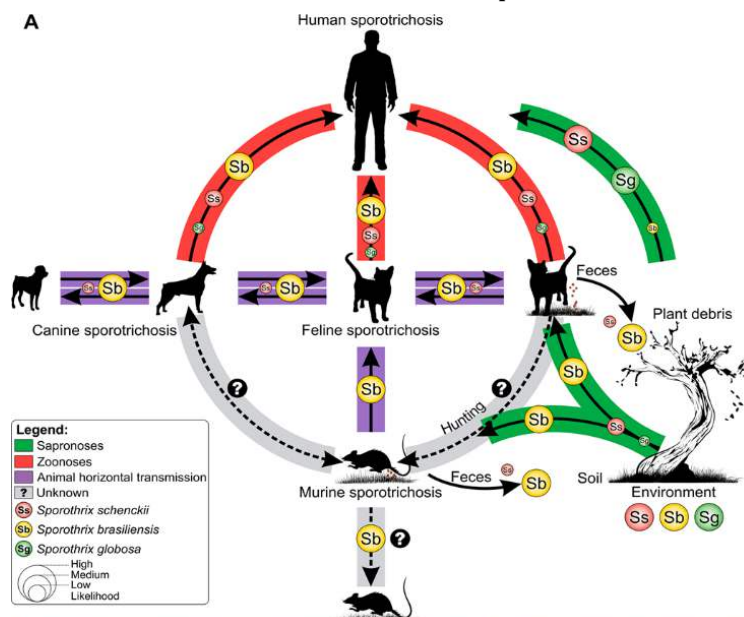


Sporotrichosis

Introduction

Sporotrichosis (“gardeners” disease) is a broad term used to describe a chronic granulomatous fungal disease, mainly of the skin and lymphatic vessels acquired through traumatic inoculation (implantation mycosis) or by inhalation of conidia, characterised by nodular lesions, caused by any of the several species of the thermally dimorphic complex of fungus in the genus *Sporothrix* ¹. The etiologic agents of sporotrichosis, *Sporothrix schenckii* (*sensu lato*), are distributed throughout the world, especially in warm temperate, tropical and subtropical zones. In the environment, at temperatures of 25°C to 30°C, *S. schenckii* is a mould with dark or hyaline conidia arranged along delicate hyphal structures in a bouquet-like appearance. *In vivo* in patient tissues, at temperatures of 37°C, it exists in a 3- to 5- micrometre cigar- or oval-shaped yeast form ².

Sporothrix sp., is found abundantly in soil, wood, sphagnum moss, thorns, decaying vegetation, and hay. Animals, such as cats (specially), armadillos, dogs, rodents, insects can also be the source of the infectious organism, thus sporotrichosis can be regarded as both a sporonosis and a zoonosis. Sporotrichosis is most often localised in the skin and subcutaneous tissues, following traumatic inoculation of the causative fungus *Sporothrix* to the dermis of individuals with outdoor vocations and occupations, through thorn pricks, scratches, and other injuries. Occupational and leisure activities, such as floriculture, horticulture, gardening, fishing, hunting, farming, mining, hunting of armadillos have been associated with sporotrichosis ³.



The vast majority (>95%) of sporotrichosis cases are caused by *Sporothrix schenckii* complex, including *S. schenckii* (*sensu strictu*) and *S. brasiliensis* and several cryptic species, which are identified in the routine laboratory as *S. schenckii*. *S. luriei*, *S. cyanescens*, *S. globosa*, *S. pallidia*, *S. nivea*, *S. albicans*, and *S. mexicana* have been reported to cause only a small minority of sporotrichosis cases. *S. brasiliensis*, transmitted to humans via cats, is confined to Brazil. This species is notable for causing a large outbreak in cats in Brazil, now continuing in its third decade ⁴.

Figure 1: Routes of transmission of sporotrichosis ⁵

Epidemiology

Sporotrichosis is probably more common but very variable in frequency with hyper-endemic areas in Brazil, Mexico, Colombia, and Peru with rates as high as 25/1,000^{6,7}. Much as *Sporothrix* is distributed worldwide, global data on disease prevalence are very limited, however, over 40,000 cases of sporotrichosis are estimated annually worldwide, making it the most common implantation mycosis compared to mycetoma (~9,000 cases globally), and chromoblastomycosis (~10,000 cases globally)⁸.

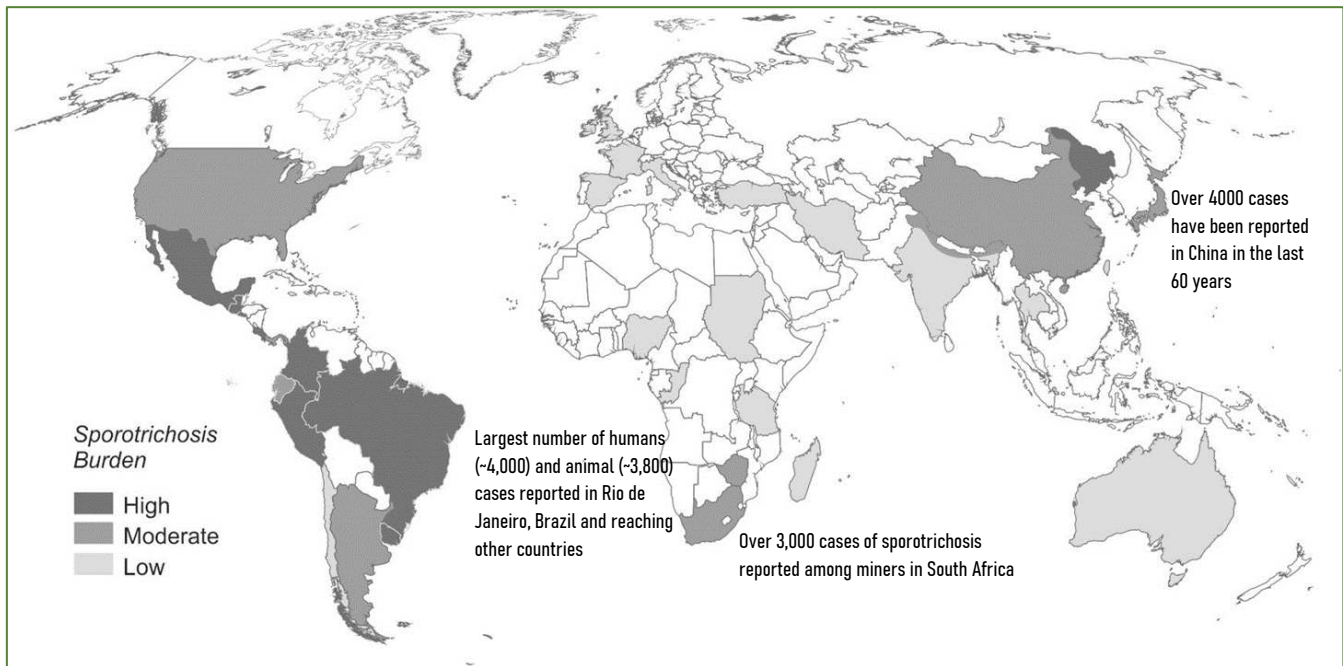
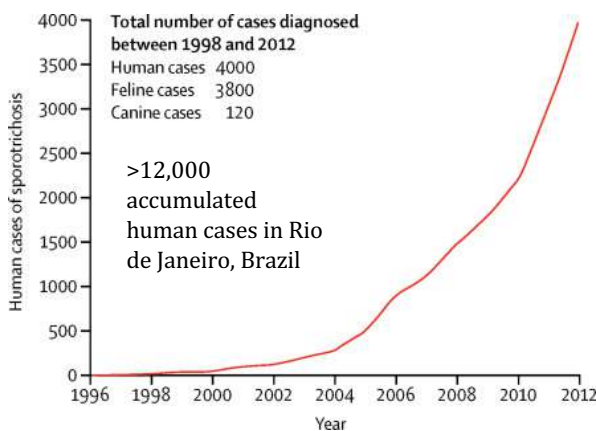


Figure 2: Global burden of sporotrichosis. Data from Chakrabarti *et al.*⁶

Current data suggest no racial predominance of sporotrichosis. Adults are affected more commonly in all reported series except for Abancay, Peru where 60% of cases occurred in children <15 years old^{7,9}. The major risk factors are trauma to the skin, outdoor occupation (e.g. gardening, mining, horticultural work etc.), animal bites and scratches, alcoholism, poorly controlled diabetes mellitus, HIV/AIDS, and chronic obstructive pulmonary disease^{2,10}. Other risk factors known to predispose to sporotrichosis are corticosteroid treatment, chemotherapy in patients with haematological malignancy, use of biologic agents such as tissue necrosis -alpha inhibitors, and transplantations^{11,12}.



Extracutaneous disease is uncommon and tends to occur in immunocompromised individuals or those with other underlying medical conditions.

Most cases are sporadic but outbreaks have been well described and often are traced back to activities that involved contaminated sphagnum moss, hay, wood or

Figure 2: Trend of cat transmitted sporotrichosis in Rio de Janeiro, Brazil

mining activities. The largest was in South Africa in the 1940s when more than 3000 gold miners



developed sporotrichosis following traumatic inoculation by wood splinters from contaminated timbers.

Another well-documented mode of transmission of sporotrichosis is zoonotic (mainly via cat scratches) and, less often, from armadillos or insect, rodent, and dog bites. In the state of Rio de Janeiro, the number of human cases jumped from 759 between 1998 and 2004 to more than 4000 in 2014 and 10,000 in 2017 mostly resulting from feline transmission ^{2,13,14}.

Clinical manifestations

Sporotrichosis is classified into two main clinical manifestations: I) *Cutaneous* – most common form, and II) *Extra-cutaneous* manifestations. Cutaneous disease may resolve spontaneously without treatment, however, a few patients may develop a disseminated (extra cutaneous) disease ¹⁰.

I. Cutaneous sporotrichosis

- Accounts for about 90% to 95% of all cases of sporotrichosis
- Upper limbs affected in ~45-50%
- Lower limbs in ~20-25%
- Head and neck in ~10-20%



- There are three main variants of cutaneous sporotrichosis
 - *Lymphocutaneous sporotrichosis* (70% to 75%): characterized by granulomatous, ulcerous and painful nodules in a linear distribution (along lymph vessels) on the limbs. The lesions may involve the conjunctiva, mouth, pharynx, vocal cords, nose, and sinuses.
 - *Fixed cutaneous sporotrichosis* (20%): painless, infiltrated, nodular lesion sometimes ulcerated or verrucous, with a violaceous halo in the site of inoculation (sporotrichoid chancre) and satellite lesions.
 - *Cutaneous disseminated sporotrichosis*: painless, infiltrated, nodular lesion, ulcers, distributed throughout the body.

II. Extracutaneous sporotrichosis (5% to 10%)

- **Bone and joint lesions:** osteoarthritis, osteolysis, tenosynovitis etc.
- **Pulmonary sporotrichosis:** acute or chronic -usually asymptomatic, following inhalation of conidia, presentation is similar to that of pulmonary tuberculosis.
- **Meningeal sporotrichosis:** Mainly caused by *S. brasiliensis* occurs in ~20% of



HIV patient with disseminated cutaneous feline transmitted sporotrichosis

disseminated disease, presenting as meningoencephalitis or hydrocephalus in immunocompromised individuals.

- **Disseminated sporotrichosis:** An opportunistic disease observed in severely immunocompromised patients,
- Other less-common presentations (e.g., laryngeal, ocular).

Clinical differential diagnosis of cutaneous sporotrichosis includes cutaneous tuberculous and non-tuberculous mycobacterial infections, leprosy, mycetoma, chromoblastomycosis, cutaneous leishmaniasis and squamous cell carcinoma.

Diagnosis

Several diagnosis approaches may be employed to confirm the clinical diagnosis of sporotrichosis, ranging from direct microscopy, cultures, histology to modern molecular assays ^{2,4,15-17}.

I. Direct microscopy

This involves direct visualisation of *Sporothrix* yeast cells obtained from clinical samples (pus, exudates, sputum, synovial fluids etc.), using an appropriate stain. Such as 10-40% potassium hydroxide (KOH) solution, gram stain, or Periodic-Acid Schiff (PAS). *Sporothrix* yeast cells are 2-6 µm in diameter. The sensitivity of microscopy is not documented.

II. Culture

Culture of *Sporothrix* in the laboratory on Sabouraud dextrose agar (SDA) is the gold standard of diagnosis; it has a better yield compared to histopathology and allows for antifungal susceptibility testing. *Sporothrix* are fast growing and characteristic features are formed within a week, and is advisable to keep for up to 4 weeks before discarding.

Dimorphism is demonstrated by culturing *Sporothrix* in blood-chocolate agar, blood agar or Brain Heart Infusion (BHI) agar at 37 °C. Moulds are formed at 25-28°C, with an initially white, creamy, bright and yeast-like; later turning white-beige, with dark pigment in the center, membranous, radiated and fast growing. Microscopically, thin, septate, branched hyphae (1–2 µm in diameter) are observed with sympoduloconidia or raduloconidia, which gives the typical “daisy or peach flower” image. All species of *Sporothrix* have the same microscopic appearance and can only be differentiated through genetic or proteomic testing.

III. Histopathology

Identification of *Sporothrix* by histological examination is difficult and is rarely achieved. To increase the chance of identification, a minimum of 20 serial sections of paraffin block are examined with both PAS and Gomori–Grocott methenamine silver (GMS) stains. A suppurative, single or multiple granulomatous reaction, with central necrotic microabscesses surrounded by epithelioid histiocytes, at the same time surrounded by plasma cells and lymphocytes may be observed. Hoeffli-splendore phenomenon (or asteroid bodies – yeasts cells surrounded by hosts’ antibody-antigen immune complexes) is observed in about 40% of the cases. Demonstration of asteroid bodies has a sensitivity of about 94% and allows early diagnosis and initiation of an appropriate treatment. It should be noted that asteroid bodies are not specific for sporotrichosis and observed in many other infectious and non-infectious granulomatous diseases.

Histological differential diagnosis includes other deep chronic fungal or mycobacteria infections and other granulomatous disorders (halogenoderma, pyoderma gangrenosum, granulomatosis with polyangiitis (Wegner’s granulomatosis) and other systemic vasculitis.

IV. Immunodiagnosics

Intradermal sporotrichin skin test is used for epidemiological purposes as well as in the assessment of immunological (cell-mediated immune) status of patients. It has recently been reported to have a sensitivity of 94.5% and a specificity of 95.2%, are specific for lymphocutaneous and fixed cutaneous sporotrichosis and may be considered useful as an auxiliary diagnostic test before a positive sample culture ¹⁸. Sporotrichosis is classified into two groups based on skin test reactions (**Table 1**). Being a dimorphic fungus, each phase of dimorphism is associated with a unique antigen i.e. mycelial (M) and yeasts (L) antigens both derived from glycopeptides and polysaccharides ¹⁶.

Serological testing has shown to be effective with high accuracy in detecting a range of clinical forms of sporotrichosis especially in rarer forms of extra-cutaneous disease and invasive or widespread disease ¹⁹. ELISA-based methods of diagnosis to detect *S. schenckii* cell wall antibodies have shown to be reliable, with a sensitivity of 90% ¹⁹, although there is only one commercially available assay which lacks comparative data. Antibody detection is a reliable, fast method of diagnosing all clinical forms of sporotrichosis. Although meningitis due to sporotrichosis is very rare, antibodies in serum or in CSF are able to be detected through ELISA, has been shown to be effective, and can be used for rapid diagnosis of meningitis due to *Sporothrix* sp. ¹⁶.

V. Molecular diagnosis

Sequencing of chitin synthase genes, internal transcribe sequences (ITS), β-tubulins, calmodulin and translation elongation factor has led to recognition of many of the currently known cryptic species of *Sporothrix*. Molecular diagnostics allows investigation of outbreaks and accurate delineation of geographical distribution of species ²⁰. Emerging proteomic tests, such as MALDI-ToF are used in some centres for rapid identification of the *Sporothrix*. However, MALDI-ToF requires a large and an updated database to allow an accurate identification ¹⁶.

Table 1: Classification of Sporotrichosis

Immunology and Clinical Parameters	Group I	Group II
Immune Response	• Normal/Augmented	• Decreased/None
Clinical presentations	• Lymphangitic • Fixed	• Cutaneous disseminated • Cutaneous superficial • Pulmonary/visceral • Osteoarticular
Parameters	• Skin test positive (+) • Scarce yeasts or asteroid bodies.	• Skin test negative (-) • Plenty of yeasts or asteroid bodies.

Treatment

Species-level identification is required prior to initiation of an appropriate antifungal agent. Susceptibility profiles of species with medical importance (*S. brasiliensis*, *S. schenckii (sensu lato)*, *S. globosa*, and *S. luriei*) showed that itraconazole and posaconazole are moderately effective against *S. brasiliensis* and *S. schenckii*. Posaconazole presents good minimal inhibitory concentrations against *S. mexicana*. Flucytosine, caspofungin and fluconazole showed no fungal activity against *Sporothrix* species ²¹. Itraconazole is the single best oral systemic antifungal agent for the treatment of sporotrichosis, with response rate as high as over 90% ²². Sporotrichosis usually has a benign course and responds well to various treatments. Historically, saturated solution of potassium iodide, initiated at a dosage of 5 drops (using a standard eye-dropper) 3 times daily and increasing, as tolerated, to 40–50 drops 3 times daily was used for the treatment of cutaneous sporotrichosis. Spontaneous regression has been reported occasionally. In clinical practice, Itraconazole (mainly), terbinafine, fluconazole, and amphotericin B are the commonly used drugs. The IDSA clinical practice guidelines recommends Itraconazole for at least 12 months for the treatment of pulmonary and osteoarticular sporotrichosis. Lymphocutaneous and other cutaneous manifestations of sporotrichosis are typically treated with itraconazole for 3 to 6 months, including sporotrichosis in children. Amphotericin B (lipid formulation preferred) is the agent of choice for more severe forms of disease and in pregnancy. Azoles (itraconazole, fluconazole and related drugs) should be avoided in pregnancy, as they are teratogenic to unborn foetus ¹⁰. Prognosis is generally good, with the majority of patients achieving full clinical cure without any sequelae.

Summary

Sporotrichosis is the most common implantation mycosis (like chromoblastomycosis and mycetoma) with a worldwide distribution caused by several *Sporothrix* species. Traumatic inoculation of the fungus into the skin is the main mode of transmission among individuals at risk. Pulmonary and disseminated disease are mainly acquired through inhalation of conidia. The vast majority of sporotrichosis cases are lymphocutaneous or fixed cutaneous forms, although extracutaneous forms may occur, especially in immunocompromised hosts. The definitive test for diagnosis of sporotrichosis is culture of the fungus from a suitable clinical sample. Molecular diagnostic techniques, immunoassays (e.g. ELISA), mass spectrometry (MALDI-ToF), allows rapid, precise identification and confirmation of the causal species. In patients with cutaneous lesions who require treatment, itraconazole is the drug of choice and is associated with good outcomes. Extracutaneous manifestations of sporotrichosis can be life threatening, especially in immunosuppressed patients, and do not always favourably respond to antifungal therapy. Amphotericin B is the drug of choice for severe forms of disease, and the only agent recommended for the treatment of sporotrichosis in pregnancy.

Public health needs:

- Global incidence of sporotrichosis is in excess of 40,000 cases, making it a significant public health problem.
- Delays in diagnosis can lead to more severe disease, which requires longer treatment times and may result in long-term consequences or even death.
- With the development and use of new diagnostic techniques a rapid, definitive diagnosis can be made, therefore reducing the possibility of spread of the disease.
- Public awareness of the disease and making sporotrichosis a notifiable disease will increase awareness and potentially decrease the rate of zoonotic sporotrichosis
- Development of a possible vaccine could reduce the incidence of feline sporotrichosis significantly.

- Effective control of feral cat populations to reduce the number of free roaming cats and therefore controlling the number of infected cats.

Dr Felix Bongomin, August 2018
Mulago Hospital, Kampala, Uganda

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