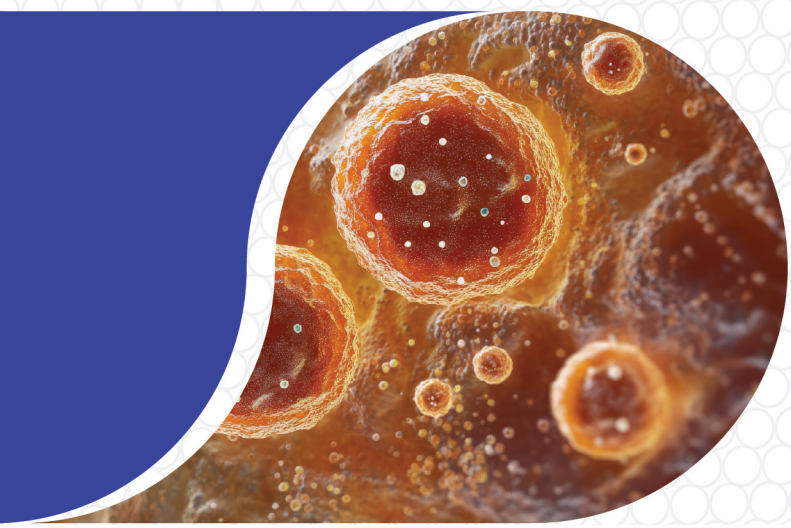
ICP Monograph on Neglected Tropical Diseases

Editor
Jayanta K Panda



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Mycetoma

Amitav Mohanty

INTRODUCTION

Mycetoma, also known as Madura Foot, is a chronic, debilitating infection that mainly affects subcutaneous tissues, causing significant morbidity and socioeconomic issues.[1] Classified as a neglected tropical disease (NTD) by the World Health Organization, it is most prevalent in the tropical and subtropical "mycetoma belt" of Asia, Africa, and Latin America, yet it is underreported and poorly understood.[2] The disease originates from both bacterial (e.g., *Nocardia, Actinomadura, Streptomyces*) and fungal (e.g., *Madurella, Leptosphaeria, Acremonium*) pathogens, with over 30 species identified.[3] It typically spreads through skin punctures from contaminated materials, leading to severe infections that may involve bones and muscles, characterized by granulomas, abscesses, and grain-producing sinus tracts. Clinically, mycetoma presents as a painless swelling that evolves into a hard mass with draining sinuses, mainly affecting limbs.[4,5] Diagnosis is often complicated by its subtle onset, requiring detailed clinical evaluations, imaging, and microbiological testing, including grain detection in discharges. The disease disproportionately affects young to middle-aged males, particularly those in occupations with high exposure to soil.[6,7] Treatment depends on the nature of the causative agent and often involves prolonged use of antibiotics or antifungals, supplemented by surgical interventions to remove infected tissues. Despite rigorous treatment approaches, mycetoma has a high rate of relapse and leads to significant disability.[8,9] Managing mycetoma presents numerous challenges, including the need for improved diagnostic and therapeutic methods, comprehensive public health strategies for prevention, and enhanced research for new treatments and vaccines.[10] Effective management also requires boosting community education and improving socioeconomic conditions in affected regions. Increased international cooperation and funding are crucial to enhance the global response to mycetoma and improve patient outcomes.[11,12]

EPIDEMIOLOGY OF MYCETOMA

Mycetoma is a chronic, progressive disease with severe impacts on bones, skin, and subcutaneous tissues, prevalent primarily in the tropical and subtropical "mycetoma belt" spanning 15° south to 30° north latitude **(Fig. 1)**.[13] This region, which includes parts of Africa, India, the Middle East, and Central and South America, reports the highest number of cases, particularly in Sudan, Somalia, India, Mexico, and Yemen. The disease's distribution reflects the influence of geographic, environmental, and societal factors conducive to the survival and proliferation of its causative organisms.[14,15]

Epidemiological patterns in endemic areas:

- *Sudan*: Records the highest global incidence, mainly due to the fungal agent *Madurella mycetomatis*, affecting predominantly young male adults in farming.
- *Mexico*: Predominantly caused by the bacterium *Nocardia brasiliensis*, with a higher occurrence of actinomycetoma, particularly in rural soil-rich environments.
- *India*: Displays a diversity of pathogens affecting both rural and urban areas, with both types of mycetoma prevalent among those in contact with contaminated soil.

Risk factors and transmission:

- *Environmental*: The disease thrives in arid and semiarid regions with occasional heavy rainfall.
- *Occupational*: High-risk groups include agricultural workers and others frequently in contact with soil.
- *Socioeconomic*: Most affected are the poorest communities with limited access to healthcare and inadequate health education. Poor protective measures and wound care increase risk.

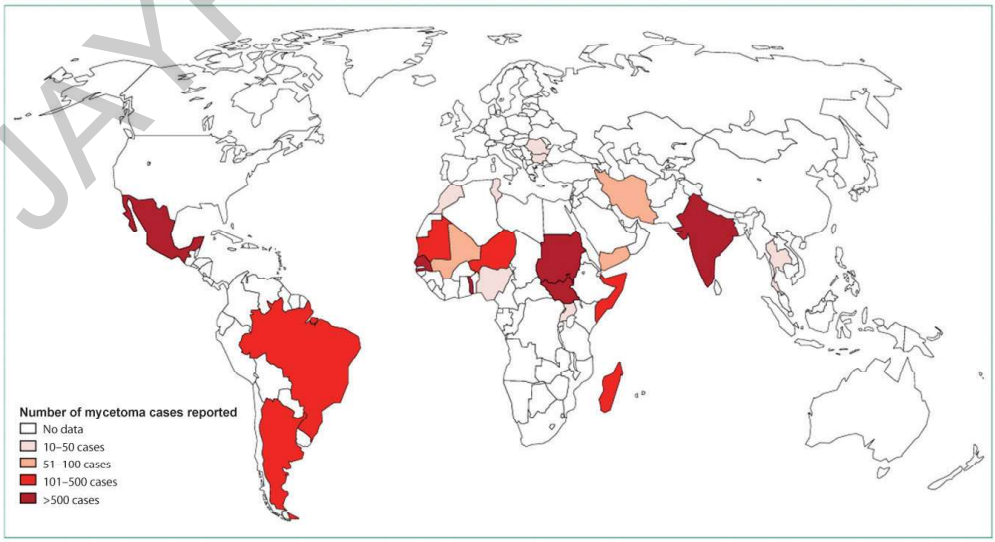


FIG. 1: Global distribution of mycetoma in 2013.[3]

Age and gender: It mostly affects males aged 20–40 years, who are often the primary earners, exacerbating the socioeconomic impact.

Transmission dynamics: It spreads through direct skin punctures by contaminated materials, suggesting an environmental reservoir.

Public health impact and challenges:

- Mycetoma's global impact is under-documented but includes substantial morbidity and disability, often requiring surgical interventions like amputations.
- Challenges include low awareness, diagnostic resemblance to other diseases, and its status as a neglected disease, which limits research funding and public health attention.

Enhanced surveillance, better health education, and more effective treatments are essential. Tackling mycetoma effectively requires international cooperation and integrated public health strategies to improve outcomes and reduce the disease's overall burden.[16-20]

ETIOLOGY

Mycetoma is caused by over 70 species of bacteria and fungi, a number that could increase with advances in molecular identification. Four fungal species—*Leptosphaeria senegalensis, Trematosphaeria grisea* (previously *Madurella grisea*), *Scedosporium apiospermum* (previously *Pseudallescheria boydii*), and *Madurella mycetomatis*—account for 90% of eumycetomas, predominantly found in Africa. Actinomycetoma, more common in Central and South America, is often caused by species like *Nocardia brasiliensis*, *Streptomyces somaliensis, Actinomadura madurae*, and *Nocardia asteroides*, which are typically present in the local water and soil.[21-24]

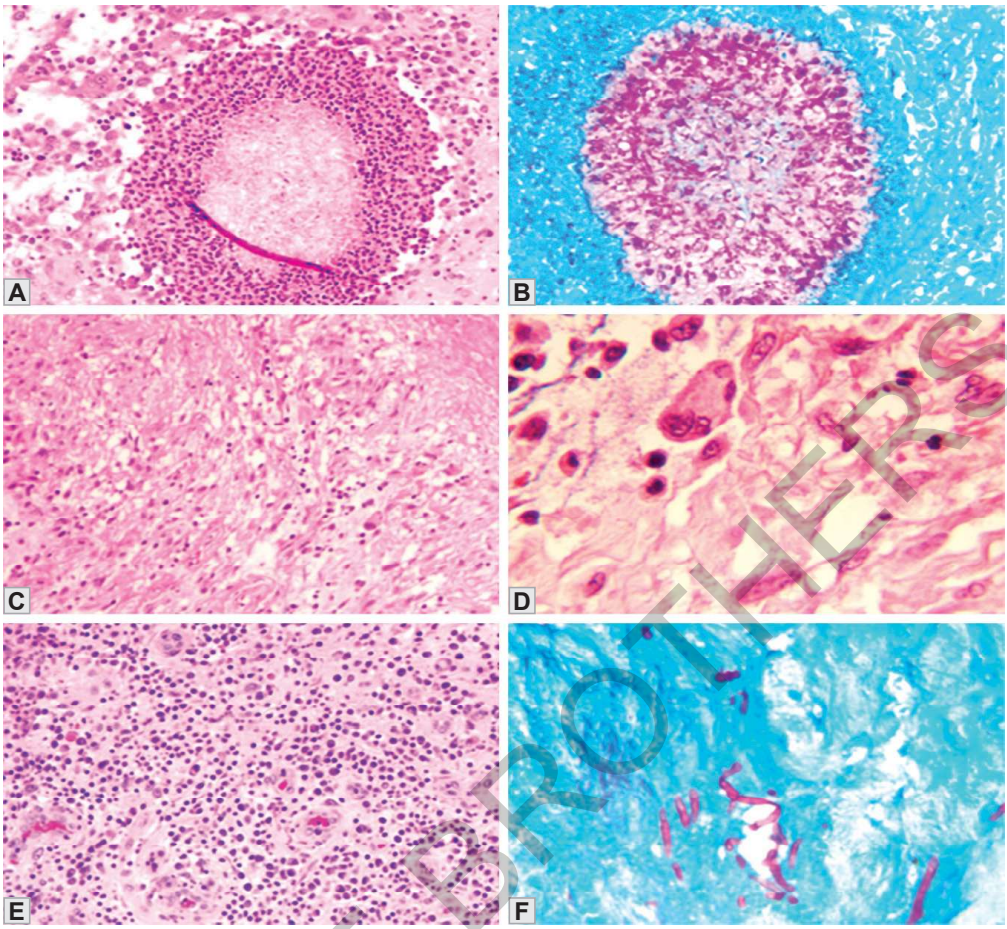
PATHOGENESIS OF MYCETOMA

Mycetoma is a chronic infection that typically affects subcutaneous tissues, manifesting as swelling and the formation of sinuses. The disease can be caused by various bacterial and fungal pathogens, leading to either actinomycetoma or eumycetoma **(Figs. 2A to F)**.[25] The interaction between environmental factors, host genetics, and microbial virulence plays a crucial role in mycetoma's development. The infection usually begins when pathogens enter through cuts or punctures, often from contaminated thorns or splinters, common in farming or herding settings.[26]

Host Immune Response and Tissue Damage

The disease progression involves several immune responses:

- *Innate immune response*: Neutrophils and macrophages, as the first defense line, attempt to destroy the pathogens. However, some like *Nocardia brasiliensis* have mechanisms to resist these immune attacks.
- *Adaptive immune response*: This involves T-cell responses and antibody production. Mycetoma often triggers a T helper 2 (Th2)-type response, which



FIGS. 2A TO F: Histopathology of eumycetoma. (A) A histological section using hematoxylin and eosin (H&E) stain at 100× magnification shows fungal elements surrounded by neutrophils and encased by plasma cells, macrophages, lymphocytes, eosinophils, and blood vessels. (B) Periodic acid–Schiff (PAS) staining at 100× magnification highlights the fungal elements. (C) An H&E-stained section at 100× magnification displays macrophages and Langerhans giant cells primarily within a granuloma. (D) At a higher magnification of 400×, H&E staining details the cellular environment within a granuloma. (E) H&E staining at 100× magnification shows epithelioid granulomas enriched with lymphocytes, plasma cells, epithelioid cells, and proliferated blood vessels. (F) PAS staining at 100× magnification indicates a small number of fungal elements within a granuloma.[34]

may be ineffective against the infection, leading to chronic inflammation and fibrosis.

- *Granulomatous inflammation*: The immune system forms granulomas to contain the infection, but these also cause the characteristic swelling and deformity associated with mycetoma.
- *Tissue damage and dissemination*: Chronic inflammation and granuloma formation ultimately damage skin and deeper tissues, including bones, and lead to the formation of sinus tracts discharging pus with grains, a diagnostic hallmark of mycetoma.[27-30]

Environmental and genetic factors significantly influence mycetoma development. For instance, genetic predispositions may affect susceptibility to mycetoma, as those affected may have different immune response genes

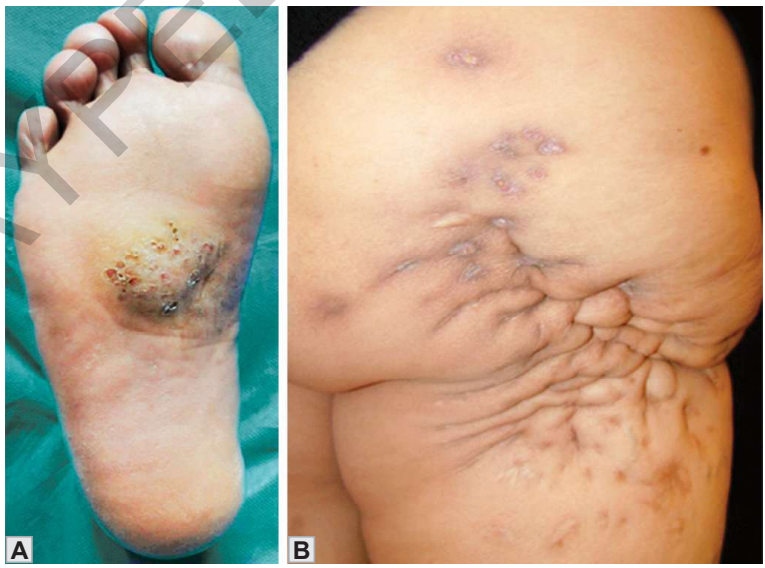
compared to those who are not. The pathogens' ability to produce virulence factors such as proteases and immunosuppressive substances also impacts the severity of the infection and its clinical outcomes. Overall, the pathogenesis of mycetoma involves complex interactions between the causative organisms and the host's immune system, influenced by genetic and environmental factors.[31-33]

CLINICAL MANIFESTATIONS AND COMPLICATIONS OF MYCETOMA

Mycetoma is a chronic, debilitating disease primarily affecting the skin and underlying tissues, often leading to severe complications like bone involvement.[34] The disease starts as a small, painless nodule at the site of entry—typically from a splinter or thorn prick—and can develop into a large swelling or mass over time. Distinguished by bacterial and fungal pathogens, it results in actinomycetoma and eumycetoma, respectively, each with distinct clinical signs **(Figs. 3 and 4)**.[34-37]

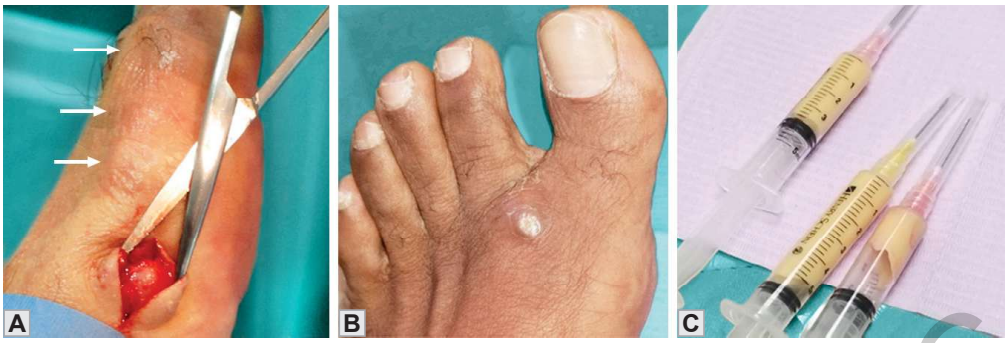
Progression and symptoms:

- *Swelling and mass formation:* Characterized by a growing, sometimes painful mass that may involve deeper tissues
- *Sinus tract formation:* A key feature where tracts form on the skin, discharging pus and grains, which are small, colored granules of the microorganisms
- *Discharge:* The discharge is often purulent, with the color and nature of the grains helping to differentiate the type of mycetoma—black or white grains in fungal cases (eumycetoma) and yellow to red in bacterial cases (actinomycetoma).



FIGS. 3A AND B: (A) A 43-year-old male with a raised, swollen actinomycetoma on the middle sole, featuring multiple sinuses and yellow discharge, caused by *Nocardia brasiliensis* over 7 years; (B) a 54-year-old female with multiple actinomycetomas at various stages on the gluteus and right thigh, caused by *Nocardia brasiliensis* over 12 years.

Courtesy: Dr Jesus Dante Guerra.



FIGS. 4A TO C: The clinical presentation of eumycetoma variants: (A) A 51-year-old male with multiple nodular eumycetomas on the left foot, without sinuses or discharge; (B) A 57-year-old male with a large 8 × 3 cm cystic eumycetoma in the first intermetatarsal space of the left foot; and (C) Thick yellowish-white gelatinous fluid aspirated from the cystic eumycetoma in (B).

Distribution and high-risk groups: Mycetoma most commonly affects the extremities, like feet and hands, which frequently contact soil. Farmers and laborers are particularly susceptible due to their work environments.[38]

Complications:

- *Bone involvement*: The infection may spread to bones, causing osteomyelitis, deformities, and functional impairments.
- *Secondary infections*: Open wounds and sinus tracts can lead to additional bacterial infections.
- *Mobility issues*: Damage to bones and joints, especially in the feet, can severely impact mobility.
- *Social and economic impact*: The disease's chronic nature and potential for disfigurement can cause social stigma, employment loss, and significant financial difficulties.

Mycetoma is more prevalent in males due to higher exposure in agricultural and similar outdoor occupations. It typically affects young to middle-aged adults, the primary income earners, enhancing its socioeconomic impact.[39,40] The clinical symptoms of mycetoma can vary significantly based on the causative organism, the host's immune system, and environmental factors. Actinomycetoma, for instance, tends to progress faster and cause early bone damage compared to eumycetoma.[41,42]

DIAGNOSIS OF MYCETOMA

Mycetoma is a chronic infection known for causing severe deformity, disability, and progressive morbidity, necessitating timely and accurate diagnosis through clinical examination, imaging, and microbiological testing.[43] Typically, patients present with painless lumps, multiple sinus tracts, and discharge-containing grains, often accompanied by firm, palpable nodules under the skin, particularly after trauma or contact with soil or thorny plants in endemic areas.[44]

Key clinical signs:

- *Swelling and mass formation*: Starts small and painless, gradually enlarging
- *Sinus tracts*: Characterized by purulent discharge with granules or grains that help identify the type of mycetoma—actinomycetoma or eumycetoma[45,46]

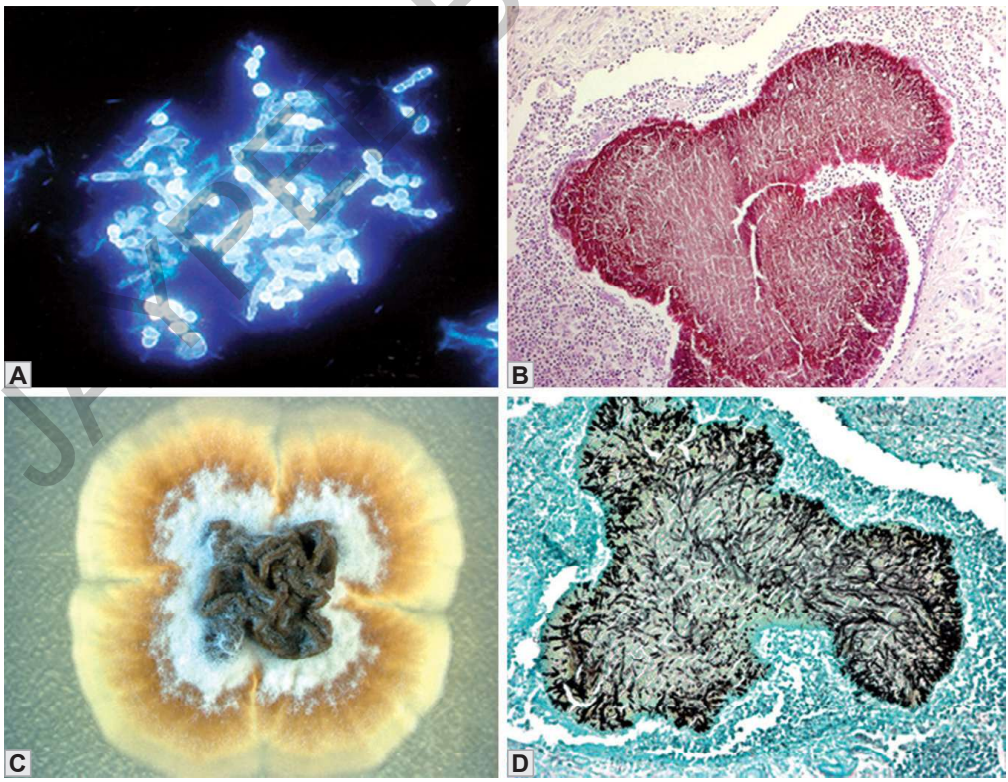
Imaging techniques:

- *X-rays:* Used to detect soft-tissue changes and bone involvement
- *Ultrasound*: Helps visualize soft-tissue extent and grain presence
- *MRI*: Offers detailed views, particularly effective in showing bone marrow involvement and the characteristic "dot in circle" sign
- *CT scans*: Provide detailed images for planning surgical interventions[47-50]

Microbiological and laboratory diagnosis:

- *Direct examination:* Grains are examined under a microscope for size, color, and consistency.
- *Culture*: Used to grow and identify bacterial or fungal pathogens
- *Histopathology*: Tissue biopsies reveal inflammation, granuloma formation, and microbial elements.
- *Molecular techniques*: PCR and sequencing detect and identify pathogens accurately, providing rapid diagnostics crucial for effective treatment.[51,52]

Serological tests are generally not reliable due to low sensitivity and specificity but may provide supplementary evidence in unclear cases. The overlapping symptoms with other diseases complicate the diagnosis, especially in nonendemic areas, which may delay treatment.[53-55] Effective diagnosis integrates imaging, microbiological testing, and clinical evaluation, with recent advances in molecular diagnostics showing promise for improving detection accuracy and speed, potentially enhancing patient outcomes **(Figs. 5A to D)**.[56]



FIGS. 5A TO D: (A) Hyphae highlighted using calcofluor stain; (B) Hematoxylin and eosin-stained tissue section showing a fungal grain encircled by inflammatory cells; (C) Fungal culture grown on Sabouraud agar; and (D) Tissue section stained with Grocott's method, revealing black fungal hyphae within the fungal grain.[57]

TREATMENT OF MYCETOMA

Mycetoma, a chronic and debilitating disease, requires a comprehensive treatment approach that varies depending on whether the infection is bacterial (actinomycetoma) or fungal (eumycetoma).[58] Effective treatment includes antimicrobial therapy, surgical intervention, and supportive care to prevent progression and minimize complications.

Antimicrobial therapy:

- *Bacterial mycetoma (actinomycetoma)*: Long-term antibiotic therapy, often lasting several months to a year, is typical. Common antibiotics include trimethoprim-sulfamethoxazole (TMP-SMX), amikacin, and others like rifampicin and dapsone based on sensitivity. Regular monitoring is essential to manage resistance and side effects.[59,60]
- *Fungal mycetoma (eumycetoma)*: Treatment involves prolonged antifungal courses. Itraconazole is frequently used, with ketoconazole, voriconazole, posaconazole, and terbinafine as alternatives for resistant infections. Ongoing follow-up is crucial to assess effectiveness and monitor for liver function.[61]

Surgical treatment:

- *Debridement*: Removes infected tissue to reduce infectious load and enhance antimicrobial efficacy
- *Amputation*: Necessary in severe cases involving deep structures like bones
- *Reconstructive surgery*: May follow significant tissue removal to restore function and appearance[62,63]

Supportive care:

- *Pain management*: Essential, particularly during and after surgical procedures
- *Wound care*: Proper care is vital to prevent secondary infections.
- *Nutritional support*: Important for undernourished patients to boost immune function and health[64,65]

Challenges in treatment:

- *Diagnostic delays*: Often complicate treatment efforts and worsen outcomes
- *Drug resistance*: A concern with both antibiotics and antifungals, especially with long-term treatment
- *Accessibility and adherence*: Lengthy, costly treatments challenge completion rates, especially in endemic regions

Research continues into less harmful, more effective treatments, including potential vaccines and new antimicrobial agents. Clinical trials are necessary to develop shorter, more effective treatment regimens. Overall, managing mycetoma requires a multidisciplinary approach to improve prognosis and quality of life for affected individuals.[66-68]

CONCLUSION

Mycetoma, a serious infection prevalent in tropical regions, significantly challenges public health, particularly in resource-limited settings. Highlighting the complexity and socioeconomic impact of the infection, this study emphasizes the need for improved diagnostic techniques and treatment strategies, especially

since it predominantly affects young to middle-aged males. Diagnostic challenges due to its similarity with other infections require advanced imaging and molecular diagnostics to prevent severe outcomes such as disability. Treatment depends on the causative agent, with bacterial infections generally responding better to antibiotics than fungal infections to antifungals, although prolonged treatment may lead to drug resistance. The study advocates for the development of new treatments and vaccines, enhanced public health education on prevention, and improved healthcare access. Recommendations include increased surveillance, fostering international collaboration, and enhancing policy support to raise the global health priority of mycetoma.

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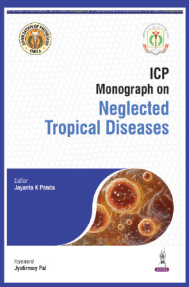

The monogram on neglected tropical diseases (NTDs) offers comprehensive coverage of major NTDs, delving into their epidemiology, pathophysiology, clinical presentation, diagnosis, and management. It presents a focused and evidence-based approach, integrating the latest research and guidelines to address the challenges associated with these diseases, particularly in resource-limited settings. With a practical orientation, it provides actionable knowledge for healthcare professionals, along with detailed visual aids such as illustrations, charts, and tables to enhance understanding and facilitate quick reference.

This work adopts an interdisciplinary perspective, emphasizing the critical roles of public health, environmental health, and community engagement in combating NTDs. It examines the global burden of these diseases while highlighting regional challenges and tailored solutions. Enriched with contributions from leading experts and practitioners, the monogram serves as an invaluable educational tool for students, educators, researchers, and healthcare professionals. Dedicated to the propagation of scientific learning, this book is a significant step toward fostering awareness and improving strategies to address the burden of NTDs effectively.

Jayanta K Panda MD(Internal Medicine) FRCP(London) FACP(USA) FICP FIMAMS FRSSDI Fellow in Diabetes(India) is a renowned academician, researcher, and clinician with over 30 years of distinguished experience in internal medicine. He is a Consultant in Diabetes, Metabolic, and Critical Care Medicine and serves as Professor in the PG Department of Internal Medicine at SCB Medical College, Cuttack, Odisha, India. A former Head of the Department of Medicine, he is a mentor par excellence, guiding UG, PG, and DNB students as a teacher, examiner, and thesis supervisor. With more than 100 publications in peer-reviewed journals and significant contributions to national and international research projects, he is a luminary in the fields of diabetology and internal medicine. Dr Panda has held leadership roles in several esteemed medical organizations, including serving as Chairperson of RSSDI, API, and IMA Odisha. He has successfully organized over 200 CMEs, workshops, and conferences, showcasing his commitment to continuous medical education. His relentless efforts during the COVID-19 pandemic earned widespread recognition. As a most sought-for speaker, Dr Panda has delivered lectures at numerous national and international forums. A member of multiple prestigious professional bodies, he continues to inspire and contribute to healthcare advancements through his unparalleled dedication to teaching, research, and patient care.

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