubation at 37ºC. The yeast-like colony has a creamy color surface. For phenotypical confirmation of *Sporothrix* species, other culture media are used, such as *corn meal agar* to define the conidia shape and color. For instance, ovoid dematiaceous conidia suggest *S. brasiliensis*, while triangular conidia are characteristic of *S. schenckii;* it is also used to distinguish *S. mexicana* from *S pallida.*[33] In addition to the thermotolerance of the *Sporothrix* isolates, the *potato dextrose agar* (PDA), a culture media poor in nutrients, is useful in comparying fungal morphology and growth (measured by the colony's diameter). *Sporothrix brasiliensis* forms dark black fast growing colonies. Exceptionally, *Sporothrix* isolates grow at temperatures above 37ºC, regardless of the species.

Assimilation of sugars such as glucose, raffinose, ribitol, and sucrose are some of the carbon compounds used in physiological tests; the *Sporothrix* isolates show different pattern of assimilation.[79]

Histopathology

The sensitivity of histopathology test in humans is low due to the paucity of fungal elements in the tissue. The inflammatory infiltrate is better observed by hematoxilyn-eosin stain, and PAS or methenamine silver is used to identify the fungal structures.[8] According to the literature, fungal structures are present in 18 to 35.3% of the cases, depending on the technique.[76,80,81] The tissue reaction consists of diffuse chronic granulomatous dermatitis, many times with a central abscess. The histological sections may exhibit hyperkeratosis, acanthosis, and intraepidermal microabscesses. The granuloma in palisade arrangement, consisting of a neutrophil and eosinophil central area, an intermediate layer with mononuclear cells, and lymphocytes and plasmacytes at the most external area, may be observed in skin lesions.[82] The presence of asteroid bodies or Splendore-Hoeppli phenomenon may point to the diagnosis of sporotrichosis. It consists of an eosinophil material surrounding the fungal cell, probably a deposit of immunoglobulin attached to the microorganism wall. However, it can occur in other infectious or granulomatous diseases (Figure 5C).[8]

Serology

Different techniques of immunoelectrophoresis, agglutination, and immunodiffusion using crude antigenic fraction were proposed for the serodiagnosis of sporotrichosis, but the sensitivity and specificity were low.[83,84] Consequently, they were replaced by more sensitive tests, such as the immunoenzymatics, especially ELISA (*Enzyme Linked Immuno Sorbent Assay*) and Western blotting, both with faster results. The use of serology, a fast and non-invasive test for the diagnosis of sporotrichosis, was possible when specific antigens were characterized and standardized. These tests are used as auxiliary tools for cutaneous forms and to diagnose systemic manifestation or atypical forms of sporotrichosis. They are useful for screening, to control treatment follow up and drug withdrawn in difficult clinical presentations. Serum antibody titers may also monitor relapses.[52,85-87]

Serological ELISA test using the *Ss*CBF (*Sporothix schenckii* Con A-Binding Fraction), a cell wall antigen from the yeast phase of *S. schenckii*, has proven efficient for the detection of IgG antibodies in the serum of patients with cutaneous sporotrichosis.[88] Tests performed in serum samples of patients with different clinical sporotrichosis forms resulted in high sensitivity and specificity rates, 90% and 80% respectively, in addition to high reactivity in feline serum samples.[85,89] ELISA test using the *Ss*CBF exhibited reactivity with other clinical specimens, such as cerebrospinal and synovial fluid, with high positivity and low cross-reaction rates.[59,85] There is an effective clinical-serological correlation which allow therapeutic monitoring, and can be used whether to maintain or suspend the treatment of difficult cases.[57,67,71] An exoantigen isolated from the filamentous form of *S. schenckii* was used in the ELISA test, with 97% of sensitivity, and 89% of specificity, when evaluating different serum samples from patients with sporotrichosis.[86]

Two other important cell wall components in *Sporothrix* spp have been studied as new biomarkers for sporotrichosis diagnosis, the glycoproteins of 60 kDa and 70 kDa, identified as 3-carboxy-muconate cyclase of the *Sporothrix proteome,* as glycoforms and isoforms.[5] Such glycoproteins seem to behave as a factor of virulence, they are expressed in the most virulent *Sporothrix* isolates, and contribute to the fungus adherence and immunomodulation.[48,90-93] The produced mAb P6E7 antibody against the gp70 caused *in vivo* protection through passive immunization of mice infected with *S. schenckii*. It is considered to be a strong candidate for a therapeutic vaccine against sporotrichosis.[91,94]

These tests are not commercially available, being restricted to certain research centers, especially due to the lack of Public Health financing in Brazil, where sporotrichosis is endemic or hyperendemic, depending on the country region.

Molecular

The phenotypical identification of the different *Sporothrix* species have, as a disadvantage, the use of tools that are usually laborious, longstanding, with variable results, especially for the species inserted in the clinical clade, which could lead to incorrect identification.[39,95-97] Nowadays, the molecular boundaries among the *Sporothrix* spp. are defined, enabling the development of numerous genetic markers for recognition and identification of clinical specimens.[44] The development of fast and low-cost genotyping methods is important for diagnosis, as well as for epidemiological studies, considering that the pathogenic species in *Sporothrix* differ in terms of their geographical range, virulence, and susceptibility to antifungal drugs.

DNA sequencing - PCR (*Polymerase Chain Reaction*) technique. The identification of *Sporothrix* isolates with clinical interest, which frequently infect the vertebrate host, may be performed by the amplification and partial sequencing of ribosomal operon, including the ITS1, 5.8s, and ITS2 regions. The ITS (*Internal Transcript Spacer*) region operates as a universal marker for the identification of *Sporothrix*.[31] The human and animal origin specimens are distributed in the *S. brasiliensis*, *S. schenckii*, *S. globosa*, and *S. luriei* clades.[32] The environmental *Sporothrix* species are located at a relatively large phylogenetic distance. However, it is worth noticing that, in the environmental clade, in addition to the ITS region, the use of protein coding genes for the recognition of cryptic species, especially in the *S. pallida complex,* will be required.[38] Protein coding genes, such as the beta-tubulin (*BT2*), calmodulin (*CAL*), and the elongation factor 1α (*EF-1α*) may be used to increase the taxonomic resolutions among the clinical interest species, or even to identify rare agents

within the *S. pallida* complex, in the environmental clade, such as *S. pallida*, *S. mexicana*, and *S. chilensis*. The region between the 3 and 5 exons of the calmodulin gene appears as the main marker for recognition of clinical interest *Sporothrix*.[98-101] In addition to the possibility of identifying the infectious agent, protein-coding genes are commonly used in studies on genetic diversity, population structure, and molecular epidemiology of sporotrichosis.[29]

PCR-RFLP - the amplification of a target sequence in the fungus genome by means of PCR, followed by amplicon digestion with one or a combination of restriction enzymes (RFLP), has been successfully used to detect inter- and intra-specific variability in several fungus species. In clinical interest *Sporothrix* spp., the identification of morphologically similar species becomes possible with the use of PCR-RFLP. After the partial amplification of the calmodulin gene (exon 3-5), the amplicon digestion with the *Hha*I enzyme takes place, producing five different restriction profiles (species-specific), representing all species with medical importance.[102] Some important advantages of this technique include low-cost, fast and easy execution, associated with the absence of need for advanced instruments.

Species-specific PCR - the identification of *Sporothrix* spp. may be performed by means of PCR, by using *primers* that selectively amplify DNA from *S. brasiliensis*, *S. schenckii*, *S. globosa*, *S. mexicana*, *S. pallida*, and *S. stenoceras*.[103] Therefore, the *primer* sequences are preserved within a single target species and inter-specifically divergent. This technique is a low-cost, fast and robust molecular tool, capable of detecting and identifying small pathogen DNA based on isolated specimens, as well as complex biological samples (biopsy, soil, mixed cultures, etc.), with no need to isolate the pathogen.

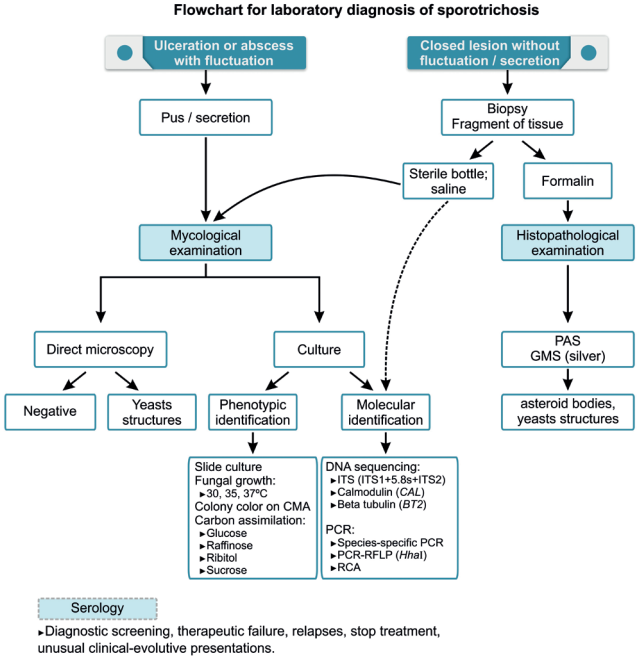

Figure 6: Flowchart for laboratory diagnosis of sporotrichosis. GMS (Gomori *methenamine silver*); CMA (corn meal agar); 'C' – carbon; ITS (*Internal Transcript Spacer*); PCR (*Polymerase Chain Reaction*)

Rolling Circle Amplification (RCA) is a method that provides high sensitivity and robustness, which may be applied from monosporic cultures to environmental samples, with potential for ecology studies.[104] The identification of *Sporothrix* based on RCA has proven to be a reliable identification tool, alternative to DNA sequencing, although little used in the mycological diagnosis, despite being a simple and powerful technique, capable of synthesizing large DNA amounts based on very low initial concentrations.[104,105]

Figure 6 represents a flowchart that synthesizes the techniques used for laboratory diagnosis of sporotrichosis.

TREATMENT

The choice of treatment for sporotrichosis depends essentially on the clinical form of the disease, the host's immunological *status*, and the species of *Sporothrix* involved.

Drug

Itraconazole, potassium iodide, terbinafine, and amphotericin B are the drugs currently available in Brazil for treating sporotrichosis. The first three are administered orally, while the last one is administered intravenously.

Itraconazole is considered the drug of choice due to its effectiveness, safety, and posologic convenience, and it is classified having an AII scientific evidence level.[72,106] It is a fungistatic drug that acts by inhibiting the synthesis of ergosterol in the fungus cell wall. It may be used in healthy patients with limited lesions, as well as in immunosuppressed patients and in the systemic form, but not in life-threatening cases of dissemination/sepsis. It is offered in 100mg capsules and must be administered along with the main meals, for better absorption. The dose ranges from 100 to 400mg/day, depending on the disease severity. The treatment should be started with 100mg/day, which is effective in most cases. It may be administered continuously or intermittently (pulse).[107] The main adverse effects reported are headache and gastrointestinal disorders, which are, in most cases, tolerable. It is hepatotoxic, teratogenic, and embryotoxic, and may not be used in patients with liver diseases or in pregnant women (risk category C). Its greatest disadvantage is the possibility of drug interaction, as a consequence of the dependent metabolism on CYP 3A4 common to other several drugs. It may cause an increase or a reduction of serum drug concentrations frequently used by elderly patients usually affected, also these drugs may reduce or increase serum itraconazole levels. Childbearing women must be warned about the risk of oral contraceptive effect reduction. In addition, there is a risk of sudden death, especially in patients suffering from congestive heart failure, due to its negative inotropic effect on the cardiac muscle.[108] Complete blood count, biochemistry, and liver function tests should be performed prior to the treatment and after 3-4 weeks. If serum levels are whithin normal ranges, the tests should only be repeated at the end of the treatment.

Potassium iodide (KI) has been used for treating sporotrichosis, since 1903, as initially suggested by Saboraud.[7] At that time, specific antifungal drugs were not available and iodide was used for several infectious and non-infectious diseases. The KI mechanism of action is not yet completely understood, despite its already known action on the immune response, destructuring granulomas, on neutrophil chemotaxis, as well as on phagocytosis of

Sporothrix cells.[109,110] The scientific evidence level is AII, the same of itraconazole, and it may be prepared as saturated or concentrated solution. In the saturated solution, each drop contains 0.07g, and in the concentrated solution, 0.05g.[111] Doses of up to 4-6g/day for adults are recommended. However, a recent study has demonstrated that doses of 1-2g/day for children, and 2-4g/day for adults, administered t.i.d with milk, juice or yogurt are effective to cure most patients.[112] The treatment starts with lower doses, increasing daily in both intakes until the effective and tolerated dose is reached. This is especially useful for the elderly and for children, as it is available in the liquid form. KI is indicated for localized sporotrichosis cases in patients whose immunity is preserved, but it may also be used in immunoreactive forms, such as erythema nodosum or reactive arthritis, due to its immunomodulatory effect. It is contraindicated for patients with thyroid dysfunction, kidney failure, iodine allergy, autoimmune diseases, and in pregnant and nursing women (risk category D). Up to now, it is not indicated for patients who have deficiency of immune response, and extensive or systemic clinical manifestations. The main adverse events are metallic taste and nausea, followed by acneiform eruption. In addition to the laboratory tests for monitoring itraconazole use, for KI it is important to check the TSH and T4 serum levels during treatment, although a slight increase in TSH serum levels is considered to be physiological.[111]

Terbinafine, a fungicide allylamine that inhibits the synthesis of ergosterol in the fungus cell wall, is an excellent therapeutic option for patients with contraindications to itraconazole or KI use, as its effectiveness in the sporotrichosis treatment is well demonstrated.[113,114] This medication is metabolized through the CYP2D6, which is not involved in many other drugs, thus it exhibits fewer drug interactions, and it is especially useful for elderly patients with other comorbidities. It is available in tablets of 125 and 250 mg facilitating pediatric administration. The recommended dose is 250 mg/day, but it may be increased up to 500 mg/day for adults. The pediatric dose depends on the child's weight and is the same recommended for treating dermatophytosis. It may cause headaches, nausea, taste alteration, and neutropenia. Terbinafine is contraindicated for patients with lupus erythematosus, and is considered a risk category B drug during pregnancy. Its use has not yet been tested for other clinical forms other than the cutaneous. The laboratory exams are the same as those for monitoring the treatment with itraconazole.

In severe, life-threatening cases, amphotericin B, deoxycholate or, preferably, liposomal, is recommended until the clinical improvement has been achieved, when it should be replaced by itraconazole.[72] Amphotericin B is a polyene that links to the ergosterol of fungal membrane, modifying its permeability. When administered intravenously, amphotericin B is cardiotoxic and nephrotoxic, thereby requiring constant evaluation of kidney function and of the serum potassium levels. The total cumulative dose recommended ranges from 1 to 3g for deoxycholate presentation, or the corresponding liposomal dose. The precautions and types of amphotericin B administration for sporotrichosis treatment are the same as those used in other mycoses for which the drug is indicated. This is the only drug recommended for pregnant women with severe disease, given that it is not teratogenic, although it may worsen metabolic disorders that are already common during pregnancy. [115]

Sporotrichosis treatment must be maintained until the clinical cure is reached, which usually occurs within 2 to 3 months. It is not necessary to maintain the drug use for 1 to 3 months after the cure, as previously recommended. Clinical cure is considered when there is no disease's activity, such as pus, exsudation, or crust in the skin lesions, even if a discrete erythema, fibrosis, or milia appear during the healing process. Systemic forms require longer treatment, ranging from 6 to 12 months.[72]

Miscellaneous

The local heat was initially used to treat chromomycosis, it is based on the fungus' thermosensitivity, and may be useful when conventional drugs are contraindicated.[115,116] Cryosurgery using liquid nitrogen may be used as a therapeutic complement in refractory cases, especially when lesions are crusty and infiltrate, as well as in isolated cases of localized lesions in immunocompetent patients. Electrosurgery and surgical removal of small lesions constitute other therapeutic options in selected cases. All therapeutic methods described may be used as monotherapy or as adjuvant treatment. Photodynamic therapy was tested *in vivo* and *in vitro* for the treatment of skin sporotrichosis.[117]

Figure 7 shows basic steps to guide the therapeutic choice in sporotrichosis, and table 2 provides the summary of the main drugs administered in sporotrichosis and their corresponding doses.

Other considerations

There are important differences regarding *in vitro* sensitivity to the main antifungal drugs and the different etiological agents, reinforcing the importance of the correct identification for properly treating sporotrichosis. *Sporothrix brasiliensis* presents the best response to antifungal drugs, while *S. mexicana* is more tolerant to drug action.[118] Epidemiological analyses reveal that the *in vitro* susceptibility profile has been changing over time, emphasizing the emergence of *S. brasiliensis* isolates tolerant to itraconazole.[119] In this context, potassium iodide, terbinafine, and posaconazole may be alternative drugs against *S. brasiliensis*, especially in refractory cases, or for those with no satisfactory *in vivo* response to itraconazole.[96,112]

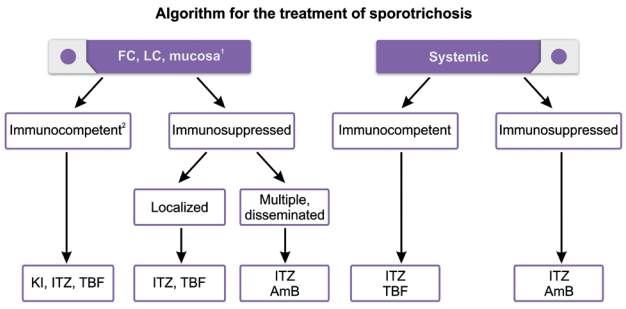

Figure 7: Algorithm for the treatment of sporotrichosis. LC – lymphocutaneous; CF – fixed cutaneous; KI – potassium iodide; ITZ – itraconazole; TBF – terbinafine; AmB – amphotericin B

[1]Hyperkeratotic or refractory cutaneous lesions: heat, cryosurgery, electrosurgery, excision/drainage, KI + ITZ or KI + TBF

[2]Children, elderly, immunoreactive forms: KI

Pregnant women: Heat, cryosurgery, AmB

Modified from: Orofino-Costa, et al. 2015[70]

Table 2: Main drugs used in sporotrichosis treatment with the corresponding dosages

Drug	**Itraconazole**[1] 100 mg capsules		Terbinafine 125 and 250mg tablets		Potassium solution
	Continuous	Pulse	Continuous	Pulse	1.42g/mL (0.07g/drop)
Adult	100-400mg/d[2]	400mg/d	250-500mg/d[4]	500mg/d	2- 4g/d
		7d/month		7d/month	
Pediatric	3-5mg/Kg/d[3]	------	62.5 – 250 mg/d[5]	----	1-2 g/d
Dosage	1-2 x/d	2x/d	1-2 x/d	1-2 x/d	2 x/d
Laboratory control[6]	Blood count, biochemistry, LFT		Blood count, biochemistry, LFT		Blood count, biochemistry, LFT, TSH, T4L

[1]Take at mealtime; [2]Start at 100mg/d; 3 Maximum of 200mg/d; [4]Start at 250mg/d; [5]Dose varies according to weight; [6]Prior to treatment, at 3-4 treatment weeks, at the end of the treatment. LFT - liver function tests Adapted from: Orofino-Costa, *et al*. 2015[70]

KI has been used in association with itraconazole, for refractory mycosis in felines. However, its use in immunosuppressed humans needs to be better evaluated due to the possibility of changes in the immunological reactivity, and worsening of the underlying disease.[120] This association has been used in humans with conidiobolomycosis.[121] The effectiveness of this combination of drugs is probably due to the different mechanisms of action and synergism of both drugs. KI capsules still needs to be tested in humans regarding absorption, pharmacodynamics, and bioavailability for the effective dose adjustment in the treatment of sporotrichosis.

The drugs 5-fluorocytosine, caspofungin, and fluconazole do not exhibit *in vitro* antifungal activity against *S. brasiliensis*, *S. schenckii*, *S. globosa*, or *S. mexicana*.[122,123] *In vitro* analyses indicate significant differences among the minimum concentrations required to inhibit the growth of *Sporothrix* spp. and the required concentration to reduce the number of colony-forming units, demonstrating the fungistatic and non-fungicide effect for the most available antifungal drugs.

PROGNOSIS

Immunocompetent individuals with skin or mucosal clinical forms usually heal in a short period of time, although fibrous scars are frequent complaints leading to functional or unesthetic sequelae. In immunosuppressed patients, especially AIDS, the disease may disseminate and cause death. Untreated patients with chronic skin lesions may develop severe clinical forms, with systemic manifestations, frequently requiring inpatient treatment.

PERSPECTIVES

For over a century, sporotrichosis was described as an occupational disease, with a strong rural profile. However, in the last decades *Sporothrix* spp. as a threat to the warm-blooded vertebrate hosts' health has emerged. The close relation between *S. brasiliensis* and the feline host is curious, so that it causes large epizooties in urban areas.[124] Indeed, zoonotic pathogens are more often associated with emerging diseases than the non-zoonotic pathogens.[125] This indicates the need to investigate the *S. brasiliensis'* transmission dynamics involving cats and humans. Such a transmission route (cat-man) broke a paradigm in a disease in which epidemiology had already been considered to be resolved, to a large extent. Ecological studies are important, given that the uncertainty regarding the fungus' reservoirs in the environment and reasons for the fluctuation *of Sporothrix* population still exists.

The knowledge of the epidemiological-molecular profile is essential to understand the dynamics of species occurrence, from the standpoint of both the characterization of a differentiated clinical standard and the response to the treatment, as well as the implementation of strategic Public Health policies intended to control epidemics. The low-cost molecular methods are important because they provide fast and accurate results, particularly during disease outbreaks. However, for countries with limited health budgets, isolating the *Sporothrix* in culture media is still the best diagnostic method, concerning both cost and positivity.

Investigations on the host-parasite interaction have evolved regarding both cell and humoral immune responses. However, recent researches involving *3-carboxy-muconate cyclase* (gp60-gp70) and the humoral activity reconducted the seek for specific antigens that could be used in the diagnosis and antibodies based vaccines.[5] Anti-gp70 antibodies are potentially useful for disease's therapy because they strongly reduce the host fungal burden, thus preventing *Sporothrix* adhesion to the extracellular matrix components, or inducing the yeasts opsonization in the host-pathogen interaction.[126]

The need to develop new antifungal drugs is encouraged by the increasing number of refractory cases resulting from the emergence of the resistance phenotype among the etiological agents.[127] Currently, researches on alternative treatments for sporotrichosis reveal promising molecules, such as terpinen-4-ol and farnesol, miltefosine, TCAN26 (a structural analogous of miltefosine) and the H3 molecule (an inhibitor of the sterol methyltransferase enzyme).[127-131] However, it should be pointed out that it is still necessary to use appropriate animal models and clinical tests to ensure the effectiveness and safety of treatment for such alternatives. ❑

ACKNOWLEDGMENTS

The authors thank the technical team at the Mycology Laboratory at the Pedro Ernesto University Hospital (UERJ), for their support during all stages of preparation of this article. The authors also would like to thank Raphael da Silva Roma for his technical computer support and his assistance in preparing the figures.

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Mailing address:
Rosane Orofino Costa
Av. 28 de Setembro, 77 - 2º andar
Vila Isabel
20551-030 Rio de Janeiro - RJ
Brazil
E-mail: rosaneorofino@globo.com

How to cite this article: Orofino-Costa R, de Macedo PM, Rodrigues AM, Bernardes-Engemann AR. Sporothrichosis: an update on epidemiology, etiopathogenesis, laboratory and clinical therapeutics. An Bras Dermatol. 2017;92(5):606-20.

QUESTIONS

1. The most common clinical presentation of sporotrichosis in Brazil is:
- **a.** lymphocutaneous
- **b.** fixed cutaneous
- **c.** osteoarticular
- **d.** pulmonary

2. Concerning the sporotrichosis transmission, it may be stated that:
- **a.** zoonotic transmission only takes place when the etiological agent is *Sporothrix globosa*
- **b.** transmission by means of trauma only happens when the etiological agent is *S. schenckii*
- **c.** respiratory transmission results from inhalation of *Sporothrix* conidia
- **d.** respiratory transmission is restricted to specific geographic regions

3. The histopathological exam in sporotrichosis shows:
- **a.** high sensitivity and low specificity
- **b.** low sensitivity and high specificity
- **c.** high sensitivity and high specificity
- **d.** low sensitivity and low specificity

4. To isolate *Sporothrix* spp. the following basic fungus culture media are preferably used:
- **a.** Cereal agar (Corn meal agar) and BHI (Brain Heart Infusion)
- **b.** Mycosel agar and cereal agar (Corn meal agar)
- **c.** Sabouraud agar and PDA (Potato Dextrose Agar)
- **d.** Sabouraud dextrose agar and Mycosel agar

5. The asteroid body found on the dermis of the patients with sporotrichosis:
- **a.** consists of non-specific inflammatory cells
- **b.** confirms the diagnosis of sporotrichosis
- **c.** represents a probable immunological reaction to the fungal cell
- **d.** suggests the host's immunodeficiency

6. It may be stated that serology for the diagnosis of sporotrichosis:
- **a.** is only indicated for skin forms
- **b.** does not provide a good clinical-laboratory correlation
- **c.** is useful in diagnosing systemic and atypical manifestations
- **d.** may not be used in organic fluids other than serum

7. Regarding infectious arthritis caused by *Sporothrix* spp., it is correct to state that:
- **a.** it is almost always polyarticular and migratory
- **b.** it is almost always monoarticular with phlogistic signs
- **c.** adjacent skin lesions are not observed
- **d.** it is polyarticular, but does not show phlogistic signs

8. Check the true statement regarding the laboratory diagnosis of sporotrichosis:
- **a.** the direct microscopy is more sensitive and specific than the culture in humans
- **b.** the gold standard is the isolation and identification of *Sporothrix* spp.
- **c.** the histopathological exam, impregnated by silver, generally exhibits abundance of fungal structures
- **d.** the molecular identification of the *Sporothrix* species has no diagnostic value.

9. Feline zoonotic sporotrichosis, predominant in the South and Southeast regions of Brazil, is mostly associated with the following *Sporothrix* species:
- **a.** *S. schenckii*
- **b.** *S. lurei*
- **c.** *S. brasiliensis*
- **d.** *S. globosa*

10. Examples of immunoreactive sporotrichosis clinical forms include:
- **a.** erythema multiforme and meningitis
- **b.** Sweet's syndrome and erythema nodosum
- **c.** infectious arthritis and erythema multiforme
- **d.** Sweet's syndrome and infectious arthritis

11. The choice treatment for localized cutaneous forms of sporotrichosis in immunocompetent people is:
- **a.** terbinafine
- **b.** fluconazole
- **c.** griseofulvin
- **d.** itraconazole

12. Recent advances in *Sporothrix* taxonomy have led to the identification of new clinical interest agents. The clinical clade includes the following species:
- **a.** *S. chilensis*, *S. pallida*, *S. mexicana*, and *S. globosa*
- **b.** *S. brasiliensis*, *S. schenckii*, *S. chilensis*, and *S. pallida*
- **c.** *S. brasiliensis*, *S. schenckii*, *S. globosa*, and *S. luriei*
- **d.** *S. schenckii*, *S. globosa*, *S. mexicana*, and *S. luriei*

13. Check the correct alternative regarding potassium iodide used in sporotrichosis treatment:
- **a.** it is recommended for systemic forms with lung involvement

b. its mechanism of action is well established, inhibiting ergosterol synthesis
c. it is useful in treating immunoreactive forms due to its immunomodulatory effect
d. it is used in systemic forms with meningeal involvement

14. Check the alternative that includes the laboratory exams to be requested prior to starting treatment with itraconazole and as a therapeutic control:
a. biochemistry, blood count, and liver function tests
b. liver function tests, blood count, and TSH
c. blood count, liver function tests, and free T4
d. biochemistry, liver function tests, and TSH

15. If required, the drug that may be administered to pregnant women affected by sporotrichosis is:
a. fluconazole
b. itraconazole
c. amphotericin B
d. posaconazole

16. Among the actions below, check the one that is not recommended as a preventive measure against the propagation of zoonotic transmission sporotrichosis cases:
a. street animals neutering
b. removal of *Sporothrix* from soil and vegetation
c. treatment of sick animals
d. incineration of dead infected animals

17. Among the statements below, check the one in which the correlation between the etiological agent and the geographic distribution is appropriate:
a. *S. brasiliensis* in Mexico
b. *S. globosa* in Chile
c. *S. pallida* in the USA
d. *S. globosa* in China

18. The biochemical compound present in *S. brasiliensis* that may be related to its virulence is:
a. quinine
b. adrenalin
c. melanin
d. erythropoietin

19. The disease most commonly present in the differential diagnosis of lymphocutaneous sporotrichosis is:
a. tegumentary leishmaniasis
b. granuloma annulare
c. paracoccidioidomycosis
d. epidermoid carcinoma

20. The important biomarker present in the *Sporothrix* cell wall that can be used for the production of a therapeutic vaccine is the glycoprotein:
a. gp40
b. gp80
c. gp70
d. gp100

Answer key
Behçet´s Disease: a review with emphasis on dermatological aspects. An Bras Dermatol. 2017;92(4):452-64

1. A	**6. C**	**11. D**	**16. B**
2. C	**7. B**	**12. C**	**17. D**
3. D	**8. B**	**13. C**	**18. C**
4. D	**9. C**	**14. A**	**19. A**
5. C	**10. B**	**15. C**	**20. C**

Papers
Information for all members: The EMC-D questionnaire is now available at the homepage of the Brazilian Annals of Dermatology: www.anaisdedermatologia.org.br. The deadline for completing the questionnaire is 30 days from the date of online publication.