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Neglected endemic mycoses

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Fungi often infect mammalian hosts via the respiratory route, but traumatic transcutaneous implantation is also an important source of infections. Environmental exposure to spores of pathogenic fungi can result in subclinical and unrecognised syndromes, allergic manifestations, and even overt disease. After traumatic cutaneous inoculation, several fungi can cause neglected mycoses such as sporotrichosis, chromoblastomycosis, mycetoma, entomophthoramycosis, and lacaziosis. Most of these diseases have a subacute to chronic course and they can become recalcitrant to therapy and lead to physical disabilities, including inability to work, physical deformities, and amputations. For many years, paracoccidioidomycosis was considered the most prevalent endemic systemic mycosis in the Americas, but this situation might be changing with recognition of the worldwide presence of *Histoplasma capsulatum*. Both paracoccidioidomycosis and histoplasmosis can mimic several infectious and non-infectious medical conditions and lead to death if not recognised early and treated. Cutaneous implantation and systemic mycoses are neglected diseases that affect millions of individuals worldwide, especially in low-income countries where their management is suboptimum because challenges in diagnosis and therapeutic options are substantial issues.

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This is the fourth in a Series of eight papers about fungal infections

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Introduction

Neglected tropical diseases (NTDs) are a diverse series of endemic diseases that prevail in tropical or subtropical climates worldwide. They are infectious diseases usually affecting people living in low-income countries in Asia, Africa, and Latin America. NTDs usually affect populations that do not travel abroad, with little political voice and low visibility. According to WHO, a high prevalence of NTDs is associated with poverty and other disadvantageous conditions.[1] Individuals affected by NTDs are often the world's poorest populations, often living in remote rural areas, urban slums, or conflict zones. Although progress has been made for some NTDs, many of these diseases are not on the public health radar, by contrast with other high-profile global diseases.[1] WHO and other organisations such as the G-FINDER project recognise several helmintic, protozoan, bacterial, and viral infections as NTDs, but most fungal infections have not yet reached such status. However, in 2016, mycetoma was included as the only fungal disease in the WHO list of NTDs, and chromoblastomycosis was added in 2017.[1–4]

The burden and medical impact of fungal diseases are largely unknown and often underestimated, especially for endemic fungal infections. Endemic mycoses can be divided into two groups: implantation (subcutaneous) mycoses in which the fungal agents generally infect transcutaneous wounds; and systemic mycoses, in which thermodimorphic fungi are inhaled causing infection and can disseminate. Fungal (mycotic) keratitis is an implantation mycosis and fulfils criteria for an NTD, although it is a global problem with occasional cases in high-income non-tropical countries; this disease will not be addressed in this paper.

Cutaneous implantation mycoses

Implantation mycoses are a heterogeneous group of fungal diseases, which present months or years after initial infection.[5] This group includes sporotrichosis, chromoblastomycosis (chromomycosis), mycetoma, lacaziosis (lobomycosis), and entomophthoramycosis (subcutaneous zygomycosis). These diseases primarily affect the cutaneous and subcutaneous tissues, but in most cases they also involve adjacent structures such as the lymphatics, cartilage, fascia, joints, and bones.[5–8] Most implantation mycoses occur in tropical and subtropical regions of the world and usually affect individuals involved in outdoor activities such as agriculture, hunting, mining, and lumbering. Less commonly, children, travellers, and visiting workers develop implantation mycoses.[5–9] These diseases mimic several infectious and non-infectious disorders and their burden is underestimated because of a lack of diagnosis in the areas where they occur (table 1).

Sporotrichosis

Sporotrichosis is the most prevalent and widespread implantation mycosis in the world. For more than a century, this disease was believed to be caused by a single species, *Sporothrix schenckii*, but more recent molecular phylogenetic methods have shown that this fungus has a wide spectrum of biodiversity with several sibling species. These species vary by virulence, mode of transmission, clinical manifestations, and response to therapy. The taxonomy of the *Sporothrix* genus has recently been revised and is now classified according to its phenotypic and biochemical characteristics together with its molecular profile. The original *S schenckii* sensu lato contains clinically relevant cryptic species with diverse geographical distribution: *S schenckii* sensu stricto and *Sporothrix globosa* cause sapronotic sporotrichosis

Key messages

- The burden and medical importance of endemic mycoses remain underestimated.
- Most of the serious endemic fungal infections have not yet reached the status of neglected diseases as defined by WHO.
- The most relevant implantation mycoses are sporotrichosis, chromoblastomycosis, and mycetoma. Most of these infections occur in underdeveloped tropical and subtropical regions of the world.
- Sporotrichosis caused by *Sporothrix schenckii* sensu lato is a sapronosis and occurs worldwide, whereas sporotrichosis caused by *Sporothrix brasiliensis* is an anthropozoonosis affecting human beings, cats, and dogs. The disease can occur as outbreaks that might affect thousands of people.
- Chromoblastomycosis is a potentially debilitating disease caused by several melanised fungi found in plants or soil. It has an occupational risk and diagnosis relies on visualisation of the typical muriform (sclerotic) cells by direct microscopy.
- Mycetoma causes high morbidity and affects poor populations living in remote areas of the world. This disease causes painless subcutaneous masses, sinus formation, and occasional discharge of grains.
- Entomophthoramycosis, also known as subcutaneous zygomycosis, causes chronic destructive lesions that can be diagnosed by a combination of microscopy, culture, and histopathology.
- Lacaziosis, also known as lobomycosis, is an exotic and mysterious disease. Most affected individuals are from the Amazon region. *Lacazia loboi*, which infects human beings and dolphins, has never been cultivated in vitro. It is recalcitrant to antifungal therapy.
- Histoplasmosis and paracoccidioidomycosis are the most relevant neglected endemic systemic mycoses in Latin American countries. These diseases are commonly misdiagnosed as tuberculosis, resulting in a substantial delay in treatment.
- *Histoplasma capsulatum* infection is expanding outside the American endemic area. It is a frequent cause of disseminated disease in endemic regions. Regions with the highest burden of histoplasmosis usually lack effective methods of diagnosis (antigen detection) and treatment (lipid formulations of amphotericin B).
- Paracoccidioidomycosis has a substantial impact on public health. It mostly affects male farmers in their productive ages, potentially making them unable to work.

worldwide. These species are ubiquitous and infection usually occurs via transcutaneous inoculation of contaminated plant debris.[28] *Sporothrix luriei* is restricted to Africa and Asia and *Sporothrix brasiliensis* is restricted to Brazil. Most Asian isolates are *S globosa*.[29–31] All causative agents of sporotrichosis can be recovered from classic environmental sources of infection for *S schenckii* sensu lato, apart from *S brasiliensis*, which is associated with feline transmission of the disease.[31–34] *S brasiliensis* is an emerging anthropozoonosis affecting human beings, cats, and dogs. Sick cats usually have a heavy *S brasiliensis* fungal burden, which can be transmitted directly in the yeast form.[34] Beyond transcutaneous inoculation related to plant or animal trauma, other ports of entry such as respiratory, conjunctival, and osteoarticular routes of infection can also occur.[35,36]

See Online for appendix

Epidemiology and geographical distribution

Areas endemic for sporotrichosis include Latin America, India, Australia, South Africa, China, and Japan.[5,31] Prevalence is not uniform and varies according to the epidemiological pattern of transmission. The highest estimated prevalence rates of infection range from 0·1% to 0·5% in some Latin American countries.[5,31] A few hyperendemic areas of sporotrichosis have been identified—namely, in Mexico, Peru, and China.[31,37–40] Case reports from several countries have been published, but outbreaks and clusters of cases can occur. The largest reported sporotrichosis outbreak involved more than 3000 miners in South Africa during the 1940s.[41] However, a larger outbreak of cat-transmitted sporotrichosis is currently occurring in Brazil. 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, mostly resulting from feline transmission. This outbreak is expanding to neighbouring Brazilian regions[34,42,43] (figure 1).

Clinical presentation

Most patients present with cutaneous forms of sporotrichosis that include fixed cutaneous (25%) and lymphocutaneous (55%) involvement.[6] Cutaneous disseminated forms are reported in immunocompetent and immunosuppressed individuals.[44] Extracutaneous involvement has rarely been described, notably pulmonary, osteoarticular, ophthalmic, and CNS infection. Meningitis is more frequently seen in immunocompromised individuals. An increased number of immunoallergic forms (eg, erythema nodosum, arthralgia, myalgia, and chorioretinitis) have been described during the continuing outbreak in Brazil.[35,36]

Diagnosis

Culture remains the gold standard for diagnosis of sporotrichosis. Clinical specimens should be inoculated on Sabouraud agar and incubated at room temperature for 1–4 weeks. Microscopy is useful only in the presence of high fungal load. ELISA serodiagnosis has shown accuracy and low cross-reactivity to detect a range of clinical forms of sporotrichosis.[45]

Treatment

The best therapeutic choice for cutaneous and lymphocutaneous forms of sporotrichosis is itraconazole, with either terbinafine or super-saturated potassium iodide as second-line options.[5,10,11] If possible, plasma concentrations of itraconazole should be monitored during treatment. For meningitis and disseminated disease, lipid amphotericin B (3–5 mg/kg per day) is a better option. The roles of posaconazole and isavuconazole have yet to be determined (table 1, appendix).

Chromoblastomycosis

Chromoblastomycosis is the second most prevalent implantation mycosis in the world. This disease is caused by melanised (dark pigmented) fungi, which are almost all members of the Herpotrichiellaceae family.[5,12] The most prevalent species causing chromoblastomycosis

are *Fonsecaea pedrosoi*, *Fonsecaea monophora*, and *Cladophialophora carrionii*. Sporadic cases may be caused by *Phialophora verrucosa*, *Rhinocladiella aquaspersa*, *Exophiala* spp, and other species of *Fonsecaea*.[17,46,47] Advances in molecular taxonomy have shown that the biodiversity of chromoblastomycosis agents has increased without substantial clinical or therapeutic correlation.[48] An inability of Toll-like receptors to

	Epidemiology and geographical distribution	Clinical presentation	Diagnosis	Treatment
Sporotrichosis	Global geographical distribution; variable sex and age distribution. Plant or soil transmission: mainly in individuals in contact with vegetation and soil (eg, agriculture activities, gardening, plant manipulation, mining, hunting, other outdoor activities). Zoonotic transmission: mainly from cats, occasionally from dogs, birds, armadillos, and fish. Opportunistic disease: alcoholism, steroids, AIDS, TNF inhibitors	Fixed cutaneous involvement: polymorphic skin lesions (eg, papules, nodules, ulcers, verrucous lesions, plaques) following trauma. Lymphocutaneous involvement: nodules, ulcers, abscesses tracking along regional lymphatic chains; regional adenopathy. Extracutaneous forms: pulmonary, osteoarticular, neurological, and ophthalmological	Mycology: microscopy has limited sensitivity. Culture of clinical samples (eg, biopsy samples, pus, exudates, or aspirates) remains the gold standard; fungal dimorphism must be demonstrated. Serology: ELISA might be helpful in CNS infection. Histopathology: non-specific in most immunocompetent patients; yeast cells, cigar-shaped cells, asteroid bodies, and Splendore-Hoeppli reaction are seen in <30% of cases apart from in immunocompromised hosts	Fixed or lymphocutaneous: oral itraconazole 200 mg per day for 2–4 weeks after lesions resolve, usually for total of 3–6 months. Refractory or intolerant patients: oral terbinafine 500 mg twice daily, SSKI 40–50 drops three times daily, oral fluconazole 400–800 mg per day (only in patients who cannot tolerate other agents). Other clinical presentations: combination of itraconazole and terbinafine, plus amphotericin B[5,10,11]
Chromoblastomycosis	Global tropical distribution, usually in men aged 30–50 years; affects farmers, gardeners, and lumberjacks; a risk factor is non-use of protective gloves, footwear, or garments when working with plants and soil products. Occupational risk for people working with palm trees, black tea and rubber plantations, etc. Possible genetic susceptibility.	Slow clinical progression usually limited to the skin and subcutaneous tissue in which initial erythematous papular lesions might gradually evolve to display varying morphologies, such as nodular, tumoral (cauliflower-like), plaque, verrucous, and cicatricial lesions. Affects feet and legs most frequently; can transform into squamous cell carcinoma	Mycology: the observation of muriform cells (sclerotic bodies) is diagnostic. Examination of scrapings, exudate, or aspirates, or vinyl adhesive tape preparations on wet mount examination. Culture with molecular identification is necessary for species identification. Histopathology: pseudoepitheliomatous hyperplasia, granulomatous reaction, and epidermic abscess associated with muriform cells are usual	Surgery effective in early stages; itraconazole (200–400 mg per day), terbinafine (250–500 mg per day), terbinafine (500 mg per day) plus itraconazole (50–100 mg per day); combination therapy (itraconazole with terbinafine or flucytosine) for severe cases, oral posaconazole (400 mg twice daily) in patients with disease refractory to itraconazole or who are intolerant of itraconazole; cryotherapy[12–14]
Eumycetoma	Men aged 20–40 years who work as herders, farmers, or other field labourers;[15] increasingly in travellers to tropical endemic areas[5,16]	Local chronic, progressive, multifistulous, suppurative, tumoral lesions discharging grains. Infection involves cutaneous and subcutaneous tissues, fascia, and eventually muscle and bone[17]	Observation of grain colour and texture; deep surgical biopsy samples containing grains that can be cultured or fixed for histopathology; immunodiffusion, ELISA, PCR with DNA sequencing; MRI or CT to determine bone involvement[2,5,18]	For *Scedosporium apiospermum* and melanised fungi causing so-called black grain eumycetoma, surgery and antifungal therapy with oral itraconazole (400 mg), often given for 7–12 months; oral posaconazole (400 mg twice daily) in patients with disease refractory to or who are intolerant of itraconazole.[5,19] For *Fusarium* spp infections, voriconazole or posaconazole are indicated
Entomophthoramycosis	Infections usually caused by fungi of the order Entomophthorales, usually in immunocompetent individuals. Basidiobolomycosis usually occurs in children and conidiobolomycosis mostly in adults[20]	Basidiobolomycosis: usually chronic and progressive course; hard nodules that spread, often over thighs and buttocks, eventually ulcerating overlying skin; other affected sites include maxillary sinus, palate, gastrointestinal tract, retroperitoneal space, and lungs.[21] Conidiobolomycosis: begins with swelling of inferior nasal cones and extends to facial and subcutaneous tissues and paranasal sinuses; subcutaneous nodules may attach to underlying tissues, causing facial disfigurement[22]	Histology: wide sparse septate, thin-walled hyphae with right-angle branching. Splendore-Hoeppli reaction present with basidiobolomycosis (sometimes with conidiobolomycosis)[20]	Most commonly used therapy is itraconazole (100–200 mg per day); potassium iodide, or terbinafine might be a second option. Amphotericin B for severe and disseminated disease[21,23]
Lacaziosis	Adult men living or working in the Amazon rainforest. Farmers, miners, hunters, rubber workers, and military personnel are at risk[24,25]	Lesions are indolent, evolving over many years; polymorphic cutaneous lesions, mostly plaque and nodules with keloid-like features; pinna of the ear most commonly affected; initial lesion followed by traumatic or autoinoculation; nodule distribution follows lymphatic system[24,26]	Microscopy of tissue smears from lesions, examination of vinyl adhesive tape preparation; cannot be cultured. Serological tests: high sensitivity but lack specificity; antigenic cross-reactivity with *Paracoccidioides* spp[26]	Wide surgical excision, electrodesiccation in early stage of disease, cryosurgery; clofazimine (300 mg per day until clinical improvement, then 100 mg per day for ≥2 years).[24] Amphotericin B, flucytosine, and azoles usually ineffective, except for localised lesions that might respond to long courses of posaconazole[27]

SSKI=saturated solution of potassium iodide. TNF=tumour necrosis factor.

Table 1: **Main characteristics of the endemic implantation mycoses**

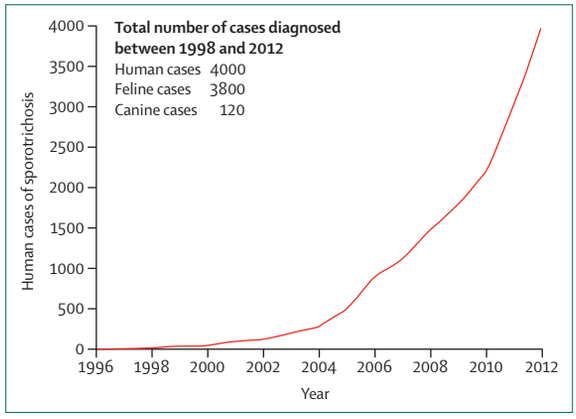

Figure 1: **Cases of sporotrichosis diagnosed in Rio de Janeiro between 1996 and 2012**
The cat-transmitted sporotrichosis outbreak is expanding to other regions in Brazil and involves human, feline, and canine hosts.[34,42,43]

recognise pathogens might be a key component of pathogenesis.[49]

Epidemiology and geographical distribution
Fungi causing chromoblastomycosis are components of plant or soil microbiota and infection follows several types of wounds, many of which occur during agricultural activities.[15,50–53] Chromoblastomycosis mainly occurs in tropical and subtropical zones in Latin America, Africa, and Oceania.[12] Most cases are reported in Brazil, Mexico, southern China, Australia, and Madagascar.[53–57] Estimated data gathered from case series reports and surveys suggest that the incidence of this disease might range from 1 per 6800 (Madagascar) to 1 per 8625 (USA) in the total populations of these countries.[15,58] This infection is likely to be present in many African countries, but is underdiagnosed.

Clinical presentation
After an uncertain period of incubation, the initial lesions arise at the site of inoculation. Over weeks and months, these can evolve to cutaneous and subcutaneous polymorphic lesions. In advanced cases, different lesion patterns have been observed.[12,13,48] The clinical forms of the disease might be associated with cytokine cellular-mediated response and in severe cases, the production of tumour necrosis factor α and interleukin 10 has been detected.[13,59,60]

Diagnosis
For confirmation of a diagnosis of chromoblastomycosis, visualisation of the typical muriform (sclerotic) cells by direct microscopy (potassium hydroxide 10–40% digestion) or in tissue sections is required. Muriform cells appear as chestnut or rounded melanised fungal elements crossed by longitudinal and transverse septa.[12,61] In culture, the organisms grow slowly on Sabouraud agar containing antibiotics, yielding a melanised filamentous fungus. For correct species identification, fungal DNA sequencing is required.

Treatment
The best therapeutic method for small initial lesions is surgical excision. Diagnosis is often delayed and systemic antifungal therapy is usually required. Long-term therapy with itraconazole is the best option for inoperable lesions. The response rate to itraconazole ranges from 15% to 80%, depending on the causative agent and severity of the disease.[12,14,62,63] Terbinafine is another option, and for refractory cases, the combination of itraconazole with terbinafine or flucytosine can be used.[63,64] The addition of physical methods such as photodynamic, local thermotherapy (heat or cold), or immunoadjuvants (eg, topical imiquimod)[63–66] might improve response rates. Of the new triazoles, posaconazole is the most attractive drug (table 1, appendix).

Mycetoma
Mycetoma is a chronic, progressive, implantation inflammatory disease characterised by severe and stigmatising deformities, disability, and high morbidity. The disease can be caused by fungi (eumycetoma) and several members of the bacterial order Actinomycetales (actinomycetoma), and it affects the poorest populations in the most remote tropical and subtropical regions of the world. Mycetoma is a disease that causes minimal mortality but high morbidity;[67] it leads to devastating deformities that can result in many negative socioeconomic effects. The lack of national and international attention and awareness has led to a knowledge gap that substantially affects patient care and impedes control.[68]

Epidemiology and geographical distribution
Although the true incidence and prevalence of mycetoma are not known, a prevalence of 14·5 per 1000 inhabitants has been reported in some endemic areas.[69,70] There are no definitive studies on the route of transmission for mycetoma. The causative organisms are thought to originate in soil or animal dung and are inoculated in the subcutaneous tissue after minor injuries such as those caused by thorn pricks. There is a clear relation between mycetoma and individuals who walk barefoot and workers engaged in manual labour in rural areas, but no one is exempt. No animal reservoir has been identified, although rare cases have occurred in several vertebrates.[2,71] The causative organisms are distributed worldwide but are endemic in several tropical and subtropical countries, making up what has been called the mycetoma belt. The belt includes, among others, central Africa (Chad, Ethiopia, Mauritania, Sudan, Senegal, and Somalia) as well as Mexico, India, Venezuela, and Yemen. The mycetoma belt is characterised by a hot, dry climate with a short, heavy rainy season. Eumycetoma is mainly endemic in Africa.[16,72]

Clinical presentation

Mycetoma is clinically characterised by a triad of a painless subcutaneous mass, sinus formation, and occasional discharge of material including pathognomonic grains. Grains are hard, differ in colour, and have the size of a coarse grain of sand. The mass is progressive and usually spreads to invade the deeper tissues and bones, resulting in local structural deformity and functional impairment. The most common sites of infection are the limbs. Rarely, the trunk, perineum, head and neck, and other body sites can be affected.

Males are more commonly affected than females. Most patients are young adults from poor socioeconomic backgrounds with minimal education. Mycetoma is frequently seen in farmers and students. About 20–25% of patients are children, who become stigmatised and often drop out of school. Most cases present with advanced disease, which is thought to be because of poor health education, scarcity of rural health facilities, and economic limitations in seeking care.[68–70]

Diagnosis

The causative organisms can be detected by cytological smears and surgical tissue biopsy examinations, grain microscopy, and fungal culture. For appropriate treatment, the distinction between actinomycetoma and eumycetoma is mandatory. Species identification is helpful for epidemiological studies, especially if molecular methods are used. Unfortunately, serology is insensitive and lacks specificity. Most of the diagnostic techniques are not available for people with mycetoma. There are also no point-of-care tests available for use in mycetoma-endemic villages.[18] Imaging is required to delineate the disease extent, especially for defining bone involvement and surgical excision options.

Treatment

Cure rate is 25–35% at best. Treatment for eumycetoma consists of prolonged antifungal therapy with second-generation triazoles. Itraconazole is the most commonly used drug,[73] but there is a potential role for voriconazole or posaconazole, or antifungal combinations, in refractory patients or even as first-line therapy. After azole therapy, surgical excision of the remaining mass is recommended.[74] Postoperative antifungal treatment is mandatory to reduce recurrence. Amputation is often needed in cases of advanced disease.[74] Current treatment options are usually associated with substantial toxicity, in addition to limited efficacy. Median treatment duration is 12 months, which makes it expensive for patients as well as for health authorities in endemic areas[5,73] (table 1).

In addition to disappointing cure rates, there is a high level of therapy dropout (55%), high need for amputation (15%), and frequent recurrence (27·5%). Because of the suboptimal management and high costs associated with standard treatment, many patients with mycetoma prefer alternative medicines. There is an urgent need for new, safe, and effective medicines for use in rural settings (appendix).[74]

Entomophthoramycosis

A less frequent implantation endemic mycosis caused by fungi of the order Entomophthorales, subphylum Entomophthoramycota, is called entomophthoramycosis or entomophthoromycosis, also known as subcutaneous zygomycosis. This disease is mostly reported in tropical and subtropical countries and encompasses conidiobolomycosis, caused by *Conidiobolus coronatus* and *Conidiobolus incongruus*, and basidiobolomycosis, caused by *Basidiobolus ranarum*.[20] These fungi are found in soil microbiota. *B ranarum* has been isolated from insects and decaying vegetables and also from the intestines of some reptiles, amphibians, and domestic and wild mammals. Although its prevalence is highest in tropical and subtropical zones in Africa, Asia, and Latin America, the burden of basidiobolomycosis might be expanding, with several cases reported in the USA.[5,75] Conidiobolomycosis is mostly reported in west Africa, South America, Saudi Arabia, Oman, India, and Taiwan.[20,22]

Clinical presentation

Human conidiobolomycosis is a slowly progressive disease that mainly affects the mucocutaneous facial structures such as the nose, cheeks, upper lip, and mucosa of the paranasal sinuses and pharynx. With progression, the lesions are usually associated with indolent diffuse oedema, leading to disfigurement and sequelae.[22,75]

Basidiobolomycosis is more prevalent in men than in women, but it also affects children. Most people infected with *B ranarum* are apparently immunocompetent. Initially, erythematous nodular lesions are observed on the trunk and limbs but with time, they can converge with a necrotic appearance and cellulitis. The infection can spread locally, affecting muscles, bones, regional lymph nodes, and even the adjacent organs. Increasing numbers of cases involve the gastrointestinal system. The clinical picture might mimic that of inflammatory bowel disease, especially Crohn's disease and malignancy.[21]

Diagnosis

Both forms of entomophthoramycosis are easily diagnosed by microscopy, fungal culture, and histopathological examination of biopsy specimens. Hyphae are broad, distorted, with very few septations, and show right-angle branching, as seen in mucormycosis. Unlike with mucormycosis, an immunoallergic reaction, the Splendore-Hoeppli reaction, an eosinophilic and amorphous deposit of hyaline material around parasites, resulting from local antigen–antibody reaction, might be observed with entomophthoramycosis. Molecular methods are useful for fungal identification of cultures and directly from tissue.[9]

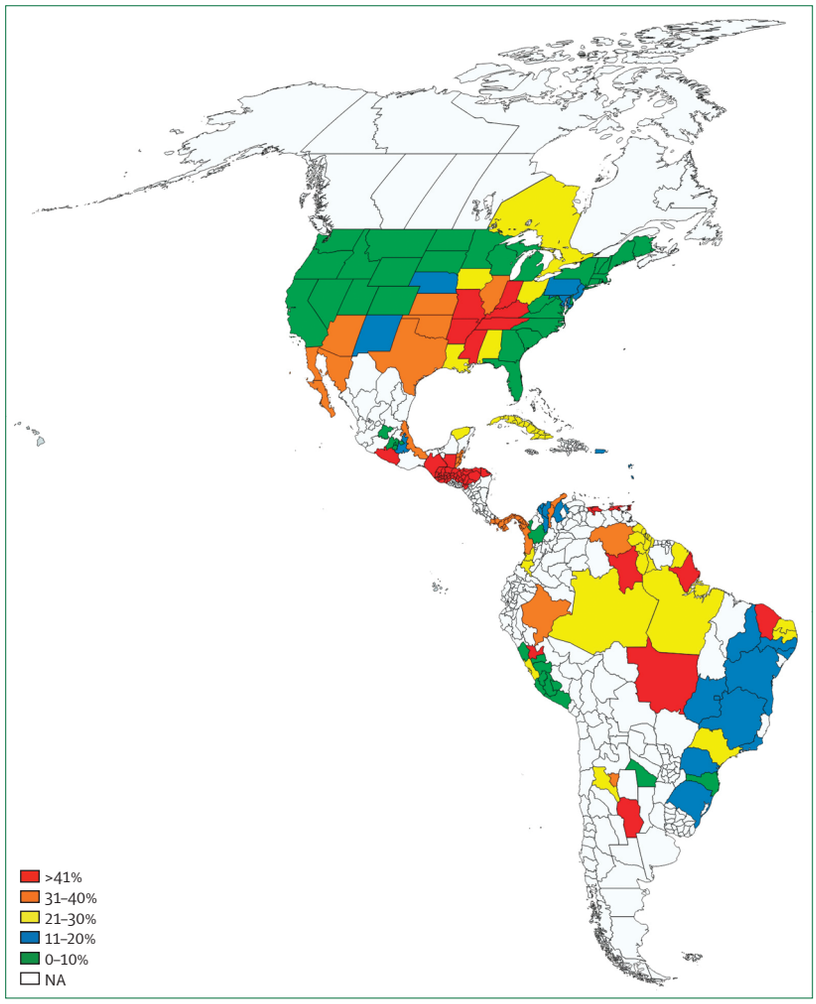

Figure 2: **Frequency of positive intradermal reactions against histoplasmin in the Americas and the Caribbean**
Data obtained from a review of 95 studies in 19 countries from 1949 to 2009.

Treatment

The use of triazoles, especially itraconazole, is considered the therapy of choice.[23] As a second option, potassium iodide has been used as monotherapy or in combination with itraconazole.[76] Surgical resection might also have a role. Voriconazole might be preferable for gastrointestinal basidiobolomycosis.[77] For severe and disseminated disease, amphotericin B formulations are indicated. No prospective therapeutic studies have been done for these infections, partly because of their rarity (table 1, appendix).

Lacaziosis

Lacaziosis, also called lobomycosis or Lobo's disease, is caused by a single fungal species, *Lacazia loboi* (formerly *Loboa loboi* and *Paracoccidioides loboi*), which infects human beings and dolphins. *L loboi* has never been cultivated in vitro. Taxonomic studies suggest that its closest relative is *Paracoccidioides brasiliensis*.[26] Lacaziosis is almost exclusively seen in South America's Amazon area, usually affecting some specific Indian populations, farmers, or people living in the rainforest.[5,24] The disease has been identified in dolphins outside the endemic area, including in south Brazil, Suriname, Florida (USA), and France;[78,79] these dolphins might have been infected when swimming through rivers from the Amazon basin.[25]

Most patients with lacaziosis are adults aged between 29 and 40 years who are apparently immunocompetent. They show slowly evolving and non-invasive polymorphic cutaneous lesions, including papules, nodules, dichromic macules, gummas, plaques, and verrucous and keloidal lesions. The pinna is commonly affected but other parts of the body surface can be involved.[24]

Diagnosis is obtained by microscopy or histopathological examinations when typical *L loboi* catenular arranged yeast forms are seen. Lacaziosis is usually refractory to antifungal therapy. A few patients have responded to a combination of clofazimine and itraconazole or to posaconazole monotherapy[27] (table 1, appendix).

Prevention and control

Cutaneous implantation mycoses present distinct challenges for prevention and control. No programmes have been designed for prevention or control of these diseases, mainly because of knowledge gaps in host susceptibility, resistance, and sources of infection. There is a pressing need for epidemiological studies to bridge that gap and to design such programmes, especially in agricultural workers.

Systemic endemic mycoses

Systemic endemic mycoses are mostly found in the Americas, Africa, and southeast Asia, where their true burden is poorly defined because of unavailability of good diagnostics in many of the affected countries and no mandatory reporting. These diseases are caused by the inhalation of asexual propagules of endemic thermodimorphic fungi, produced by their mycelial phase in soil. The estimated incidence of the endemic systemic mycoses is mainly based on results of skin test surveys. This test can be helpful in understanding if an individual has been previously infected by fungi such as *Histoplasma capsulatum*, *Paracoccidioides brasiliensis* or *Paracoccidioides lutzii*, or *Coccidioides immitis* or *Coccidioides posadasii*, but is unhelpful in the diagnosis of infection.[80,81]

The epidemiology of these infections seems to be shifting, partly because of global environmental changes, new agricultural practices such as intensive mechanisation, and increased use of fungicide. Other factors such as human migration and adventure tourism, use of immunosuppressive drugs, and organ transplantation are also contributing to increases in disease. We focus on two endemic fungal diseases in immunocompetent people that are often neglected by public health authorities and in

antifungal drug development. Infections in immunocompromised people are addressed in other papers in this Series.[82,83]

Histoplasmosis in non-AIDS patients

H capsulatum, a thermodimorphic fungus, is the infectious agent of histoplasmosis, a disease that is endemic mainly in the American continent but is now being recognised more globally[81,84] (figure 2). Histoplasmosis is considered a disease of worldwide distribution, with hyperendemic areas. The presence of the pathogen and clinical disease are described in large geographical areas, including most of Asia and Africa. In Europe, imported cases occurring in HIV-infected residents or travellers from South America have been identified, notably in France, Spain, and Italy. A small number of autochthonous cases have been reported in Australia.[84]

Epidemiology

Environmental sources of *H capsulatum* include bat and bird guano, compost, soil, and other organic substrates. Both sexes and individuals of all ages can be infected.[85] Outbreaks of histoplasmosis have been reported and the fungus has been frequently recovered from the soil in these endemic areas.[84,85] Exposure to *H capsulatum* microconidia usually causes no clinical symptoms or results in a self-limiting acute disease. However, immunocompromised individuals, especially transplant recipients and patients with AIDS, might develop progressive disseminated disease with a high fatality rate. Other populations are also at increased risk, including patients taking immunosuppressors such as calcineurin and tumour necrosis factor inhibitors.[86] Solid organ transplant and haematological stem cell transplant recipients are also at increased risk for histoplasmosis. Transplant recipients usually present with disseminated infection, which can occur years after transplantation. Cohort studies estimated the 1-year cumulative incidence for histoplasmosis in solid organ transplant recipients to be between 0·1% and 0·5% in the USA.[87,88]

Clinical presentation

The clinical manifestations of histoplasmosis are so varied that this mycosis is commonly referred to as the syphilis

	Epidemiology and geographical distribution	Clinical presentation	Diagnosis	Treatment
Acute pulmonary histoplasmosis	Variable sex and age distribution, associated with exposure to environmental sources (eg, caves, ruins, sites contaminated with bird or bat guano); normally immunocompetent hosts	Often subclinical, self-limited, and mostly unrecognised. Fever, chills, cough, and dyspnoea, which might progress to a full-blown acute pulmonary syndrome requiring mechanical ventilation support. Inhalation of a small inoculum might result in a subacute disease, with a more insidious course	Imaging: patchy infiltrates and mediastinal adenopathy; inhalation of a small inoculum might show only focal infiltrates; can mimic a viral or atypical pneumonia. Mycology (acute % and subacute %): pathology 20% and 42%; culture 42% and 54%; antibody 64% and 95%; antigen 83% and 30%	Usually not required for self-limited disease. Amphotericin B is preferred for severe disease
Chronic pulmonary histoplasmosis	Patients with previous chronic respiratory disease	Chronic cough with sputum, dyspnoea, fever, and weight loss	Imaging: can reveal cavitary lesions that might mimic pulmonary tuberculosis. Mycology: pathology 75%; culture 67%; antibody 83%; antigen 88%	Itraconazole (200 mg three times daily for 3 days, then 200 mg twice daily) at least for 12 months; monitor clinical response
Mediastinal lymphadenopathy	Younger populations; can present as an early complication (mediastinal adenitis and mediastinal granuloma) or a late complication (mediastinal fibrosis); immunocompetent hosts	Compressive symptoms from adjacent structures. In mediastinal fibrosis, compressive symptoms are more severe	Imaging: chest imaging reveals a homogeneous (mediastinal adenitis) or heterogeneous (mediastinal granuloma) mediastinal mass, may obstruct adjacent structures (mediastinal fibrosis)	Only indicated if direct evidence of compressive symptoms. Mediastinal adenitis: steroids and itraconazole (for 6–12 weeks). Mediastinal granuloma: surgical resection and itraconazole (for 6–12 weeks). Mediastinal fibrosis: surgery, bronchial artery embolisation, and vascular stents
Disseminated	Immunocompromised hosts (patients on TNF inhibitors, transplant recipients)	Fever, weight loss, hepatosplenomegaly, and mucosal and skin lesions. Cutaneous manifestations are mostly common in Latin America (~50%), which might be caused by specific strains. Septic shock and multi-organ failure (uncommon). CNS involvement with meningitis or focal brain lesions can also occur (rare)	Imaging: miliary infiltrates, but other abnormalities or even the absence of lesions can also be seen. Mycology: pathology 76%; culture 74%; antibody 75%; antigen 92%	Liposomal amphotericin B (3 mg/kg per day) is the drug of choice. If not available, amphotericin B deoxycholate (1 mg/kg per day) can be used. Both must be followed by itraconazole for at least 1 year

Percentages in the table represent the sensitivity of the diagnostic tests. TNF=tumour necrosis factor.

Table 2: **Main characteristics of histoplasmosis**

of the fungal world or the great imitator, because it can mimic several other disorders,[89,90] particularly tuberculosis. Acute pulmonary histoplasmosis, sometimes with erythema nodosum or erythema multiforme, is usually self-limiting. Subacute disseminated histoplasmosis can present with fever of unknown origin and weight loss, hoarseness, gastrointestinal ulceration or strictures, endocarditis, and meningitis, sometimes with pulmonary involvement. Adrenal masses, usually bilateral, are a distinctive presentation. Chronic cavitary pulmonary histoplasmosis is a rare disease that may be seen in individuals with underlying pulmonary disorders and might be confused with smear-negative tuberculosis.

Diagnosis

Diagnosis of histoplasmosis is often difficult. Biopsy, including bone marrow aspiration or adrenal or gastrointestinal biopsy, is commonly needed to obtain tissues or fluids for culture or histopathology. The histological finding of small intracellular budding yeasts using fungal stains of *H capsulatum* is diagnostic, although it can be mistaken for trypanosoma, leishmania amastigotes, or *Talaromyces marneffei* yeast cells.[85] Cultures are very useful for diagnosis in individuals with disseminated disease, but the organism can take up to 4 weeks to grow.[85] Standard blood culture methods are not reliable for *H capsulatum* detection; the Isolator lysis-centrifugation method (Wample Laboratories, Cranbury, NJ, USA) is preferred but usually not available. Molecular detection by PCR is useful.[91] Detection of antibodies against *H capsulatum* can be useful for diagnosis in immunocompetent individuals, especially in subacute disseminated and pulmonary disease, but the precipitin assay is not very sensitive. Histoplasma antigen can be detected in many patients with disseminated disease, allowing for an early diagnosis.[92] Unfortunately, in countries with the highest burden of disease, access to this diagnostic test is restricted.[93]

Treatment

For subacute disseminated histoplasmosis and chronic pulmonary histoplasmosis, itraconazole is the drug of choice.[94] Itraconazole use is limited by several factors, including poor bioavailability, high cost, and drug interactions.[95] Amphotericin B (especially liposomal) might be preferred as initial therapy for very ill patients (table 2, appendix).

Paracoccidioidomycosis

In Latin America, paracoccidioidomycosis is the second most prevalent endemic mycosis. The burden of this disease has a substantial impact on public health of countries in the endemic area. An estimated 10 million Latin Americans are infected and 1–2% will present with some clinical form of the disease weeks to several decades after exposure.

Epidemiology

The annual incidence of paracoccidioidomycosis ranges from 1 to 3·7 new cases per 100 000 inhabitants with mortality of 1·65 per million inhabitants in Brazil.[80,81] This disease is caused by two distinct species: *P brasiliensis* and *P lutzii*, which are found in geographically different areas.[96,97] Soil is the main natural source for infectious airborne conidia and people living in rural areas are the main population at risk. Both sexes are equally likely to get infected, but development of clinical disease, especially the chronic form of the disease, is more

	Epidemiology and geographical distribution	Clinical presentation	Diagnosis	Treatment
Acute or subacute (juvenile)	Visited or lived in the endemic area; boys and girls are equally affected in pre-puberty; exposure to environmental sources: earth or soil contact	Short incubation period, often disseminated and progressive. Fever, generalised lymphadenopathy, liver and spleen enlargement, skin and bone and joint involvement. Respiratory and mucosal symptoms are uncommon	Mycology: microscopy and culture of clinical samples (eg, lymph node aspirates, scrapping of cutaneous lesions). Histopathology: mostly a suppurative and granulomatous reaction with multi-budding yeasts (pilot wheel and Mickey Mouse shapes). Serology: positive IgG antibodies detected by double immunodiffusion, ELISA, or counter immunophoresis, 48 kDa antigen reaction, PCR	Amphotericin B deoxycholate, 1 mg/kg up to 1–1·5 g (cumulative dose). Lipid amphotericin B, 3 mg/kg in cases of toxicity to conventional amphotericin B. After amphotericin B, itraconazole (for 6–12 months) or co-trimoxazole (for 12–24 months) for maintenance is required. Alternative: intravenous co-trimoxazole (160 mg trimethoprim and 800 mg sulfamethoxazole per day)
Chronic (adult)	Visited or lived in the endemic area, men, smokers, farming, forestry, or building occupation. Occasionally seen in travellers returning from an endemic area	Weight loss and respiratory symptoms, dyspnoea, productive cough. Oropharyngeal ulcerated lesions, cutaneous, lymphatic, neurological, adrenal involvement, rarely CNS involvement	Imaging: non-specific. Usually perihilar masses, liver and spleen enlargement, osteolytic lesions, CNS masses	Mild to moderate severity: itraconazole, 200 mg per day for 6–12 months or co-trimoxazole (160 mg trimethoprim and 800 mg sulfamethoxazole) for 12–24 months; alternatives: voriconazole 400 mg per day or posaconazole 800 mg per day; monitor clinical response. Severe disease: same as the acute and subacute forms

Table 3: **Main characteristics of paracoccidioidomycosis**

frequent in men than in women, with an average male-to-female ratio of 13:1.[80,98] Women are protected from the disease by oestradiol, which prevents the inhaled filamentous forms of the fungus converting into the pathogenic yeast form.[98] Occasional non-autochthonous cases of paracoccidioidomycosis have been reported outside Latin America. These cases represent re-crudescence of latent infection occurring up to 50 years (mean 15 years) after departing the endemic area.[99]

Clinical presentation

Paracoccidioidomycosis infection probably occurs early in life. Similar to other systemic endemic mycoses, the primary pulmonary infection is unapparent and most infected individuals will remain disease-free for life. A small proportion of patients will develop one of two patterns of disease: the acute or subacute form (juvenile type) or the chronic or adult type. In both forms, dissemination might occur and many organs can be affected, especially the lungs, oropharynx, lymph nodes, skin, adrenal glands, and CNS. The acute form is characterised by a short period of evolution, from 15 days to 3 months, and is more severe with dissemination to other organs.[100] If undiagnosed, the natural evolution of paracoccidioidomycosis disease usually results in death. Both clinical forms can mimic several infectious and non-infectious disorders, including cancer, sarcoidosis, tuberculosis, and histoplasmosis.[97,100]

Diagnosis

Diagnosis of paracoccidioidomycosis can be easily achieved by observation of typical multiple budding yeast forms (resembling a pilot wheel) in wet mounts or histopathology sections. Sputum can be positive in 60–70% of patients with the chronic pulmonary form of the disease; lymph node aspirates have higher sensitivity.[99] Culture is usually positive but it might take weeks for the fungus to grow. A decrease in serum antibodies is helpful for monitoring therapy and can also be helpful for diagnosis.[99,100] Antigen detection and PCR are used for diagnosis but although standardised, are not fully validated.[101,102]

Treatment and complications

Unlike some other pathogenic fungi, *Paracoccidioides* spp are very susceptible to antifungal drugs and respond well even to the sulphonamides. Itraconazole is the therapy of choice for all mild to moderate forms of the disease. A second-line choice is co-trimoxazole, but because this compound is fungistatic only, a long treatment duration is required. For severe and disseminated clinical disease, induction therapy with amphotericin B is required followed by itraconazole.[103] Paracoccidioidomycosis is mainly a granulomatous disease. After therapy, complications frequently occur including microstomy, lung fibrosis, Addison's syndrome, and neurological impairment (table 3, appendix).

Search strategy and selection criteria

We searched PubMed on July 19, 2016, using a structured search strategy with the terms ("humans") AND ("endemic" OR "neglected" OR "implantation" OR "subcutaneous") AND ("histoplasmosis" OR "Histoplasma" OR "chromoblastomycosis" OR "chromomycosis" OR "chromoblastomycosis" OR "sporotrichosis" OR "Sporothrix" OR "mycetoma" OR "lacaziosis" OR "lobomycosis" OR "Lacazia" OR "entomophthoromycosis" OR "subcutaneous zygomycosis" OR "conidiobolomycosis" OR "basidiobolomycosis" OR "paracoccidioidomycosis" OR "Paracoccidioides") AND ("burden" OR "epidemiology" OR ["clinical presentation"] OR "diagnosis" OR "treatment" OR "therapy" OR "therapeutics" OR "complications"). No date limits or language restrictions were applied.

Conclusions

Neglected endemic mycoses are an important public health problem worldwide. A general lack of public health awareness of the importance of these diseases is making them a priority in areas where diagnostics and treatment are needed. Populations in tropical and subtropical rural endemic areas remain at a continuous risk of infection. Early diagnosis with simple and rapid tests is not available for most patients. There are substantial health-care expenditures associated with the endemic mycoses. Prevention, rapid diagnosis, and therapy are urgently needed. Surveillance and epidemiological studies are needed to understand the true burden of these diseases.

Contributors

FQ-T contributed to manuscript design, data collection, data interpretation, and writing of the following topics: introduction, sporotrichosis, chromoblastomycosis, lacaziosis, entomophthoramycosis, paracoccidioidomycosis, and conclusions. AHF contributed to data collection, data interpretation, and writing of the mycetoma topic. DRF, DHC, TC, and ACP contributed to data collection, data interpretation, and writing of the histoplasmosis topic. TC and ACP contributed to English revision. FQ-T and ACP contributed to revision of the final version of the manuscript.

Declaration of interests

We declare no competing interests.

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