Mycetoma

Introduction
Mycetoma is an old and still neglected disease characterised by massive deformities and disabilities and enormous negative impact on patients and community.1,2 The disease is endemic in many tropical and subtropical regions across the world with high prevalence in the “Mycetoma belt.”3,4,5 The belt stretches between 15°S and 30°N, and it includes the countries of Sudan, Somalia, Senegal, India, Yemen, Mexico, Venezuela, Columbia, Argentina, Iran, and others.6,7,8

Mycetoma is a chronic debilitating subcutaneous granulomatous inflammatory disease classified as eumycetoma (caused by fungi) and actinomycetoma (caused by bacteria).9,10 Its pathogenesis is poorly understood, probably with environmental, genetic and immunogenic factors all incriminated.11,12,13

Figure 1: Typical microscopic appearance of mycetoma grain

Causative Organisms
The most common bacterial causative agents are Nocardia brasiliensis, Actinomadura madurae, Streptomyces somaliensis, and Actinomadura pelletieria.11 The most common fungi causing disease are Madurella mycetomatis, Madurella tropicana, Madurella fahali and Scedosporium apiospermum.14,15,16,17 In general, actinomycetoma is more prevalent in Mexico and South America while eumycetoma is more frequently seen in the African continent but within a country, the mycetoma type distribution is variable and differs per region.18,19,20,21,22,23,24

There remain many controversies on the infection entry route although traumatic inoculation of causative organisms into the skin and subcutaneous tissue is the popular theory.25 The incubation period of mycetoma is unknown, yet, in experimental animals, a three months incubation period was reported.26

Epidemiology
The true annual incidence and prevalence of mycetoma globally are not well documented as it is a badly neglected and not a reportable disease.26,27 There are probably between 20,000 and 50,000 cases worldwide, based on literature reports. Most cases are reported from Sudan, Mexico and India. Population prevalence data are available for Mauritania (3.5/100,000) and Sudan (1.8/100,000). High rates are also found in Mexico, Senegal, Niger and Somalia. The few published reports on the epidemiology of mycetoma are mostly hospital-
based describing patients with late presentations. The most common age of infection is young adulthood (70% of the cases are between ages 11 and 40), with some children and older people affected. In most countries men are affected more than women.

Figure 3: The 'Mycetoma Belt' depicted by case report numbers and reports to WHO (27)

Mycetoma affect those doing outdoor activities and both genders are equally committed to these activities. The majority of patients are farmers, workers, and students. Mycetoma frequently affects the poorest of the poor in remote endemic regions of low socioeconomic status, and the disease contributes further to their poverty and community economic loss.

Clinical Presentation
Mycetoma patients tend to present late for medical treatment and the cause of that is multifactorial. The disease is slowly progressive and initially painless. Other factors delaying medical help include the patients’ low socio-economic status and health education level, financial constraints, long distances to secondary care facilities and the insecurity of many medical and health facilities in endemic villages.

The disease is characterised by the triad of a painless subcutaneous mass, multiple sinuses and purulent or seropurulent discharge that contains grains. Grains are of various colours, sizes and consistent with the causative organism. Their colour can be black, white, yellow or red and that gives a clue to the causative agents. The subcutaneous mass usually spreads to involve the skin and the deep structures, resulting in destruction, deformity, and loss of function, and occasionally it can be fatal.

Mycetoma frequently affects the foot and hand and that is seen in more than 80% of patients. Occasional cases of head and neck, chest, abdominal wall, perineum or gluteal region are recorded.
The Differential Diagnosis
In endemic regions alternative diagnoses include thorn and foreign body granulomas and many benign soft tissue tumours such as fibroma and lipoma and infections such as chronic osteomyelitis.\textsuperscript{5,6,7}

Diagnosis
The identification of the mycetoma causative agent to the species level and the disease extent and spread along the tissue planes are both crucial and essential for appropriate treatment and management.\textsuperscript{49} Individual grains, extracted from a sinus, have a distinctive appearance under direct microscopy, but their appearance is insufficient to determine the infection genus or species. Grains that are cultured may sometimes be positive. Surgical biopsy is important to obtain grains for culture and molecular identification and histopathological examination.\textsuperscript{50-59}

Figure 5: Extensive heel and foot disease

Culture requires a range of media, including fungal, bacterial and mycobacteria plates and/or liquid culture. All of the bacteria and fungi causing mycetoma are tricky to identify, requiring years of experience and there are many variants and isolates that resemble others. Formal genetic identification using sequencing is most reliable. Susceptibility testing is not standardized and has not been well-correlated with treatment outcome.

Various imaging modalities are useful to define the extent of disease. Conventional X-ray, ultrasound to identify grains and MRI all have an essential place in determining the disease spread and to establish a plan of management.\textsuperscript{60-63} Currently, the available diagnostic tests and
techniques are invasive, tedious, expensive and not field friendly. Most of them do not exist in endemic regions, and patients need to travel far to establish the diagnosis.  

**Figure 7**: The ultrasound appearance  

**Figure 8**: X-ray of a patient with eumycetoma foot of eumycetoma showing multiple big cavities  

**Treatment**  
Generally, actinomycetoma responds to a combination of chemotherapeutic agents. This combination is mandatory to avoid the development drug-resistant and for better disease eradication. Current combinations recommended include co-trimoxazole (980 mg BD/day) and amoxicillin-clavulanic acid (1 gram/day). Second-line treatment is a combination of amikacin sulphate (15mg/kg/day) and co-trimoxazole (980 mg BD/day) given in a form of cycles - each cycle is 5 weeks. The treatment may last for more than one year, and the cure rate is 70-80%.  

**Figure 9**: Actinomycetoma of the shoulder before and after antibiotic therapy  

The treatment of eumycetoma is prolonged with a low cure rate, high recurrence and dropout rates. It is a combination of antifungal treatment (currently itraconazole 400mg/day) and surgical excision. The excision ranges in extent from wide local excision, repetitive debridement to amputation. Surgery is indicated when the lesion is localised and for cases resistant to medical therapy, and it may be life-saving in advanced disease that is complicated by secondary bacterial infection, sepsis, massive bone involvement, and poor general condition. Some data indicate that voriconazole may be a better choice for certain organisms, notably *Medicopsis (Pyrenochaeta) romeroi*. 
Outcome
The majority of patients with actinomycetoma respond to therapy and are cured, unless the deep visceral invasion such as the brain or pelvic organs are affected. Some residual disability is seen, especially when joints are affected.

Eumycetoma patients usually respond poorly to medical therapy. Improvement is slow and hard to evaluate, even after months of therapy. Many patients eventually fail to complete education or lose their jobs and become a burden on families and the community. 5,6,7,8

Figure 10: Late stage eumycetoma that is an all too common eventual outcome

Community management and prevention
Recently the Mycetoma Research Center (MRC), Sudan had reported on a new holistic approach to manage mycetoma patients locally at the village level. The MRC has established a regional mycetoma center in one of the endemic mycetoma villages in Sudan. The patients were treated locally in that center, the local medical and health personals were trained in early case detection and management, the local community was trained on mycetoma advocacy, and environmental conditions improvement. This comprehensive approach has also addressed the patients’ socioeconomic constraints that deter timely presentation and treatment. This approach has also included active involvement of the local health authorities, community and civil society and donor contributions to deliver the optium management. (3)

Summary
To date and despite progress in mycetoma research, a huge knowledge gap remains in mycetoma pathogenesis and epidemiology resulting in the lack of objective and effective control programmes. Currently, the available disease control method is early case detection and proper management. However, the majority of patients present late with extensive disease and for many of them, heroic substantial deforming surgical excisions or amputation are the only prevailing treatment options. Likewise, there is no point-of-care diagnostic test for mycetoma. Urgent collaborative work is necessary to reduce patients suffering and to decrease the overall impact from this truly debilitating disease.

Public health needs:
- Global annual incidence and prevalence of mycetoma is not known, but it contributes to poverty exacerbation in many of the poorest countries. Improved burden statistics are required.
- Delays in diagnosis leads to more severe disease, which increases the need for major surgery, long-term disability and death. Campaigns to encourage affected patients to present early to medical centres for care will facilitate better outcomes.
• Widespread availability of trained microscopists, histopathologists and fungal culture technology (all WHO Essential Diagnostics), combined with imaging, are necessary to achieve definitive diagnosis and develop optimal treatment plans.

• Itraconazole, voriconazole and amikacin are required for therapy, combined with surgical expertise and monitoring capability.

• Public awareness of the disease and making mycetoma a notifiable disease will increase awareness and potentially decrease the rate of complications.

• Research to better understand environmental sources of the causative fungi, and the disease transmission are essential to deliver evidence-based advice to communities on prevention.

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