# Mycetoma

## Policies and Management Guidelines for Service Provision and Essential Good Clinical Practice

**The Mycetoma Research Centre**
WHO Collaborating Centre on mycetoma
University of Khartoum
Khartoum-Sudan

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## Forwards

Mycetoma is a member of the neglected tropical diseases family that enjoys meager attention across the globe. The current mycetoma management and the treatment outcome are unsatisfactory. Presently, there is neither control nor preventive programme nor clear policies to deliver adequate and safe treatment with equity. Furthermore, the health and medical services at the mycetoma endemic areas are meager which contribute to late the presentation with enormous disease in the majority of the patients. Moreover, the management of mycetoma nowadays is based on personal experience on few case reports and case series.

Hence, there is a great demand for evidence-based management of mycetoma patients. That includes proper diagnosis using simple, safe, reliable and cost-effective diagnostic techniques and efficient, safe and affordable treatment. Counselling and health education are badly needed to encourage patients for early reporting and treatment. Community involvement is essential to raise awareness and to improve the environmental conditions to reduce mycetoma medical, social and economic impacts.

In May 2016, the 69th World Health Assembly adopted a resolution on mycetoma calling on all actors to join forces to control the public-health impacts of the disease. The resolution further urges the Member States to improve early detection, treatment and surveillance and requests wider support to national health authorities to move forward with four key areas: epidemiology, health education, access to adequate diagnostic and medical treatment and capacity building.

In response to these issues and the poor mycetoma management, these Mycetoma Policies and Management Guidelines for service provision and essential good clinical practice were developed.

We hope these Guidelines will pave the way for objective and evidence-based patients' management and act as a roadmap towards mycetoma elimination while ensuring better use of existing capacities, technical and financial resources

I would like to praise the remarkable efforts offered by the Mycetoma Research Center Working Group, Khartoum, Sudan supported by the Mycetoma international experts and technical advisors from other neglected diseases that oversaw the development of this document.

**Prof. Ahmed Hassan Fahal**

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University of Khartoum, Khartoum, Sudan, 2018

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## bbreviations

| | |
|---|---|
| ALP | Alkaline phosphatase |
| *A. madurae* | *Actinomadura madurae* |
| *A. pelletierii* | *Actinomadura pelletierii* |
| CMC | Central Mycetoma Center |
| CIE | Counter-Immuno-Electrophoresis |
| DMC | District Mycetoma Centers |
| ELISA | Enzyme Linked ImmunoSorbent Assays |
| FNAC | Fine Needle Aspiration for cytology |
| H&E | Haematoxylin & Eosin stain |
| ID | Immunodiffusion |
| LAMP | Loop-mediated isothermal amplification |
| MMC | Mycetoma Management Center |
| *M. mycetomatis* | *Madurella mycetomatis* |
| MNC | Mycetoma Network Centers |
| MRC | Mycetoma Research Center |
| MRHC | Mycetoma Referring Health Center |
| PCR | Polymerase Chain Reaction |
| PHC | Primary Health Care |
| RFLP | Restriction Fragment Length Polymorphism |
| RPA | Recombinase Polymerase Amplification |
| RCA | Rolling Circle Amplification |
| RMC | Regional Mycetoma Center |
| *S. boydii* | *Scedosporium boydii* |
| *S. somaliensis* | *Streptomyces somaliensis* |

# Section 1

## Mycetoma Policies and Management Guidelines Formulation

## About these
## Mycetoma Policies and Management Guidelines

These guidelines were developed by the Mycetoma Working Group, the Mycetoma Research Centre (MRC), WHO Collaborating Centre on Mycetoma, Sudan, based on the MRC 25 years' experience in the management of more than 8243 mycetoma patients.

The MRC was established in 1991 under the umbrella of the University of Khartoum. It was set up at Soba University Hospital to provide an integrated, high-quality medical care for mycetoma patients, superb research and excellent education and teaching in the various aspects of Mycetoma. The centre is recognised globally as a world leader and an authoritative advisor in mycetoma management and research.

The staff members are of medical, health and science backgrounds; they are interested in all facets related to mycetoma and have good track records in patients' management, teaching, research and community development activities. Through clinical and basic research, the centre staff has continually explored new approaches for mycetoma patients' management.

The MRC provides a holistic approach to patient care whereby medical care is provided by multidisciplinary teams. This has been made feasible by the tight links between the different specialised teams making MRC unique in its delivery of medical care.

These guidelines were compiled, edited and revised by Dr. Louran Zein EL Abdin, Ali, Dr. Buthyna Mamoun Ali, Prof. Abdulla Elkhawad and Prof. Ahmed Hassan Fahal.

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## The Mycetoma Policies and Management Guidelines 2018

Although Mycetoma is endemic in more than 55 countries around the globe, information and experience on disease identification, diagnosis and treatment are meager.[1, 2] Hence, these guidelines developed by the Mycetoma Research Center (MRC), University of Khartoum, WHO Collaborating Centre on Mycetoma, to help in the management of patients with mycetoma.

Also, these guidelines set the ground rules for disease control and prevention in countries affected by the disease. They include the best available policies and procedures for screening, diagnosing and treating mycetoma patients.

Presently, treatment of Mycetoma is the cornerstone for disease prevention and control. With the current limited access to treatment, most of the patients interrupt treatment or end up with repeated mutilating surgical interventions and/or limbs amputation.[3] Therefore, treatment accessibility and availability is beneficial to patients. It reduces the patient delay in getting treatment, cost of the illness and prevents disease complications due to massive disease development. [4]

These guidelines have been prepared for setting the priorities for mycetoma control activities. With the current existing knowledge about the disease and the drugs in use for patient management, the principal strategy for mycetoma control is to:

1. Promptly identify individuals infected with mycetoma.
2. Quickly and effectively treat infected individuals

Mycetoma treatment takes prolong time, in promising cases, it takes not less than one year and a half to confirm the patient cured. [5, 6] Therefore, keeping patients under care until they complete treatment can be very challenging; thus an extensive case management section is included to reflect this important public health aspect of mycetoma control.

# Section II

## The Mycetoma Research Centre
## University of Khartoum

## Mycetoma Research Center, University of Khartoum

In the early seventies of the last century, Sudan responded to the mycetoma threat by establishing The Khartoum North Mycetoma Clinic, for patients' medical care and research.

In 1991, The Mycetoma Research Centre (MRC) was established under the umbrella of the University of Khartoum. It was set up at Soba University Hospital. The centre is recognised globally as a world leader and an authoritative advisor in mycetoma management and research. It is a WHO Collaborating Centre on Mycetoma.

The centre is dedicated to the continuing discovery and development of scientific knowledge and clinical skills applied to the care of mycetoma patients and to eradicate mycetoma, as a life-mutilating disease, through the advancement of medical care, research, education and disease prevention.

MRC provides an integrated, high-quality medical care for mycetoma patients, excellent education, teaching and training in the various aspects of mycetoma, exceptional community development activities and to conduct excellent research, (www.mycetoma.edu.sd).

The MRC staff members are from medical, health and science backgrounds. They have rich track records in patients' management, teaching & learning, research and community development activities. During the last few years, more than 8243 patients with mycetoma have been seen and managed at MRC.

MRC runs twice weekly outpatient referral clinics, where patients seen and managed by a multidisciplinary team of specialists combine both medical and surgical expertise. All patients have free medical consultations, medical treatment while some get free surgical treatment.

According to MRC records, mycetoma is highly prevalent in western and central parts of Sudan; in Gezira, White Nile, Sinner, Darfur, Kordofan States. [7, 8]

## Vision

The MRC vision and its collaborators is to have Mycetoma World Free

## Mission

Is to ensure evidence-informed mycetoma care and practice. This is stemming from knowledge and innovation generated from research and track knowledge of mycetoma experts and regular monitoring and evaluation of activities directed to control mycetoma.

## Values

### Multi-Disciplinary Team Building:

Management of mycetoma is long and includes medical, surgical and rehabilitative intervention. Therefore, a multidisciplinary approach is essential for proper patients care and better management results.

### Community Leadership:

Mycetoma patients resident in remote rural regions. Most of them are illiterates, lives in poor hygiene setting and present late for treatment. Thus, the community involvement is essential to improve patients support, seeking behaviour, and their living conditions.

### Patients Centred Care:

Mycetoma services are designed and delivered around reduction of patients suffering because of the disease, treatment seeking and its financial and social cost to them. This approach extends to daily staff interaction with patients, their families and communities.

### Equity:

Mycetoma management availability and improvement is a human right issue. Mycetoma affected communities deserve support and effective treatment like other patients affected by other diseases

### Networking:

Mycetoma control requires clinical know-how, financial resources and social mobilisation. Collaboration and coordination of the bodies with such capacities, at national and international levels is essential for making real progress in disease control.

### Access:

Making service proximate to patient residence and free management services with sustainable free of charges medicines provision are core for improving patient detection and reduction drop out of patients during management process

### Quality:

Provision of standardised management and close follow-up of the patients combined with community engagement activities is necessary for better patient treatment result and reduction of disease complications. Regular monitoring and evaluation activities are useful tools for service maintenance and improvement.

### Evidence-informed practice:

Research, innovation and knowledge transfer are the cornerstone to MRC mycetoma control practice. MRC activities are linked regular disease study and application of MRC discoveries in patient management and care

## Community Outreach Activities

The MRC had led many community outreach activities at mycetoma endemic states where health education sessions, field surveys and patients' treatment were conducted. In the later, patients were seen and diagnosed in the community using lesions ultrasound and cytological smears examinations. Patients were surgically treated by mobile surgical teams in the villages and patients with complicated disease were referred to MRC for further management. Environmental improvement activities were carried out in these endemic villages.

These activities had improved patients' access to treatment and quality of care. Community leaders and villagers were actively involved in these activities and that had promoted their health and improved the local environment conditions that believed to be the main source of transmitting mycetoma.

The MRC had produced many health education materials in the form of videos, leaflet, posters and booklets which were used in community health education activities, (www.mycetoma.edu.sd).

## Service Decentralization

The MRC in collaboration with the Sinner Ministry of Health had established a Mycetoma Centre at Wad Onsa village in East Sinner Locality, Sinner State. The centre has a surgical theatre complex, two wards, outpatients clinic, laboratory, pharmacy and ultrasound suite with a telemedicine facility for patients' consultation and follow up. Many patients were seen and managed both medically and surgically in the centre. That had led to early case detection and treatment, better outcome and prognosis and had increased mycetoma awareness.

## Research & Development

To address and bridge the massive knowledge gaps in mycetoma, the MRC had conducted several studies and that included basic, clinical and epidemiological studies. That had resulted in publishing more than 150 articles in highly reputable journals, several book chapters and a book on mycetoma.

The MRC staff had supervised several PhD and Master students. The MRC had established excellent research collaboration with many national and international research institutes that let to staff training and technology transfer as well as North to South collaboration.

## Mycetoma Control Policy

Currently, the overall strategic objectives of mycetoma control are:

- Bridging the Knowledge Gap:

Knowledge gap is badly affecting the diagnosis and treatment of mycetoma patients. The current disease burden is not known. Therefore, the most priority area for research is the disease mapping and the estimate of prevalence and incidence worldwide.[9] Furthermore, research to avail tools for early diagnosis that can be implemented in the rural environment where the burden of disease exists is highly needed.[10]

Also, improvement of the cultural and molecular techniques to determine the infective agents as well as serological tests for diagnosis and follow-up of patients on medical treatment are mandatory.

- Improve access to treatment:

Clinical and programmatic guidelines are necessary to standardise the management and improve practitioners practice. Training package for health care providers is essential for capacity building and improvement of health providers in disease suspect, diagnosis and management to ensure service decentralisation.

In addition to description of mycetoma diagnosis and treatment guidelines, they also set the standards operation procedures for the minimum set of capacities for integration of mycetoma treatment within health system infrastructure as cost-effective approach for service decentralisation.

- Ensure high service quality:

Improvement of mycetoma drug's efficacy is strategic for improvement of mycetoma patients' treatment outcomes. Clinical trials to adopt new therapy for treatment of mycetoma are the best approach for the time now. [11] Combination therapy approach can shorten the treatment duration due to a synergistic effect, reduce toxicity and cost, improve patients' compliance and prevent drug resistance.

A multi-disciplinary team is the essential approach for the management of mycetoma. This team should be properly trained to work together in patient's clinical assessment, care, treatment and follow-up. [12] This can be achieved through well-structured training program based on valid and reliable research results. Furthermore, training of health providers at all levels of the health system is important to improve patient's detection and treatment outcomes.

Availability and regularity of access to medicines are important for mycetoma patients. A good system of drugs distribution is important to health facilities enrolled in mycetoma treatment. Supervision is important for problem-solving, on job training and continuous work improvement.

# Section III

## Disease Background

## Mycetoma Epidemiology

### Global Mycetoma Epidemiology

Mycetoma worldwide distribution varies widely. It is endemic in many tropical and subtropical regions and prevails in the Mycetoma belt. [13] This belt includes the countries of Sudan, Somalia, Senegal, India, Yemen, Mexico, Venezuela, Columbia, Argentina, and many others. [14-18] The African continent seems to have the highest burden and prevalence of the disease. [8-12] It has also been extensively reported from India. [19, 20] However, mycetoma has been reported in many temperate regions as well. [21] There are a few reports on mycetoma from the USA, Sri Lanka, Germany, Egypt, Turkey, Philippines, Japan, Lebanon, Thailand, Tunisia, and Yemen. [22-24]

Globally, only a few large epidemiological studies have been performed to estimate the disease prevalence. These studies were conducted by Abbott in Sudan during the period 1952–1955, which showed an estimated prevalence of 4.6 per 100,000 inhabitants. Lopez-Martinez and colleagues in Mexico between 1956 and 1985 reported estimated prevalence of 0.6 per 100,000 inhabitants and more recently by Fahal and associates from Sudan who reported a prevalence of 14 per 1000 in an endemic village. [25, 26])

## Mycetoma Epidemiology in Sudan

Although Sudan is considered the mycetoma homeland, there are few updated data on its prevalence and incidence. [27] The history of mycetoma in Sudan is long and exciting. Treatment by cautery and/or amputation was practiced during the time of the Mahdeya (1885-1899).[28] However, the first documented report of a case of mycetoma in Sudan was published by Balfour in 1904. It was noted that the disease was common amongst Northern Sudanese that, the foot was affected most and the commonest type was the black grain eumycetoma variety. These findings, which were documented more than a century ago, are still valid. [28] Since then many studies have been carried out in Sudan on the mycetoma. [28-32]

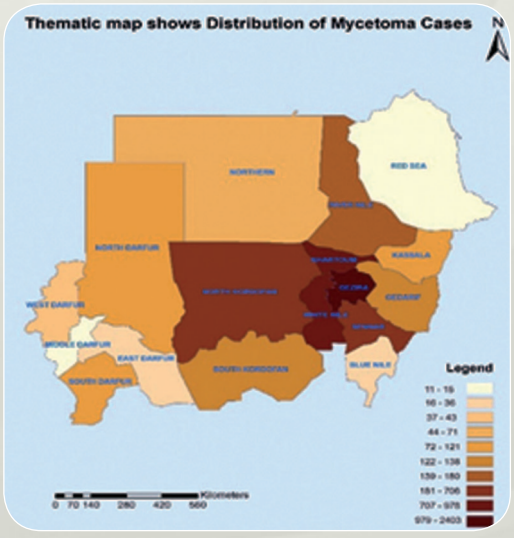



Fig. 1: Mycetoma Geographic distribution in Sudan

## Mycetoma Pathogenesis

Unlike the life-threatening systemic fungal infections, there is no clear immune defect or deficiency known which could explain the development of mycetoma. Serological studies with the *M. mycetomatis* specific antigens showed that Translationally Controlled Tumour Protein, Fructose bisphosphaealdolase and pyruvate kinase antibodies were elevated in both mycetoma patients and endemic controls. However, only the patients developed mycetoma. This suggested that all people from the endemic area have contacted this fungus at some stage, but only a small portion developed the disease. [33]

Mahgoub and colleagues in 1973 reported partial cell-mediated immunity deficiency in a group of mycetoma patients. [34] This finding was supported by animal studies since mycetoma was only successfully induced in athymic mice than in immunocompetent mice. [35] However, on the other hand, Bendl and his colleagues had studied 31 patients with mycetoma, but no immune defects were detected in that cohort. [16]

Since mycetoma was observed in endemic areas, more frequent in certain families, either an environmental or a genetic factor seems to be important in the development of mycetoma.

Genetic studies addressed the role of single nucleotide polymorphisms (SNPs) in genes involved in the function of the immune system were reported. The role of SNPs in genes neutrophil function was addressed, 11 SNPs in eight genes involved in neutrophil function were studied. Significant differences were found in genes encoding for interleukin 8 (CXCL8), its receptor CXCR2, thrombospondin-4 (TSP4), nitric oxide synthase 2 (NOS2) and complement receptor 1. The genotypes more commonly found in mycetoma patients for CXCL8, its receptor CXCR2 and TSP4 all were associated with a higher CXCL8 production in other studies. [36, 37]

## Mycetoma Clinical Examination

A patient suspected of having mycetoma if:

I. The patient presents with the triad of:
   a. A painless subcutaneous mass
   b. Multiple sinuses formation
   c. Purulent or sero-purulent discharge that contains grains.

II. The patient presenting with mass only but, from high endemic areas and/or with history of local trauma

III. The patient presents with mass is having a relevant occupational history (farmer or shepherd).

IV. The patient presents with mass is resident or with a history of visiting animal corral area.

## Clinical Interview

- A medical evaluation, including a detailed history of the current illness, mainly about the lesion:
    a. Painless swelling with multiple sinuses
    b. Discharge and grains
    c. History of trauma
    d. Family history of mycetoma
- Systematic review
- Past medical history:
    a. History of mycetoma +/- surgical operation with local or general anaesthesia
    b. Past medical history of chronic illnesses
- Social history
    a. Suspect occupation
    b. Residency or history of living in mycetoma endemic areas
- Family history of similar condition in family or area
- Gynaecological history
    a. Pregnancy
    b. Lactation

## Physical Examination of Mycetoma patients

Examination of individual suspected of having mycetoma lesion include the:

a. Lesion site,
b. Lesion size, classified into three grades according to the lesion size and the bone involvement:

Grade 1: lesion 1-5 cm in diameter

A. without bone involvement
B. with soft tissue swelling
C. with periosteal reaction
D. with massive bone involvement

Grade 2: lesion 5-10 cm in diameter

A. without bone involvement
B. with soft tissue swelling
C. with periosteal reaction
D. with massive bone involvement

Grade 3: lesion >10 cm in diameter

A. without bone involvement
B. with soft tissue swelling
C. with periosteal reaction
D. with massive bone involvement

c. The discharge: grains +/- pus
d. Other findings include sweating in the affected limb and exist of varicose veins

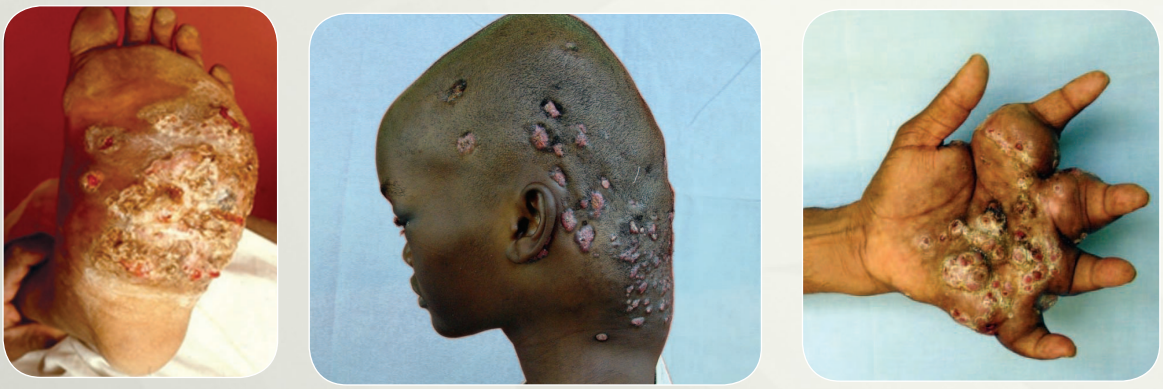


Fig. 2: Massive actinomycetoma

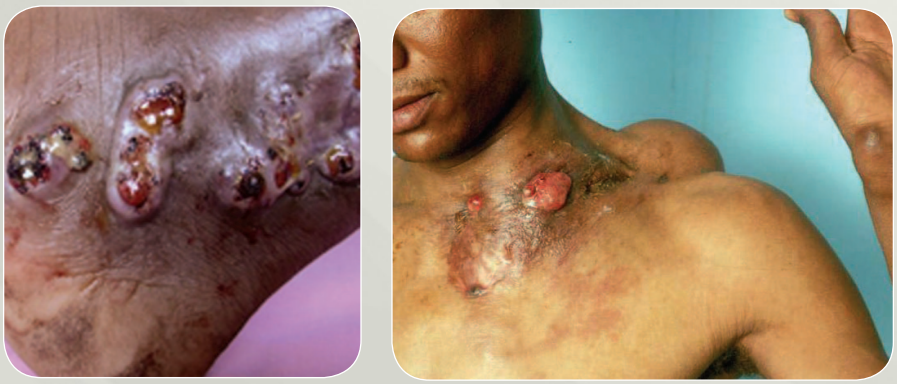
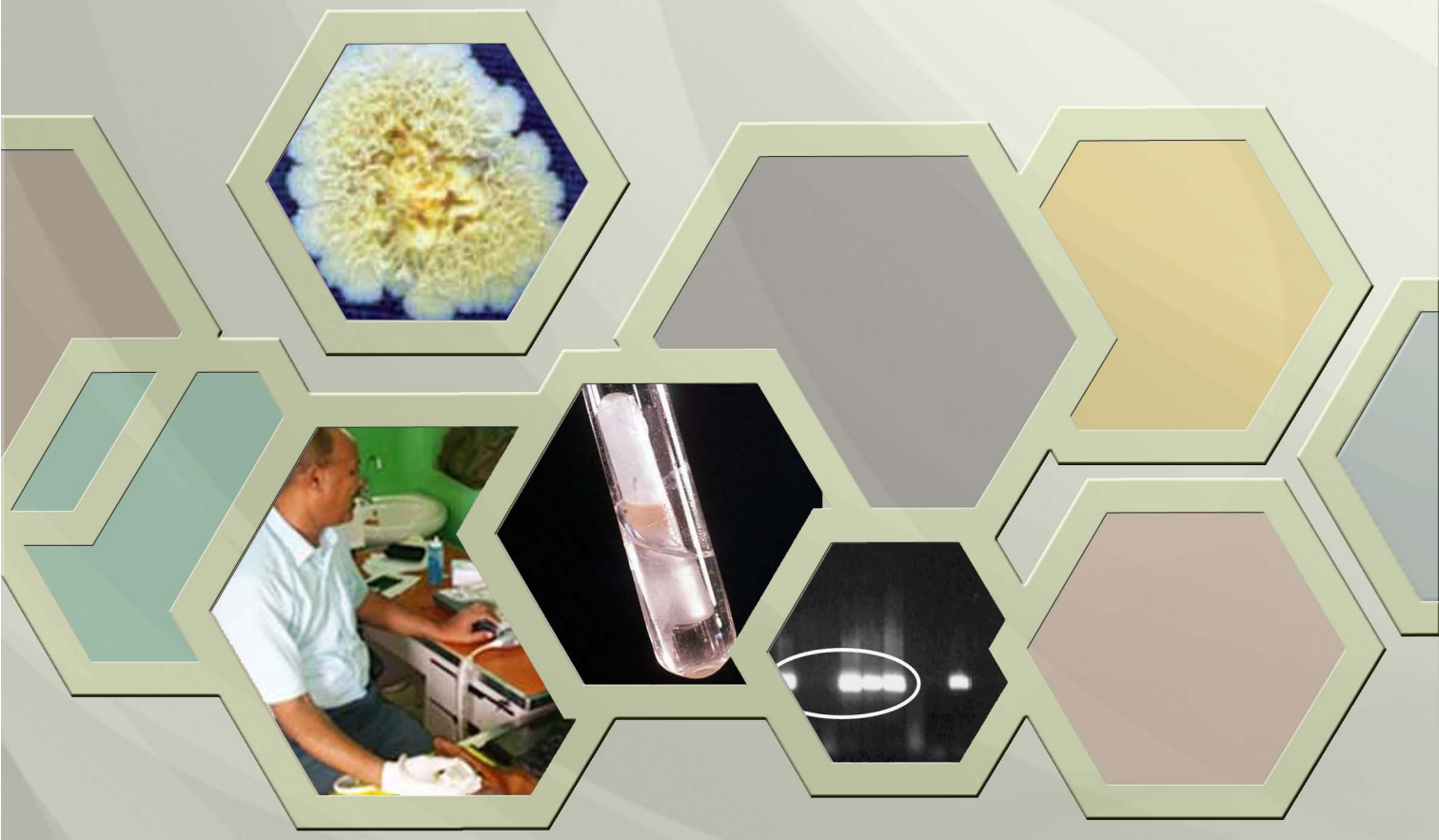


Fig. 3: Typical mycetoma lesion

# Section IV

## Mycetoma diagnosis



The proper treatment of mycetoma depends mainly on accurate diagnosis. The diagnosis of mycetoma, its type and extent are based on meticulous clinical interview and examinations, and a battery of investigations and that include various imaging techniques, organism identification using grains culture, phenotypic morphological identification, molecular techniques and cyto-histopathological identification.

## Mycetoma Imaging

Clinical examination alone neither identifies the causative organism nor detects the spread of disease along the different tissue planes and bone. Various imaging techniques are in use for the diagnosis of mycetoma, its type and extent and that include the following:

1. Conventional radiography
2. Ultrasonography
3. Magnetic Resonance Imaging
4. CT scan

## Conventional Radiographs:

Conventional radiographs are used to identify the limits of lesions and to determine if the bone is affected as this is essential to plan the appropriate treatment. In advanced cases, this technique can differentiate between eumycetoma and actinomycetoma. [38]

Several different radiological signs should be sought, and that include:

- Soft tissue granuloma, which appears as a dense shadow or as scattered multiple soft tissue shadows with calcification and obliteration of the fascial planes (Fig.1).
- The cortex may be compressed from outside by the granuloma leading to bone scalloping.
- When the bone is involved, there may be a periosteal reaction. This will lead to the formation of sun-ray appearance and Codman triangle, an appearance that may be indistinguished from that of osteogenic sarcoma. (Fig. 2)
- Formation of cavities that may be multiple punched out throughout otherwise bone of normal density. These cavities are large in size, few in number with well-defined margins in eumycetoma (Fig. 3).
- The cavities in actinomycetoma are usually smaller in size, numerous and have no definite margins (Fig. 4).
- In the skull, the bone changes are purely sclerotic with dense bone formation and loss of trabeculation (Fig. 5).
- Osteoporosis at and distal to the affected part is sometimes observed in mycetoma, and this may be due to disuse atrophy.
- Chemotherapy may cause radiological improvement consisting of remoulding, absorption of the sclerotic bone and reappearance of the normal trabecular pattern.

Radiographic classification of mycetoma to determine the extent of lesions based on radiographic records of 516 patients seen in the Mycetoma Research Centre, Khartoum, Sudan was reported. [38]

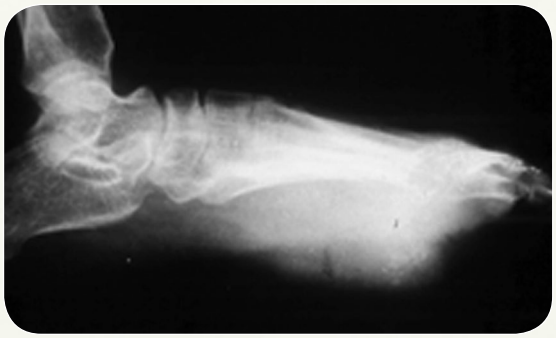


Fig. 1: The Soft tissue granuloma

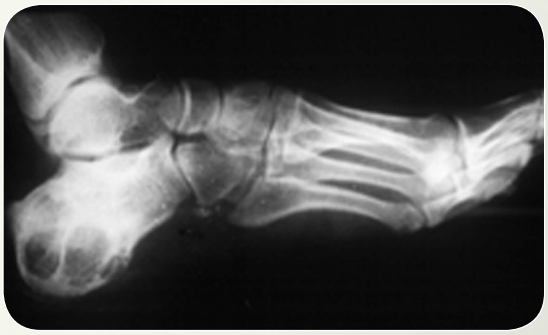


Fig. 3: Eumycetoma bone cavities

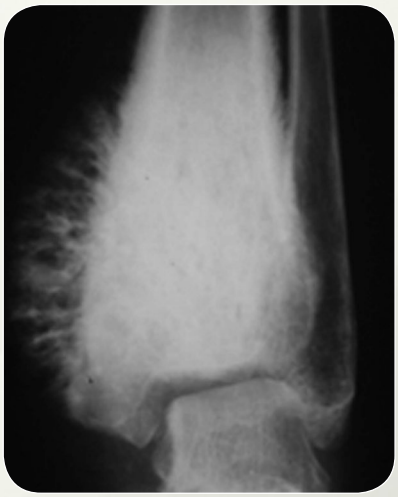


Fig. 2: The Periosteal reaction

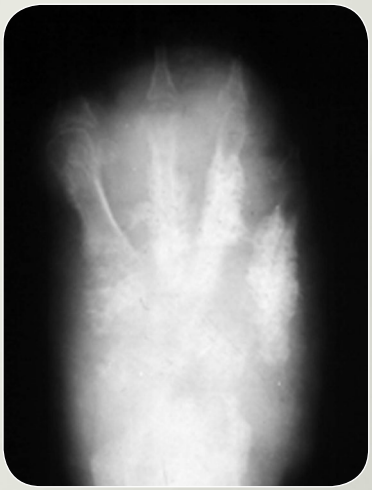


Fig. 4: Actinomycetoma bone cavities

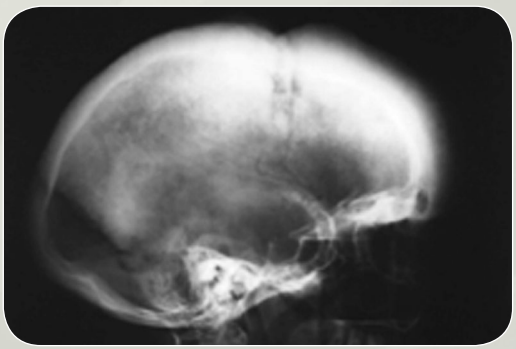


Fig. 5: Mycetoma skull bone changes

This classification can be used for patient management planning, communication between different clinicians and for reporting findings, (Table 1).

## Radiographic classification of bone involvement in mycetoma

Source: Abdel Bagi & Fahal. [38]

| Stage | Pattern of spread | Effect | Finding |
|---|---|---|---|
| 0 | Limited to entry side | Soft tissue swelling | No bone involvement |
| I | Expanding granuloma | Extrinsic pressure | Displacement or scalloping |
| II | Emending bone infiltration | Bone irritation | Periosteal reaction or reactive sclerosis |
| III | Localize bone invasion | Erosion or cavitation | Solitary bone involvement |
| IV | Longitudinal spread | Joint involvement | Localised along single ray |
| V | Horizontal spread | Invasion of adjacent structure | Localised to forefoot, midfoot or hindfoot |
| VI | Multidirectional spread | Total disruption | Multiple rays and multiple rows involved |

- X-Ray should be taken in at least in two views; anterio-posterior and lateral views.
- In other situations, extra views can be requested such as the oblique, open month and others.
- Two joints; one above and one below the affected bone should be included in the view.

## Ultrasonic imaging of mycetoma

Mycetoma has a characteristic ultrasonic appearance. Ultrasound imaging can differentiate between eumycetoma and actinomycetoma and between mycetoma and other non-mycetoma lesions.

In eumycetoma lesions, single or multiple thick-walled cavities with no acoustic enhancement are present. They usually contain multiple isolated sharp, bright, hyper-reflective echoes corresponding to the grains. The cavities may contain only debris and filaments.

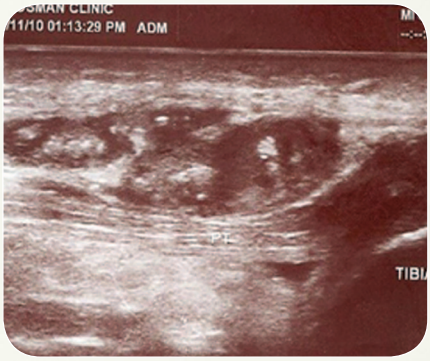



Fig. 8: Ultrasonic appearance of eumycetoma lesion

In actinomycetoma lesions, the findings are similar, but the grains are less distinct. This may be due to their smaller size and consistency, individual embedding of the grains or the absence of the cement substances in some species. The grains echoes are commonly settled at the bottom of the cavities.

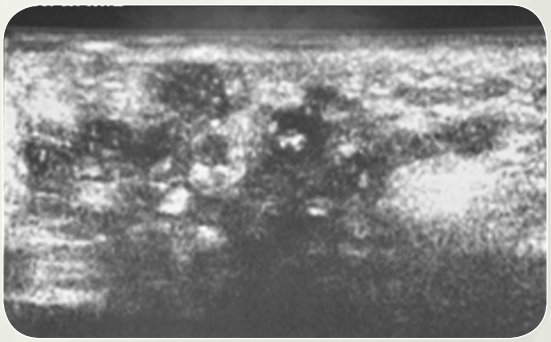


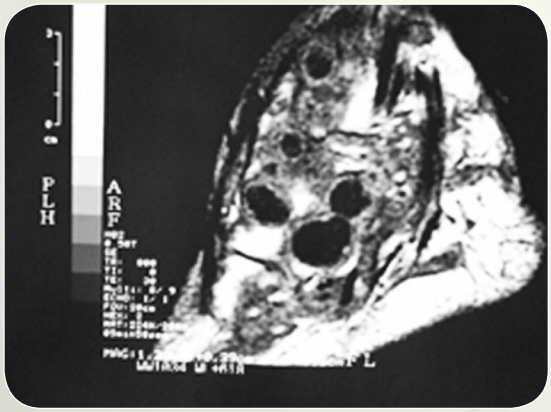
Fig. 9: Ultrasonic appearance of actinomycetoma lesion

The ultrasound technique is safe, simple, accurate and useful in patients' diagnosis and following and planning surgical treatment. [39]

- The lesion should be scanned in different planes using probe size 7.5 mhz
- Doppler ultrasound can be used to assess the lesion vascularity

## Magnetic Resonance Imaging (MRI)

It is useful to determine the extent of the lesions and the invasion of structures. It has greater sensitivity than radiographs, ultrasound, and CT scan.



Mycetoma lesions appear as conglomerates of small (2-5 mm) round hyperintense lesions, representing granulation, interspersed within a low-intensity matrix denoting the fibrous tissue. The low-signal intensity signs which are named "dot-in-circle" which indicate the presence of grains, is highly characteristic of mycetoma.

Fig. 10: MRI appearance of mycetoma lesion

### MRI Grading System

The Mycetoma Skin, Muscle, Bone Grading System (MSMBS) was recently proposed, it grades disease severity, compares patients and helps to manage them, (Table 2). [40, 41]

The mycetoma MRI appearance should be differentiated from chronic osteomyelitis, granulomas, soft tissue tumours, bone tuberculosis and cold abscesses. MRI however, is only available in well-equipped hospitals.

**The patients' categories according to the lesion size and x-ray findings**

| Category | Category 1 | Category 2 | Category 3 |
|---|---|---|---|
| Lesion size | <5 cm | 510- cm | >10cm |
| Normal X-Ray Findings | 1A | 2A | 3A |
| Soft Tissue Mass | 1B | 2B | 3B |
| Periosteal Reaction | 1C | 2C | 3C |
| Bone Cavity | 1D | 2D | 3D |

## CT scan

It is not specific but it can be used to assess the bone involvement by mycetoma.

Using imaging techniques, the major differences between eumycetoma and actinomycetoma are:

1. Few, large cavities with well-defined margins on x-ray suggest eumycetoma.
2. Grain-related sharp, bright hyper-reflective echoes on ultrasound suggest eumycetoma.

- In general, for small early lesions, ultrasoun examination is recommended.
- Meanwhile, radiography and MRI are recommended for large lesions.

## Organisms Identifications

More than 56 micro-organisms are claimed to cause mycetoma. For identification of the mycetoma causative organisms, several tools and techniques are available, and these include the following:

1. FNAC and cell block technique
2. Surgical biopsy histopathological examination
3. Grains culture
4. Molecular techniques
5. Serology

## Fine Needle Aspiration for Cytology (FNAC) & Cell Block Technique

Mycetoma can be accurately diagnosed by smear cytological examination using Fine Needle Aspiration (FNA) and cell block technique. It has a distinct appearance in a cytological smear characterised by the presence of polymorphous inflammatory cells consisting of an admixture of neutrophils, lymphocytes, plasma cells, histiocytes, macrophages and foreign body giant cells and grains. In sections, the grain is closely surrounded by and occasionally infiltrated by neutrophils causing its fragmentation. Outside the neutrophil zone, monocytic cells and giant cells are seen. This is surrounded by granulation tissue rich in fibroblasts and blood vessels.

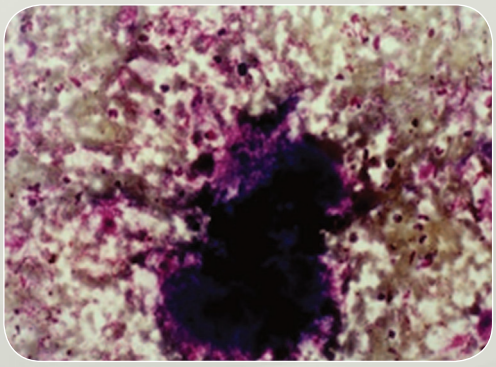


Fig. 11: Cytological smear showing Actinomadura pelletierii grain surrounded by inflammatory infiltrate

This technique allows morphological identification of mycetoma and its classification into eumycetoma and actinomycetoma. This is important as the treatment depends mainly on the aetiological agents. The technique is simple, economical, rapid, and sensitive and can be tolerated by patients. It can be used for diagnosis, collection of material for culture and immunological studies and for mycetoma epidemiological surveys. [42, 43]

## The technique

1. The lesion is cleaned thoroughly with an antiseptic solution.
2. A fine needle, gauge 20, attached to a syringe is inserted into the lesion, negative pressure is applied, and the needle is moved up and down in at least three different directions, till sufficient aspirated material is obtained.
3. This material is usually bloody, and it is therefore left to clot, stained with H&E or quick duff.
4. The slides are then examined microscopically.
5. Cell blocks are fixed in 10% formalin-saline, processed for paraffin section and stained with H&E.

## The Histopathological Diagnosis

The technique is attractive in that it do not needs aseptic procedure or fixed time schedule required for culture. However, it lacks the precision of culture, and it needs deep surgical biopsy which may enhance the spread of the organism. [44]

Deep surgical biopsies are commonly performed under general or spinal anaesthesia, and tru-cut needle biopsies can be used under local anaesthesia. [3]

- Biopsy should be divided into two parts one should be placed in a sterile container with normal saline for grains culture.
- The other part should be fixed in 10% formal saline for histopathological examination.
- Different stains can be used to identify the organism's morphology and the tissue reaction to the organisms. [45]

There are three types of tissue reactions against the mycetoma causative organisms were described: [44,46]

**Type I:** The grain is surrounded and sometimes invaded by an intense neutrophil polymorphonuclear leucocyte infiltrate.

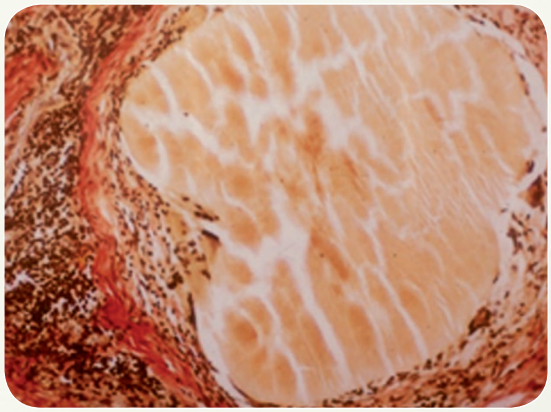


Fig. 12: Streptomyces somaliensis grain surround by Type I tissue reaction

- **Type II:** There is a vascular layer containing macrophages, lymphocytes, plasma cells and giant cells. The giant cells usually contain fragments of the grain. Some macrophages may have a foamy cytoplasm.

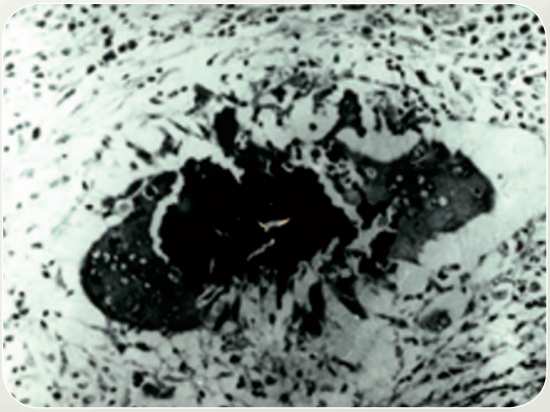


Fig. 13: Madurella mycetomatis grain fragments surround by Type II tissue reaction

- **Type III:** Formation of pure epithelioid granuloma.

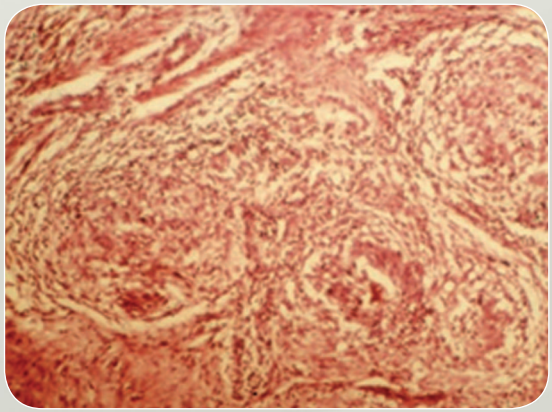


Fig. 14: Formation of pure epithelioid granuloma

## Grains Culture

The mycetoma causative organisms can be identified by their textural description, morphological and biological activities in pure culture. The biological activity may include acid fastness, optimal temperature, proteolytic activity, utilisation of sugars and nitrogenous compounds.

The grains are the source of the culture, they should be alive and free of contaminants, and they are usually obtained by deep surgical biopsy. Grains should be sent immediately in sterile containers to the laboratory for culture. Many culture media are in use; they include Sabouraud agar, blood agar and Malt extract agar. [47] Identification of the mycetoma causative organisms remains difficult with standard mycological procedures and can be delayed for several weeks.

## Grains culture techniques

- For culture, grains are usually washed several times in sterile saline, crushed with a sterile glass rod, and plated onto appropriate media.
- If direct microscopic examination of the grain reveals evidence of actinomycetes, isolation media should not contain antibiotics.
- Blood, brain-heart infusion, Löwenstein and modified Sabouraud agar supplemented with 0.5% yeast extract are commonly recommended for the isolation of actinomycetes
- If direct microscopic examination of grains is indicative of eumycetoma, grains can be additionally washed with antibiotics and spread over Sabouraud agar plate supplemented with antibiotics.
- Commonly used antibiotics are gentamicin sulphate (400 µg/ml), penicillin G (20U/ml), streptomycin (40 µg/ml) or chloramphenicol (50 µg/ml)
- It is also advisable to include a plate without antibiotics since the growth of some *Madurella* and actinomycetes strains appear to be inhibited by these antibiotics
- Plates should be incubated at $25^0$C and $37^0$C irrespective of whether the causative agent is bacterial or fungal in origin.

## Molecular diagnosis of mycetoma

Several molecular techniques have been introduced and applied as diagnostic tools in the field of infectious diseases since the early 1990s. [48] These techniques have proven to be useful for fast and accurate identification of the pathogen and therefore provide proper diagnosis.

In mycetoma, accurate identification of the pathogen is considered the key to correct diagnosis and to ascertain appropriate therapy. In the past, identification of mycetoma causative agents was mainly based on morphologic and culture criteria in addition to physiological properties of these agents. However, most of the clinical isolates from mycetoma are non-sporulating and therefore applying phenotypic morphological identification for such isolates can lead to misidentification, misdiagnosis and consequently erroneous therapy.

As a result, several molecular techniques have been developed for mycetoma to overcome the limitations of the conventional diagnostic techniques.

**These techniques include:**

## 1. Polymerase Chain Reaction (PCR) based methods:[48]

PCR amplification of a selected barcode marker followed by sequencing is the most common molecular approach used for identification of mycetoma causative organisms.

- For the bacterial agent of actinomycetoma (Actinomadura, Nocardia, and Streptomyces), 16S rRNA is the most frequently used technique. [49]
- For fungi causing eumycetoma, ITS is considered as a universal fungal barcode marker. [48]
- For some genera like Aspergillus, calmodulin (CaM) and β-tubulin (BenA) can be used as alternatives. [50]
- For Fusarium, (translation elongation factor 1-α (TEF1) is a recommended gene. [51]

PCR amplification by specific primers combined with Restriction Fragment Length Polymorphism (RFLP) analysis has been developed to identify *M. mycetomatis*. [52]

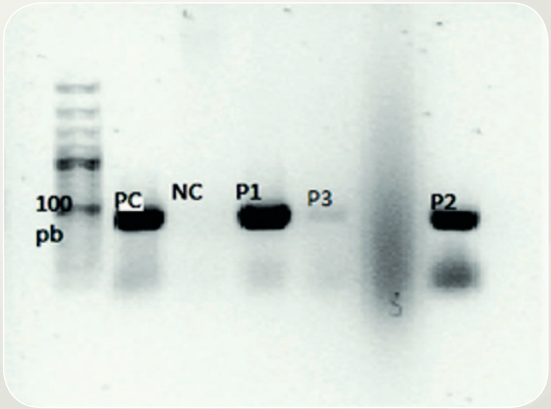



Fig 15: Showing PC: Positive control
NC: Negative Control.
P1, P2 and P3: DNA samples

## Isothermal Amplification-Based Methods:

These are rapid simple and cost-effective methods, which have been recently introduced for identification of mycetoma causative agents. [53]

### A. Rolling Circle Amplification (RCA)

RCA was developed for rapid identification of eight eumycetoma agents, and these are *Falciformispora senegalensis, F. tompkinsii, Madurella fahalii, M. mycetomatis, M. pseudomycetomatis, M. tropicana, Medicopsis romeroi*, and Trematosphaeria *grisea*. [54]

The RCA method is based on the detection of specific nucleic-acid sequences by utilising of what is known as padlock probe and subsequent enzymatic amplification under isothermal conditions.

### B. Loop-mediated isothermal amplification (LAMP)

LAMP was developed for identification of *M. mycetomatis* and *Scedosporium boydii*. *M. mycetomatis* specific LAMP has been evaluated for the identification of the fungus from culture as well as from clinical sample. [53]

### C. Recombinase Polymerase Amplification (RPA)

It has also recently been introduced as a rapid and specific detection and identification method for *M. mycetomatis*. [53] The technique uses two opposing primers and are recombinase that facilitates the insertion of the primer in the template DNA without the requirement of denaturation. Unlike other isothermal techniques, RPA reaction can be performed in temperatures from 30 to 45 °C and incubation times of 5 to 15 or 40 minutes.

The reaction can be combined with sequence specific probe for real-time monitoring and with lateral-flow (LF) strips for end-point detection. The method has successfully been applied for detection of *M. mycetomatis* from patient's grain and thus provides a promising tool for diagnosis of eumycetoma.

## Serodiagnosis

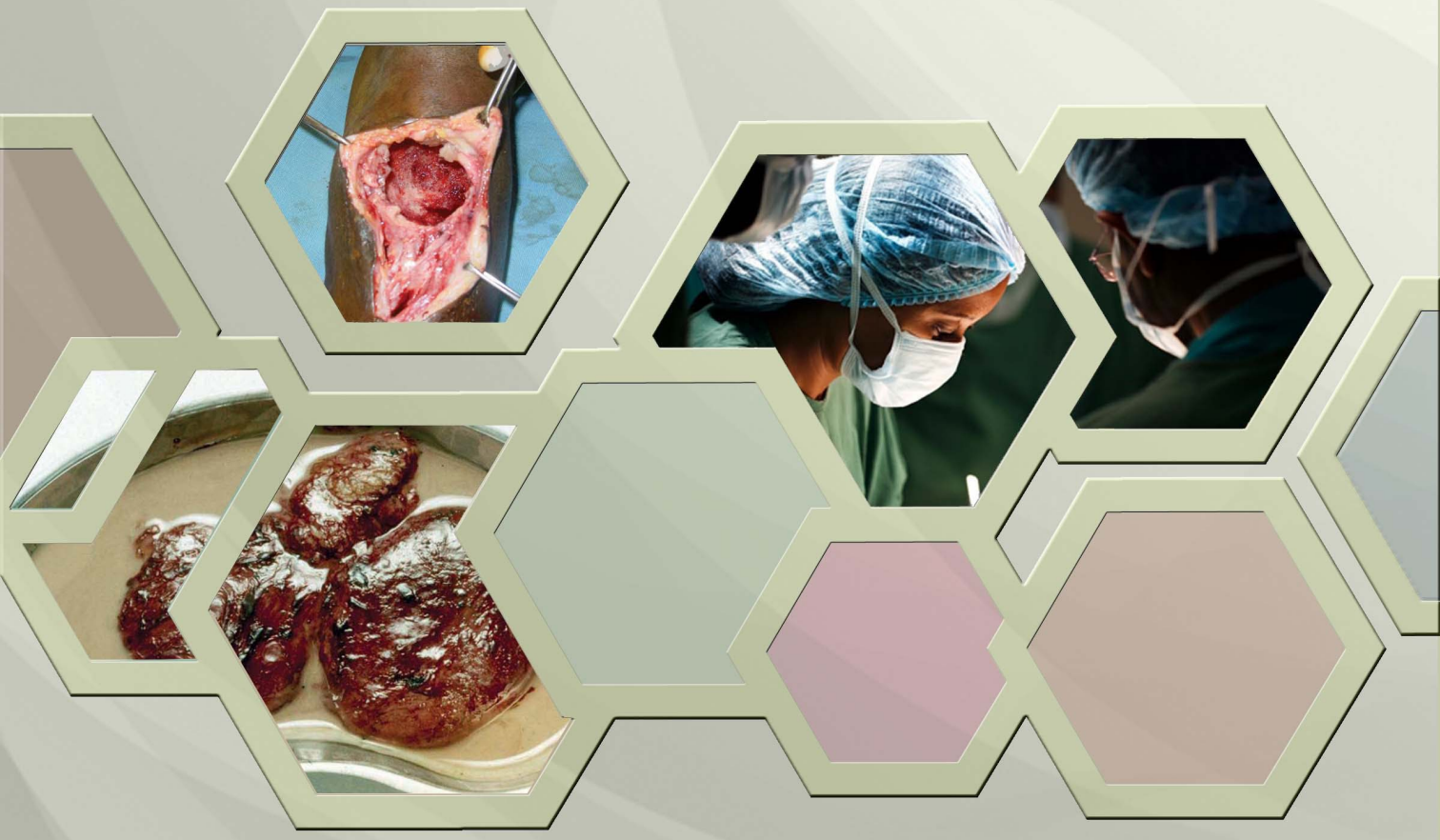
Due to the invasive procedures needed to obtain grains, and the long incubation times needed for identification of causative agents, attempts have been made to develop serological assays for the diagnosis of mycetoma.

Immunodiffusion (ID), Counter-immuno-electrophoresis (CIE) and Enzyme-Linked ImmunoSorbent Assays (ELISA) have been developed to detect mycetoma causative organisms using crude cytoplasmic antigens of these agents.[55, 56] CIE and ID are two techniques that are based on the formation of antibody-antigen precipitin lines in agar gels. The ID and CIE methods have been more widely used especially for *M. mycetomatis*. [55]

Recently, many centres stopped using this assay because the lack of standardisation of the antigen preparation resulted in a variation in the outcome of this diagnostic tool and cross-reactivity between the different causative organisms.

# Section IV

## Mycetoma Treatment:



## Mycetoma Treatment

Mycetoma is a long-standing medical condition. The treatment depends mainly on the aetiological agent, the site and extent of the disease. Various antifungal agents have been tried for eumycetoma with little success. [28] This is perhaps surprising, as the eumycetoma causative agents are low-grade infective organisms and their eradication should be readily achieved by the administration of safe systemically given antifungal drugs. [28]

Actinomycetoma is amenable to medical treatment with antibiotics and other chemotherapeutic agents. Combined drug therapy is always preferred to a single drug to avoid drug resistance and for disease eradication. [27-29] Cure is possible, although a prolonged period of treatment is needed. Combined medical and surgical treatment facilitates surgery, accelerates healing and reduces the chance of relapse; however, a good number of patients respond to medical treatment alone. [29, 30] Medical treatment for both types of mycetoma must continue until the patient is clinically, radiologically, ultrasonically and cytological cured.

Recurrence is more common after an incomplete or irregular course of medical treatment. With drug non-compliance, there is a good chance for the organism to develop drug resistance.

The postoperative recurrence rate varies from 25 to 50%. [27, 31] The available treatment for eumycetoma although not very effective, has many side effects. They are expensive, and the cost may reach more than US$ 7,500 per year per patient. [27] Most of the patients do not afford the cost of treatment. Furthermore, the drugs are not always available in endemic regions. The treatment is of a variable duration and may continue for 2-3 years with a mean of 18 months.

## Treatment of Eumycetoma patients

Currently, the available treatment regimen for eumycetoma is a combination of antifungals and surgery. Oral Itraconazole 400 mg/day or Voriconazole 400–800mg/day are the drugs of choice. The treatment duration ranges from six months to several years with a mean duration of 12 months.

Medical treatment helps in lesion size regression. Also, it hardens the capsule which eases excision of the lesion while preventing leakage of the grains to prevent recurrence. The medical treatment is given for six months, and that is followed by surgical intervention in the form of wide local excision, debulking and curettage of the bone.

Both drugs are probably excreted in the milk, and therefore mothers who are under treatment should not breast feed. There are no adequate and well-controlled studies on the effects of these drugs in pregnancy. Therefore, they should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus.

The patients can be categorised into three categories according to the lesion size. Each category divided into four sub-categories according to the bone involvement.

- **Category 1**

Lesion less than 5 cm in diameter

A. No bone involvement
B. With Soft tissue mass
C. With periosteal reaction
D. With bone cavities

- **Category 2**

Lesion between 5 -10 cm in diameter

A. No bone involvement
B. With soft tissue mass
C. With periosteal reaction
D. With bone cavities

- **Category 3**

Lesion more than 10 cm in diameter

A. No bone involvement
B. With soft tissue mass
C. With periosteal reaction
D. With bone cavities

## Category 1

Patient with localised small lesion<5 cm confined to the subcutaneous tissue:

1. Itraconazole 200mg BD daily for three months
2. Wide local excision ± bone curettage
3. Patient continue on medical treatment not less than three months after the surgery
4. Follow up:
   a. First 6 months after operation: every six weeks for evidence of recurrence and monitoring the hepatic functions.
   b. If develop symptoms or signs of recurrence during this period, ultrasound is requested and if evidence of recurrence is present patient should counti on medical treatment followed by wide local excision and to the follow-up.
   c. If the patient completed the first six months follow up without symptoms and sign of recurrence, request ultrasound:

i. if there is evidence of recurrence the patient should undergo wide local excision with medical treatment
ii. If no lesion detected by ultrasound, the ultrasound should be repeated twice every three months,
iii. If recurrence detected, the patient should continue on medical treatment and undergo wide local excision.
iv. If no lesion detected patient confirms cured and treatment stop.

5. Post-treatment patient follow-up:
   a. Ultrasound every three months for one year. If lesion detected re-start the treatment.
   b. In the second and third years, ultrasound every six months should be done.
   c. Then annual ultrasound should be done for five years to ensure the patient is completely cured.

## Category 2

Patient with localised lesion 5-10 cm with or without bone

1. Itraconazole 200mg BD daily for six months
2. Wide local excision ± bone curettage
3. Patient should continue on medical treatment not less than six months after the surgery
4. Follow up: the same as category one

## Category 3

Category 3A: Lesion > 10 cm without bone involvement.

1. Itraconazole 200mg BD daily for six months
2. Wide local excision
3. Patient should continue on medical treatment not less than six months after the surgery
4. Follow up: the same as category one

Category 3B & 3C: lesion > 10 cm with soft tissue swelling and periosteal reaction:

1. Itraconazole 200mg BD daily for six months
2. Follow up during this first six months to detect signs of improvement which are:
   a. Regression of mass size
   b. Healing of the sinus
   c. Reduced disability
3. If patient showed improvement continue treatment the same as category 3A
4. If there is no improvement and the disease become very aggressive, the patient should undergo surgery after three months in the form of
   a. Debulking of the lesion to prevent disease progression to category 3D.
5. History and examination to detect secondary bacterial infection:

i. Pus discharge
ii. Feeling of pain while mycetoma is a painless condition.

6. If there is secondary bacterial infection:
    a. Sinuses swab for culture and sensitivity should be taken.
    b. Antibiotics for two weeks to one month accordingly are given.
7. Regular dressing
8. Continue Itraconazole treatment as the same. If there is improvement continue the follow up as category 3A
9. If no improvement patient should undergo debulking surgery and restart of treatment for another six months.
10. Check for drug resistance

If there is no drug resistance:

1. Check treatment compliance
2. Re-start treatment for another six months after the debulking and closely follow up the patient every six weeks
3. Regular dressing:
    i. Observe the decrease in the amount of grains
    ii. Lesion localisation
    iii. Whether there is further lesion development

11. If the lesion becomes well localise patient can undergo wide local excision to be categorised as 3A
12. If the lesion became diffused not localise,
    iv. the patient can undergo debulking surgery again after the three months
    v. Another six months treatment and close follow-up every six weeks
    vi. Regular dressing.
    vii. If any secondary bacterial infection detected it should be treated as mentioned above.
    viii. Continue as mentioned until the lesion become localised to conduct the wide local excision and to be followed as category as 3A
13. If there is drug resistance (no improvement while there is good treatment compliance and no secondary bacterial infection).
    1. Change to the second line of treatment; Voriconazole 400-800 mg daily for six months.
    2. The patient continued treatment and followed up as mentioned above.

## Category 3D

Lesion > 10 cm with massive bone involvement.

The chance of cure for this patient's category is low. Most of the patients present with long history of the disease. The majority of the patients end by amputation, for that this category needs close follow-up and serial surgical interventions.

1. Itraconazole 200mg BD daily for three months
2. Regular lesion dressing
3. Debulking with bone curettage after three months medical treatment, x-ray should be done to identify the cavities for adequate debridement.
4. If signs of secondary bacterial infection were detected it should be treated as mentioned above
5. If the drug resistance is suspected the patient should undergo serial debulking surgery.
6. Culture and sensitivity of the gains should be done and change immediately to the second line of treatment; Voriconazole 400-800 mg daily for three months followed by surgical intervention and continue as mentioned above.
7. Regular check of hepatic function test and full blood counts for correction of anaemia due to the chronic illnesses
8. Patient should be followed regularly, if improved then continue on the regular debulking and medical treatment and continue as Category 3C
9. If no improvement was detected the patient could be a candidate for amputation.
10. The indications for amputation are:
    a. Aggressive disease not responding to medical and surgical treatments.
    b. X-ray and MRI showed further extension of the lesion in the bone.
    c. Massive secondary bacterial infection.
    d. Poor general condition, anaemia, other concomitant diseases.
    e. Patient's preference.

## In case of treatment failure

a. Check patients' treatment compliance and/or proper adherence to treatment guidelines.
b. If the treatment is not according to the guidelines, the patient should be started on proper management.
c. If the patient was treated according to the guideline with no improvement, then amputation is advised to avoid further progression.
d. Patients follow up, and continuation of treatment after amputation is as category one after surgery.

# Drug toxicity

Both Itraconazole and Voriconazole are hepatotoxic drugs. Therefore, during each follow-up visit, liver function test should be requested to check the liver functions.

If the level of the ALP started to increase slightly beyond the normal level (44-147 UI),

1. Check whether the patient is taking any hepatotoxic drug or any drug enhance the mycetoma drugs toxicity.
2. If a hepatotoxic drug is given
    a. If the drug is not essential, then it should be stopped to decrease the insult to the liver
    b. Check the liver functions after two weeks. If it is normal restart the medical treatment
    c. If it is abnormal, no treatment should be given and recheck after another two weeks if still abnormal, consider surgery.
    d. If it is essential and for long duration such as lifesaving medications like chemotherapy shift to the surgical line of treatment.
3. If the patient is not taking any hepatotoxic drug or any drug enhance the mycetoma drugs toxicity, reduce the drug dose to 100mg BD. Continue for two weeks and check the enzymes again.
    a. If it is normal restart with 200mg BD.
    b. If the liver enzymes levels are increasing stop the treatment for four weeks and check them again. If the enzymes are normal restart treatment with 100mg BD, If they are still abnormal consider surgical treatment
    c. Request abdominal ultrasound and viral screening and refer the patient to a gastroenterologist.

If the levels of the liver enzymes had increased aggressively with clinical evidence of hepatic impairment, the patient should be admitted to hospital and managed in close collaboration with a gastroenterologist and consider surgery at a later stage.

## Special Mycetoma Cases Treatment

Mycetoma treatment differs according to the age, gender and its site and extent.

### Childhood Mycetoma:

Due to the long-term disease treatment, children with mycetoma are subjected to high absence from school, and sometimes it ends by early school leaving. Stigma of the disease adds further burden to patient social and psychological health. Therefore, children with mycetoma should get high priority in treatment availability and surgical intervention schedule.

Mycetoma among children should be treated the same as mycetoma among adult.

Regardless the lesion grade, children with mycetoma need close monitoring and follow-up.

Drugs calculated according to the child weight.

The acceptable level of ALP among children is up to 450UI due to bone growth.

## Mycetoma among females

Management of mycetoma among female is the same as male, but the main challenge is that mycetoma drugs may be teratogenic and contraindicated during pregnancy and lactation period. Therefore, the gynaecologist is to be consulted. Pregnancy test is mandatory for any female with mycetoma. If the test is negative treatment can be started according to the patient category. If the test result is positive, treatment is surgical only, and no medical treatment is adviced. Female patient among reproductive age should be referred to the gynaecologist to start contraceptives.

In general, mycetoma treatment for pregnant and lactating women is subjective. It depends upon disease category, gestational age, condition and age of the child during lactation.

## Treatment of Mycetoma at special sites (trunk, head and neck)

When Mycetoma affects the limbs, the disease prognosis is better with low morbidity and mortality. However, when it affects the trunk, pelvis, head and neck the disease, the prognosis becomes poor, and morbidity and mortality turn to be high. Therefore, the management of eumycetoma in these sites takes special considerations. The golden rule is to conduct the surgical intervention as early as possible.

As a general rule, in these special cases of eumycetoma, if there is no improvement of the patient during the first medical treatment cycle, the patient can undergo surgical excision to avoid disease progression that causes high morbidity and mortality.

### If the patient classified as category 1A or 2A and 3A

1. Itraconazole 200mg BD daily for three months.
2. Wide local excision
3. Follow up and monitoring the same as mentioned above in treatment of Category 1A, 2A, 3A in other sites.

However, if there is a good response to medical treatment, it can be extended up to six months provided there is a remarkable sign of improvement such as regression of the lesion size, healing of the sinuses, and there is the possibility of close monitoring of the patient during this period.

### If the patient classified as category 3C, 3D

1. Confirm mycetoma diagnosis as mentioned above (imaging and histology or cytology)
2. Start treatment regimen as indicated above in this category of patients.
3. Further investigations are needed to see whether there is deep infiltration. This is to assess the disease progression, patient condition and management plan:
    a. If the disease is affecting the skull, MRI is requested to assess the deep infiltration.
    b. If the disease is affecting abdomen and chest, CT scan is requested.
    c. If the disease is affecting the pelvis MRI is requested.

## Skull Eumycetoma Category 3B, 3C, 3D

If the MRI showed an intracranial lesion, then start the patient on medical treatment for three months followed by immediate craniotomy. This can be in line with other clinical manifestations of brain occupying lesion. After craniotomy continue on medical treatment.

The prognosis of the disease and improvement of the patients depend on the close follow-up of the patient, which should be every six weeks and the accuracy of the surgical manoeuvre.

During follow-up of such patient, the existence of subcutaneous lesion and intracranial infiltration should be considered in the management plan and follow-up of this patient.

- For the subcutaneous one, the follow up is the same as mentioned above in this category management plan.
- For intracranial infiltration after craniotomy, history and examination for new neurological symptoms and signs should be taken. If there are any positive findings, MRI is requested and consult neuro-surgeon.
- If there are no symptoms, follow up the patient as with subcutaneous lesion.

If this patient completed the management cycle as mentioned above in subcutaneous eumycetoma:

1. Confirm cure of the subcutaneous lesion as indicated above
2. MRI brain scan and the third ultrasound where normal then treatment should stopped. The post medical treatment follow-up should be as indicated above.
3. If there is signs of recurrence repeat the management cycle mentioned above.

## Pelvis Eumycetoma Category 3B and 3C, 3D

Management of eumycetoma in this site is the same as skull eumycetoma but, the surgical intervention is subjective depend on the level of organs infiltration, patient's condition and response to the disease to medical treatment. The type of surgical intervention at this disease site depends on extent of the disease, the patient condition and surgeon decision.

## Trunk Eumycetoma

Management of eumycetoma at this site is the same as skull eumycetoma management. The Investigations of the disease at this location is by CT scan especially for category 3. The surgical treatment at this site depends on the disease extent, the patient condition and surgeon decision.

## Spinal cord Eumycetoma

If eumycetoma caused cord compression, it needs for urgent surgical intervention by orthopaedic or neurosurgeon.

## Joint Eumycetoma

Compare to other special sites; this is a common site for eumycetoma. Intra-articular, eumycetoma is associated with loss of joint function. Also, it may end in amputation. Therefore, eumycetoma in this site needs close follow up to avoid this outcome.

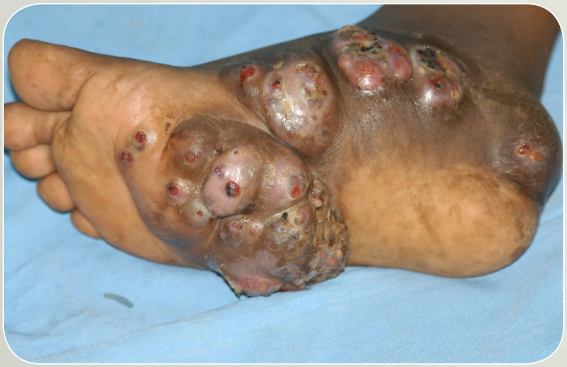
If the lesion is massive, MRI is needed to assess the intra-articular extension. If it present, surgery is recommended with consultation with the orthopaedic surgeon.

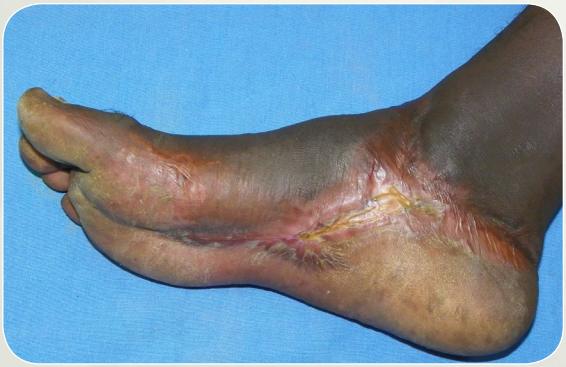
### Patients with co-morbidity

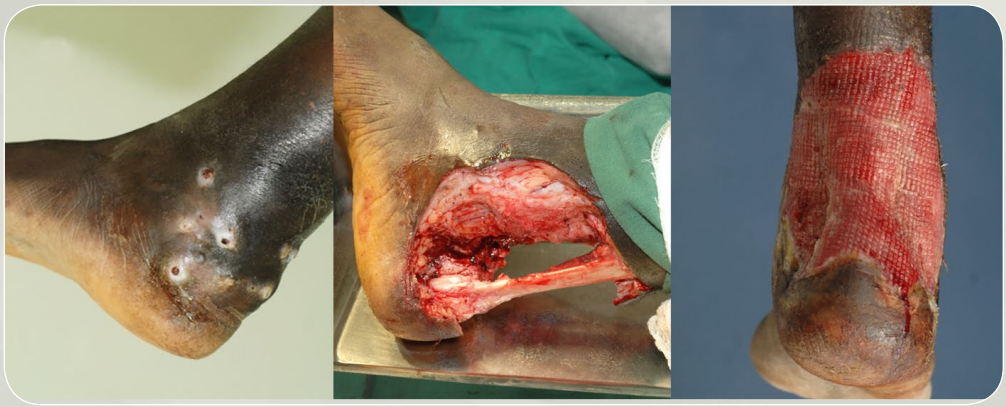
This group includes patients having diabetes mellitus, renal transplant, on immunosuppressive drugs, tuberculosis and people living with HIV/AIDS. Patients with co-morbidity usually are immuno-suppressed. They need close follow-up as a team with their managing physician.

The idea is to prevent the disease progression, local control of the disease and avoid the occurrence of recurrence. This depends on choosing the accurate time for surgical intervention and medical treatment to deal with the issues mentioned above. Surgical intervention timing depends on the patient general condition, disease response to medical treatment and judgment of the managing team.

## The surgical treatment





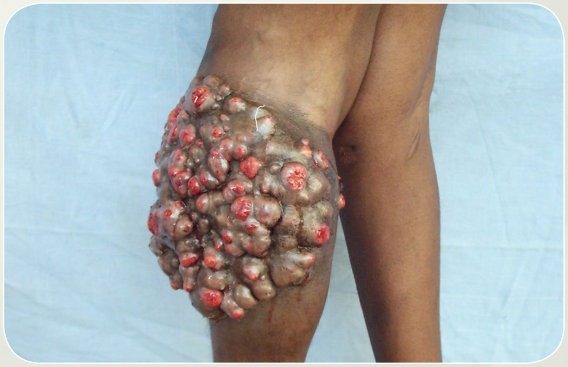


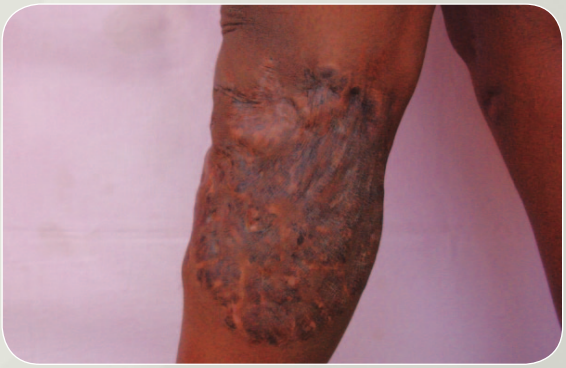
## Treatment of Actinomycetoma:

Treatment of this type of mycetoma is the same as eumycetoma; it is a combination of medical treatment and surgical intervention but, the response of actinomycetoma to medical treatment is good and hence few of the patients undergo surgical treatment. Generally, actinomycetoma is amenable to medical treatment with antibiotics and other chemotherapeutic agents combination. Combined drug therapy is always preferred to a single drug to avoid drug resistance and for disease eradication.[27, 29, 57, 58] Cure is possible in actinomycetoma, although a prolonged period of treatment is needed. Currently, the first line of the medical treatment of choice is co-amoxiclav (amoxicillin trihydrate equivalent to 500 mg amoxicillin and potassium clavulanate equivalent to 125 mg of clavulanic acid) BD for adult, for children the dose is 15-25 mg/kg BD. This drug is combined by co-tri-moxazole 960mg BD for adult while, for children, 480 mg BD combined with plus folic acid to provide acidic media for the drug absorption.

The second line of treatment is amikacin sulphate in a dose of 15mg /kg given in two doses daily combined with 960mg co-tri-mazole BD in the form of cycles till cure. Each cycle consists of three weeks of amikacin sulfate and five weeks of co-tri-moxazole. Amikacin is nephrotoxic and ototoxic, and patients need close follow-up and monitoring of the renal and hearing functions during treatment.

### Pre and Post Medical Treatment of Actinomycetoma





- The length of the treatment period is variable, but normally it takes around one year and a half till cure.
- Patient follow-up is every six weeks, for clinical assessment i.e. the lesion size reduction, closure of sinuses, skin return to normal and to measure the renal functions and the hearing function
- Medications should continue until the lesion completely subsided and the investigations showed cure.
- Cure means the subcutaneous mass disappearance, healing of sinuses and normal skin and this should be confirmed by investigations.
- Patient can be confirmed cured if three regular ultrasound results are negative.

### During follow-up

- If the ultrasound showed recurrence, the treatment should be restarted.
- Surgical treatment is indicated in the follow conditions:
    - Patient preference.
    - Small localised lesion amenable for excision.
    - No or poor response to medical treatment.
    - Surgery is a lifesaving procedure.
    - If there is contraindication to medications used in treatment

## Surgical treatment of Mycetoma

Surgical intervention is an integral component in the diagnosis and management of mycetoma.

Surgical treatment is indicated for small localised lesions and in massive lesions to reduce the mycetoma load and to enable better response to medical therapy. It is also a life-saving procedure in patients with massive disease and sepsis. [3]

Surgical options for mycetoma treatment range from a wide local surgical excision, repetitive debridement excisions to amputation of the affected part. Adequate anaesthesia, a bloodless field, wide local excision with adequate safety margins in a suitable surgical facility and expert surgeons are mandatory to achieve the best surgical outcome.

Surgical intervention in mycetoma is associated with considerable morbidity, deformities and disabilities particularly in advanced disease. These complications can be reduced by educating patients to seek medical advice earlier when the lesion is small, localised and amenable to surgery. There is no evidence for mycetoma hospital cross infection. [32]

### Post-surgical treatment care

#### Eumycetoma lesion dressing:

Lesion dressing is important for:

1. Any lesion with active sinuses
2. Massive mycetoma lesion.
3. Secondary bacterial infection
4. Open wound after surgical treatment.

It can be done at health centre service or home-based levels.

#### Home-Based Dressing:

This method is used for patients at rural setting, living in high distance from health facilities or having problem of mobility due to the disease. It is also mainly recommended for massive mycetoma lesion, active sinuses and secondary bacterial infection, but for post-surgical interventions dressing should be done by health care provider.

Patients are adviced to do this dressing as follow:

1. Bring sufficient amount of water (depend on lesion size) and boil it to sterilise it.
2. Put the water in a plastic pool and wait until it becomes warm.
3. Add hydrogen peroxide to the water with a concentration of 10 ml per litre.
4. The patient put the lesion site mainly, foot or hand for half an hour in the pool.
5. Patient tries to compress the lesion to discharge the grains and pus from the sinuses
6. Use a clean cloth to dry it.
7. Then use sterile gauze for wound covering.
8. This can be done once or twice per day according to the patient's condition.

### Health care setting dressing:

This type is recommended for post-surgery wound and special sites eumycetoma and in patients with bacterial infection and for mycetoma patients living close to health centres.

## Special reconstructive surgery

### Skin graft and flaps:

Can be done after wide local excision with no symptoms and signs and radiological findings of recurrence.

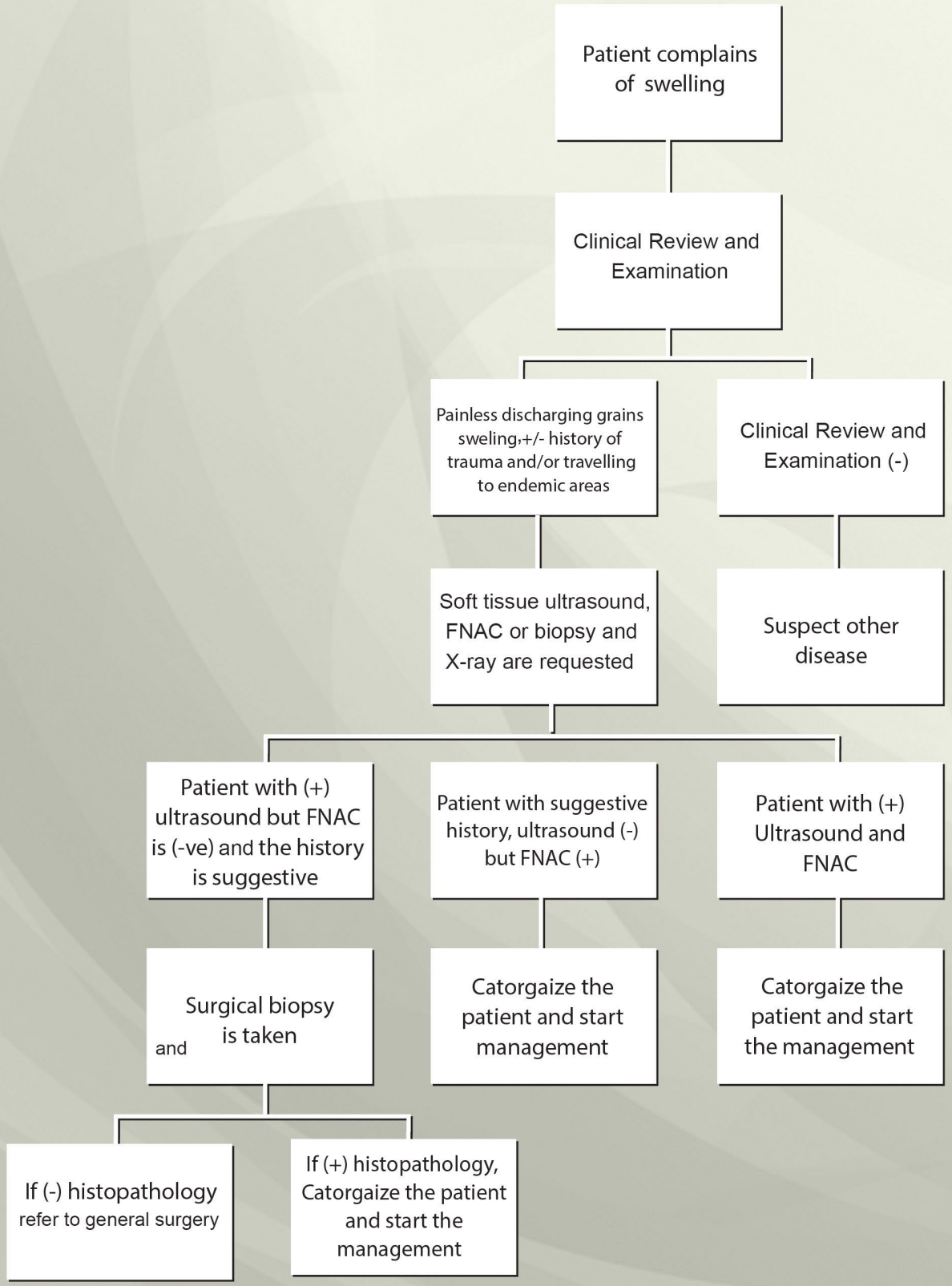
### Tendon reconstruction:

This surgery is done after the patient is completely cured.

## Eumycetoma Patients Management Plan

| Category | Pre-Operative Medical Treatment<br><br>Duration (months) | Operative Treatment | Post-Operative Medical Treatment<br><br>Duration (months) | Remarks |
|---|---|---|---|---|
| Category 1 | | | | |
| A | 3 | Wide local excision | 3 | If no recurrence or residual lesion ultrasonically, stop treatment after normal<br><br>Ultrasound follow every three months for one year |
| B | 3 | | | |
| C | 3 | | 6 | |
| D | 3 | Wide local excision+ bone curettage | | |
| Category 2 | | | | |
| A | 6 or more | Wide local excision | 12 | If no recurrence or residual lesion ultrasonically, stop treatment<br><br>Ultrasound follow every three months for one year |
| B | | | | |
| C | | | | |
| D | | Wide local excision+ bone curettage | | |
| Category 3 | | | | |
| A | or more 6 | Wide local excision | months 12 | If no recurrence or residual lesion ultrasonically, stop treatment<br><br>Ultrasound follow every three months for one year |
| B | | | | |
| C | | | | |

# Diagnosis of Mycetoma patient



## The patients' categories according to the lesion size and x-ray findings

| Category | Category 1 | Category 2 | Category 3 |
|---|---|---|---|
| Lesion size | <5 cm | 510- cm | >10cm |
| Normal X-Ray Findings | 1A | 2A | 3A |
| Soft Tissue Mass | 1B | 2B | 3B |
| Periosteal Reaction | 1C | 2C | 3C |
| Bone Cavity | 1D | 2D | 3D |

# Section V

## Follow Up, Monitoring & Evaluation

## Patients follow up

Mycetoma management is a prolonged process. Therefore, special efforts should be made to ensure that patients comply with this process. As long as patients understand the nature of the disease, management plan and its duration, they are more likely to follow the management plan to achieve a cure. Therefore, a close and caring relationship between the patients and healthcare providers is mandatory.

### Challenges to management access

Many MRC studies showed that there is delay in patient treatment initiation. Most patients present late with advanced and complicated disease, after seeking treatment with traditional healers.

Some patients are not managed properly in different healthcare settings and referred late to mycetoma specialised care centres.

Efforts need to be made to ensure mycetoma referring health facilities are able to detect and refer suspected mycetoma cases early and promptly. These efforts should include training of these health facilities staff on the diagnosis and treatment of mycetoma and regular visits to these facilities especially in endemic regions.

An efficient patients' referral system in these health facilities should be designed, and the bottleneck constraints should be regularly identified and solved.

At mycetoma specialised management facilities, the duration between the receiving and screening patients and treatment initiation should be regularly evaluated and improved to avoid treatment delay and disease complications.

### Management Encouragement Plans:

As mycetoma is a chronic medical and health condition with long management duration, patient management success depend on sharing of sufficient information about the disease and its management with patients and their social relations.

Health care workers should adopt positive attitude and good communication skills while treating patients. These skills include careful listening to patients complaints, ensure patients understanding the disease and treatment information and engaging patients in the management plans.

During treatment and follow-up visits, patient social contacts should receive health education and orientation messages on mycetoma.

Patients enrolled in treatment, and his/her close relatives should be able to know:

- What is mycetoma
- Types of mycetoma
- How one can get it
- Where is mycetoma available
- Whether it can be transferred from a person to another

- Mycetoma treatment methods
- Mycetoma management duration
- Treatment follow-up
- Whether mycetoma can be cured or not
- Possible disease complications and how to avoid it
- How the drugs should be taken
- Major drugs side effects and their symptoms and signs
- What to do when develop mycetoma drugs side effects

**Management Progress Monitoring:**

Management progress in mycetoma is vital to assess success and to change and modify processes. Management progress is measured by the lesion size regression, reduction and closure of the discharging sinuses and disability improvement as well as by certain investigations such as lesion ultrasound examination, hepatic and renal functions measurements. These criteria are assessed every 5-6 weeks during patients follow-up visits until the management plan is completed.

Disease-oriented patients can help in knowledge dissemination to their community. This can help in the mobilisation of other suspected patients' to seeking early diagnosis and treatment to minimise the disease negative medical and socioeconomic impacts on patients, family, community and health authorities.

As most of the mycetoma patients are located in remote, poor rural localities, community leaders and activists, social counsellor and social workers should be involved and included in the mycetoma management team. They can identify the patients' socioeconomic problems that hinder patients' treatment compliance and can suggest solutions for that.

The identified socioeconomic problems such as geographical distance, transport cost, poverty, lack of health education and others should be discussed with the patients and social and health authorities to solve them for successful management plan.

These socioeconomic problems hindering implementing the management plan can also be identified by direct patients interviews in the health facilities or during home visits.

As part of the services quality audit process, regular meetings and interviews between patients and their social contacts and the community leaders and activists, social counsellor and social workers should be done for early problems identification and solutions findings.

## Service Delivery Modality

With current knowledge gap in mycetoma prevention and control, provision of high-quality medical services is necessary for disease control and reduction of its socioeconomic impacts on the affected communities. Therefore, exist of set of health facilities providing mycetoma care is important. These services organisation and interlink important for ensuring proper patients diagnosis and successful treatment outcomes.

## Services provision Structure:

As mycetoma is a chronic medical and health problem with many socioeconomic impacts and needs specialised diagnostic facilities and both medical and surgical treatment, the patients' management can be at different health care facilities levels.

Service provision for the management and control of mycetoma depend on health system arrangement, capacity and decentralisation. In addition, the disease prevalence whether there are certain high endemic areas or the reported cases are scattered all over the country.

Hence, a network of mycetoma management health facilities should be established. It is recommended to be structured at three levels according to the disease endemicity and health system structure and in most of the countries and these are the district, regional and central levels.

The network can be named The Mycetoma Network Centers (MNC), and that should be arranged into Central, Regional and District centres. This network is managed by central level specialised body which acts as apex to this mycetoma control management structure.

The Regional and Central Mycetoma Centers provide patient care services, in addition, to manage and supervise the centres and facilities under their responsibilities.

## Regional Mycetoma Centers

These are responsible for patients' management and planning, monitoring and evaluation of the District Mycetoma Centers.

## District Mycetoma Centers

These are responsible for patients' management and referral to the Regional Centers.

### The Mycetoma Network Centers **(MNC)**

These consist of the following:

1. District Mycetoma Health Centers
    a. Mycetoma Referring Health Centers
    b. District Mycetoma Units
2. Regional Mycetoma Centers
3. Central Mycetoma Center

### Mycetoma Referring Health Center (MRHC)

This is the base for mycetoma care and control activities. It is located at a primary health care setup at a district level, and it is one of 5-7 satellite units linked to a District Mycetoma Centers.

Its major roles are to:

1. Offer only screening examination to identify suspect mycetoma cases among patients seeking care in these facilities and refer them for diagnosis and management decision at District Mycetoma Unit.
2. Provide follow-up of patients with category 1 & 2 with early mycetoma
3. Act as hubs for community behaviour change, health education and community awareness activities.
4. Receive actively detected suspected cases by active community-based organisation or non-governmental organisations and refer them to the District Mycetoma Center.

### District Mycetoma Center (DMC)

This centre is part of the District Mycetoma Health Centers, and it is responsible for:

1. Provision of complete management of patients with early mycetoma.
2. Patients' management and treatment outcome data collection and reporting.
3. Monitoring and supervision of Mycetoma Referring Health Centers

Usually, the DMC is based at a regional hospital level. Depending on population need or health system structure and it can be integrated either in existing district or secondary hospital.

In endemic areas, an existing Primary Health Care facility can be upgraded to provide mycetoma management and care services.

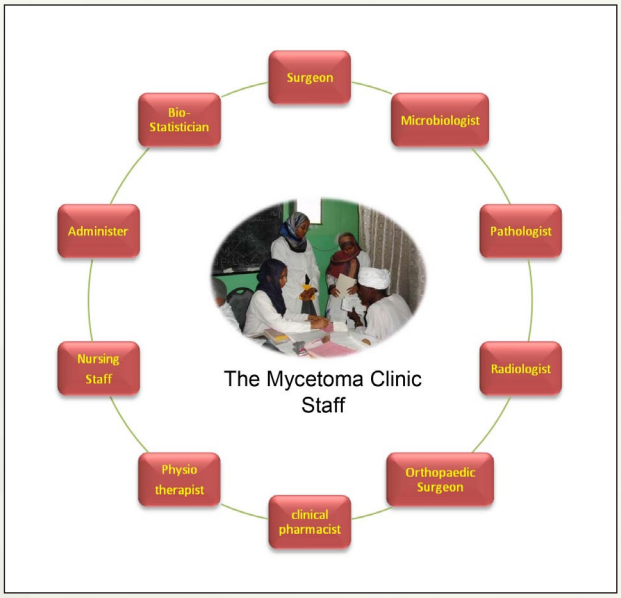
Diagnosis of patients and treatment can be made at this level. Mycetoma while advanced disease can be referred to Regional Mycetoma Centers.

### The minimum requirements for establishing DMC are:

1. Outpatient clinic
2. Minor theater
3. Wards
4. pharmacy
5. Laboratory Department with
    a. Chemical pathology
    b. Haematological
    c. Microbiology
    d. Histopathology
6. Imaging department
    a. X-ray
    b. Ultrasound

## The treating staff will consist of

1. Surgeon (Team Leader)
2. Medical doctors
3. Nursing team
4. Microbiologist
5. Pathologist
6. Radiologist
7. Physiotherapist
8. Clinical pharmacist
9. Psychotherapist
10. Counselor
11. Anesthetist
12. Orthopedic surgeon
13. Plastic surgeon
14. Bio-statistician
15. Administrator




Each DMC should have a mycetoma focal person. This person usually is the leader of the mycetoma patients' management team, and his/her major responsibility is to ensure that:

1. Mycetoma control activities are correctly implemented in the DMC covered area and its MRHC satellite
2. All staff involved in mycetoma patients management are well trained
3. All mycetoma patients are diagnosed and receive treatment according to guidelines
4. Mycetoma patients management drugs and supplies are available and uninterrupted
5. Mycetoma patients' records are complete, and reports are submitted on a regular basis.

## Regional Mycetoma Centre (RMC):

It is the second level of mycetoma management services. Each Regional Mycetoma Center supervise and support 5-9 District Mycetoma Centers.

RMC is specialised mycetoma management centre that provides the following:

1. High-quality mycetoma patients services
2. Complicated mycetoma patients Management.
3. Mycetoma patients rehabilitation services
4. Coordinate active case finding, campaigns with DMC teams, Mycetoma Friend Association and other related stakeholders
5. Support and supervision of DMC, MRHC, through regular visits and on job training activities.
6. Provide training for new staff, refreshment training and training on new management techniques.

7. Ensure uninterrupted availability of diagnostic and management supplies.
8. Maintain a system of quality control of diagnostic services.
9. Review received reports from DMC, analyses them and report to the central level.
10. Coordinate with relevant government authorities, non-governmental association such as Mycetoma Friend Association branches and community to mobilise support for mycetoma control activities.

## Central Mycetoma Center

Is responsible for overall management of all activities related to mycetoma. Its major function is to provide support to all Mycetoma Network Centers, invest on research and development and ensure the promotion of mycetoma activities.

This centre teamed by full-time staff specialised on mycetoma management and research.

The main functions of Central Mycetoma Centre are to:

- Coordinate the national efforts to control mycetoma programmes.
- Mobilisation of support from technical and fundraising bodies.
- Coordinate the process of policy making and update, strategies development and operational planning.
- Promote mycetoma care services availability, sustainability and access among affected communities.
- Ensure early diagnosis and management of patients to prevent disease complications and reduce the disease burden on the patients and programme.

- Training of health personnel to ensure adoption of the programme guidelines and proper treatment of patients with competent teams
- Regular supervision to maintain good clinical practice, problem-solving and sharing of knowledge and experience.
- Quality control of mycetoma diagnostic services and quality assurance of mycetoma management practices.
- Timely and regular supply of drugs to ensure patient access to care and avoid interruption of treatment.
- Recording and reporting system to ensure flow of information on the disease burden, appropriateness of the used regimen and assessment of program performance to shape the appropriate strategies.
- Cater for research and development and invest in advanced research topics to enhance disease control, prevention and elimination.
- Increase the national community awareness on the disease and its complications through adequate health promotion activities
- Promote use of information and research to inform policy update and management practices in mycetoma

## Diagnostic services

Good diagnostic services are mandatory for accurate diagnosis of mycetoma patients and proper treatment and follow up.

Diagnostic services for mycetoma include imaging and laboratory services.

The imaging services include:

1. Conventional radiology
2. Ultrasound
3. CT scan
4. MRI

The laboratory services include.

1. Clinical chemistry
2. Microbiology
3. Molecular diagnostics
4. Histopathology

These diagnostic services should be available within the already existing health services providing mycetoma management services. To ensure patients in remote endemic areas, have access to diagnosis and treatment and to reduce disease burden on the affected communities, a network of diagnostic service satellites centres should be established close to the highly affected mycetoma endemic areas as well.

Central reference diagnostic Centre should be established to supervise the Regional and District Diagnostic Centers, to ensure high-quality staff at all levels training and quality assurance activities.

A complete system of quality assurance should be developed with internal and external checks followed by corrective actions.

Determination and surveillance of mycetoma drugs resistance are important for early drug resistance detection and to ensure adequate patients care.

### Accordingly, the role of the diagnostic services in mycetoma should include:

1. Mycetoma diagnosis confirmation
2. Monitor patients treatment
3. Mycetoma drug resistance surveillance
4. Causative organisms monitoring
5. Staff training
6. Research & Development

## Patients care Monitoring

Sufficient information about mycetoma patients' management should be collected, reported and analysed in regular and systematic manner. Regular collection of this information and reporting instrumental for problems identification and management plans update and improvement.

This information is important to understand the disease characteristics, patient's treatment progress and to plan and design control programmes. Furthermore, this information help in early problems identification, improvement of treatment modality and expansion of services.

The more these information collection formats and records are simple, direct and standardise, the more they can easy to be filled, compiled and analysed. Furthermore, this information becomes more reliable to be used in decision-making.

## Important mycetoma records are:

1. Investigations request forms
2. Patient treatment card
3. Patient identity card
4. Patient register book
5. Patients case notes
6. Laboratory register book

## Diagnostic records

To establish the diagnosis of mycetoma many laboratory and imaging tests need to be requested and done. These investigations are requested during the first visit and the follow-up of the patients. Special form should be designed and filled by the healthcare provider.

In these forms, the result of the patients' investigations should be recorded. Information about individual patient should be entered in imaging and laboratory units register

## Patients Case Note

When patient diagnosed as mycetoma patient Case Note is issued. The Case Note summarises the patient demographic features; such as age, gender and residence. Information on the patient's diagnostic investigations results, management plan, follow updates and the treatment outcomes are recorded.

The mycetoma patient's Case Note is confidential as it contains the patient private information, the diagnosis and management plan. Patients should be informed that some information can be shared with other health care providers as they may need to know the patient condition before other treatment prescribed.

Patient Case Note should regularly be transcribed into relevant computer programmatic software. Greater care should be given to this information entry, to ensure quality and completeness of patients' information. In a situation where it is not possible to have digital patients' information

recording system, mycetoma team can use registration books.

The important elements of the patient Case Note include the:

- Patient demographic characteristics
- Mycetoma type:
    - Actinomycetoma
    - Eumycetoma
- Patient type:
    - New patient: is the patient who had no mycetoma treatment previously or medical treatment less than one month without surgical intervention.
    - Relapse patient: if the patient who completed the management plan and declared cured then developed mycetoma lesion again.
    - Treatment failure: is the patient on regular mycetoma management without improvement and then started on the second line of treatment.
    - Return after default: is patient took the treatment for three months and stopped treatment and then returned for treatment
    - Transfer in: is a patient who diagnosed and registered in a DMC and being transferred to another DMC. This patient keeps his/her original registration number from the previous DMC and to be re-registered

## Treatment results

By the end of the management cycle mycetoma patients' treatment result can be classified into the following categories:

1. Interrupted treatment: The patient had started the treatment and dropped the treatment for less than six months and then resumed the treatment.
2. Defaulter: The patient had started the treatment and dropped the treatment and follow-up for more than six months.
3. Completed treatment: The patient had completed the recommended treatment and follow up.
4. Cure: The patient had completed the recommended treatment and follow-up and remained disease free for one year confirmed by ultrasound examinations.
5. Post-operative Recurrence: recurrence occurred within six months after surgical treatment.
6. Relapse or Post-treatment Recurrence: recurrence after complete one year of free state.
7. Drug-Resistant Patient: The patient enrolled in the first line of treatment without improvement and confirmed drug-resistant by culture and sensitivity of the causative organism.
8. Dead: Patient died at any time during the treatment cycle.
9. Transferred Patient: The patient diagnosed and referred from another health facility to the MRC for management decision.

## Patients information reporting:

It is recommended that each DMC reports quarterly on a regular basis, case finding and management outcome of mycetoma patients in its catchment area. This allows regular monitoring of mycetoma care and control activities, problems identification and regular update and improve on ongoing mycetoma teams activities.

The reported information is to be compiled at RMC using mycetoma recording and analytical software system.

The quarterly reports should be prepared and submitted no later than the end of the month at which it has been completed by RMC teams.

At the regional level, DMC data verification for accuracy and coherence should be done at this level before reporting to the central level.

Also, it is recommended to ensure simple information analysis of data conducted by the managing team to assess region performance in reaching national goals and targets, ensure service availability sustainability and improve management quality.

Mycetoma patient's information should be compiled at the central level to reflect an overall view about mycetoma notification and quality of management of cases. Then national report can be prepared and shared with concerned authority nationally and internationally.

## Quarterly case detection report:

This includes all information about the patients enrolled in management during the specific quarter, usually the recently ended one. It entails all information about the patients; their type, management category, management decision, and the type of mycetoma they got. Also, the report includes classification of patients according to gender and age group.

## Quarterly management outcome report:

Management of mycetoma takes at least 15 months for patients with category1. While for category 2 and 3 it takes 18 months. This when there is no recurrence development or existence of poor management progress.

For reporting of management result of patients, health centres teams are expected to report the treatment result of patients treated in certain quarter in the second quarter of the year after next. Management result report findings mirrored case detection report; the explanation for any differences should be given for the detailed content of the quarterly management result report).

When report prepared, it should be sent to the next level to eventually reaching the central management level as mentioned above. When different reports research the central level, the national report shall give detailed view about progress on the management of patients, availability and sustainability of services and quality of patients management. Management outcome reports are crucial for ensuring regular services promotion and update.

## Mycetoma Supply System

The availability of mycetoma diagnostics and management supplies are crucial for services sustainability and proper management of patients. Mycetoma management teams at all levels are responsible of maintaining sufficient stock of mycetoma diagnostics and management supplies through regular supply.

Each level of mycetoma management is responsible for the regular provision of feedback reports about supplies consumption and expected date of stock out.

Clear supply management system, standard operation procedures for supplies ordering and accurate inventory system keeping are necessary to avoid interruption or delay in the start of patients' management.

Important supplies for mycetoma diagnosis and management are:

1. Diagnostic supplies:
    a. Laboratory
    b. Imaging
2. Patients' Management supplies
    a. Surgical supplies
    b. Treatment drugs
    c. Rehabilitation supplies
3. Administrative supplies
    a. Computer hard and software
    b. Stationaries
    c. Others

## Maintenance of Supplies:

The amount of the needed supplies for each facility that provides mycetoma management services are calculated using the case detection reports. The ideal way is to:

- Calculate the needed supplies for diagnosis and management of one patient (A).
- Then multiply (A) with the total number of patients on treatment in the previous quarter.
- Then multiply needed supplies multiplied for all patients by two to ensure exist of reserve to avoid stock out.

Ordering of supplies is done in the same time of submission of quarterly case finding reports (the second week after the end of the quarter). For supplies ordering, health providers use the quarterly order form for supplies.

It is recommended to integrate mycetoma supplies management system. This integration ensures cost effectiveness through using the existing channel of supplies management by central supply management system, its staff and stores. Also, this integration provides opportunity for good supplies dispatch, maintenance and audit through central supply network of allocated trained teams all over the country.

# Section VI

## Community Leadership in Mycetoma Control

## Community Leadership in Mycetoma Management and Control

Mycetoma patients commonly resident in remote rural regions, most of them are illiterates, lives in poor hygiene setting, of low socio-economic status, and of low health education and hence they commonly present late for treatment, and all these hurdles contribute to the poor treatment outcome and prognosis. Community involvement in the management of these patients is essential to ease these management hurdles

As the management of mycetoma is a long and tedious process, it is clear that the mycetoma management need a teamwork and community leaders and activists are essential team members

Community engagement in disease prevention and control will lead the following:

- Early case detection through community led active case finding campaigns.
- Early disease is amenable to treatment and has good outcome.
- Reduction of patients' treatment interruption and drop out.
- Reduce affected communities exposure to factors contribute to disease transmission.
- Increased mycetoma awareness.
- Reduction of mycetoma socioeconomic burden

Community leaders' involvement will enhance in conveying messages to the community in their own culture and traditions.

Villagers' involvement will promote their health and improvement of local environment conditions that believed to be the main source of transmitting mycetoma Thus, this approach is important to improve patients support, seeking behavior, and their living conditions.

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