MEDIA BRIEFING - MYCETOMA

New hope for mycetoma: the flesh eating tropical disease

So neglected that repeated amputation is the main treatment

Summary: To the un-trained eye, mycetoma looks like a mix of leprosy and elephantiasis. This chronic, progressive and life-mutilating tropical disease affects poor people in rural areas who go barefoot – mostly 20-40 year old males. It attacks the skin, the deep muscle structures and the bone, often entering the body via thorn pricks or lesions in the feet. In over 80% of patients it leads to major deformity, amputations and even death.

Mycetoma is painless at the start so patients present late. After walking for days or weeks to the clinic, patients often need amputations, so many run away and never come back, especially those suffering from mycetoma of the groin or neck.

There are two versions of this “flesh eating” disease – one caused by bacteria and the other caused by a fungal infection. Although there is an expensive antibiotic oral treatment that works relatively well for the bacterial version, for the fungal version in Sudan and other African countries it is more difficult to diagnose and treat and results in amputations.

When patients seem to improve with amputation or to be cured, too often the disease starts up again, progressively “eating the body” from the extremities upwards. Once the central part of the body is involved, surgical options are limited and patients often die. Although recent lab research has shown promising candidates for treatment, the pharmaceutical companies have not yet made drug donations for clinical trials in Sudan.

Mycetoma is endemic in tropical and subtropical areas known as the ‘Mycetoma belt’ (between latitude 30 North and 15 South). The belt includes Sudan, Mauritania, Senegal, Somalia, Ethiopia, Chad, Yemen, Venezuela, Mexico, India and others. In the past few years, the Mycetoma Research Center in Khartoum, Sudan, recorded around 6,500 patients.

Mycetoma is so neglected that it is not even a notifiable disease, with no legal requirements to report it, so no surveillance systems exist.

After decades of neglect, in February 2013, experts from around the world met for the first time and committed to work together as the “Mycetoma Consortium”. Work is underway to raise the profile of the disease to attract new partners and to better understand the causes and effects. In July 2013, mycetoma was included for the first time on the official WHO website http://www.who.int/neglected_diseases/diseases/mycetoma/en/

The aim is to also research and develop new, effective, affordable diagnostics and treatments (ideally costing no more than 10 USD per treatment) that can be used in the field to treat patients and avoid amputations. The next step is to reach out to pharmaceutical companies and partners to raise funds and bring real hope and help to patients.
Some mycetoma pictures, courtesy of Dr Fahal and his team in Khartoum:

Who does mycetoma affect and who is at risk?

The disease affects poor farmers or animal herders who go barefoot or wear sandals that do not completely cover their feet. The organism may enter the skin through a thorn prick. There is neither a known vector nor animal reservoir. There is no person to person transmission although relatives living in the same locality may develop the disease perhaps because of shared environmental factors. Genetic, immunological predisposition (possibly induced by co-infection) should also be considered.

What is the treatment for mycetoma?

Mycetoma is caused by bacteria - actinomycetoma, most common in Mexico and by fungi – eumycetoma, most common in Sudan and in Africa. Access to treatment is poor because of lack of awareness, a lack of control programmes and fear of surgery.

For the fungal version, mostly in Africa, surgery and recurrent and progressive amputation is often the only available treatment. The only current available treatment lasts 12 months, is expensive, not effective and poorly tolerated (ketoconazole) - is sub-optimal, as it reduces the lesion but does not eradicate the fungus.

The bacterial form (mostly in Mexico) is more treatable and there are antibiotics, though they are expensive and take months. The high cost and length of treatment has proven to be too difficult and costly for the patient, family and the health authorities.

In the last ten years, real progress in research in the lab has shown that the fungi causing mycetoma responded well to promising newer treatments: - voriconazole (Pfizer) and posaconazole (Schering).

Unfortunately, these new agents have not yet been studied in patients and their cost is prohibitive. Voriconazole for example, is an expensive medicine used in Europe and the US for other fungal diseases, produced by Pfizer Company (USA).

Researchers have been trying for years to secure the help of pharmaceutical companies for drug donations for clinical trials in Sudan, but without much success. The Mycetoma Consortium, which includes many of the original researchers, has a new global action plan to change this, to bring new hope to patients suffering from this neglected tropical disease

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What is the cost of doing R&D?

Multi-national pharmaceutical companies estimate that it costs around USD $1 billion to bring a new drug to market. This includes R&D and marketing. Mycetoma is a truly neglected tropical disease, for which there are some “low hanging fruits”, or existing treatments which could be adapted or tested.

As a not-for-profit venture leveraging in kind contributions from other stake holders such as pharmaceutical companies, academics etc., it could cost as little as USD 20 million to prove efficacy and to obtain registration for use of a therapy for mycetoma.

For this to happen, pharmaceutical companies would first need to support clinical testing of existing promising drugs in Sudan and other affected areas. Clinical trials also cost money. To help with uptake and use, WHO would then need to recommend the new treatment for mycetoma, which should also be available for less than 10 USD per patient per treatment.

New hope for mycetoma: key challenges and plan of action:

Advocacy - Work together as the Mycetoma Consortium to raise the profile of the disease to attract new partners and to raise funds – to better understand the disease and to research and develop new diagnostics and treatments that can be used in the field to treat patients and avoid amputations.

To raise the profile of the disease with WHO and globally, so that it becomes the 18th disease on the WHO neglected disease list and is part of the national, regional and international health plans. This also helps with raising funds, drug discovery and registration.

Epidemiology - To increase access to health care; to better manage, early diagnose, treat and track patients to better understand the extent of the problem, and how it spreads:

- Accurate data on incidence and prevalence
- Natural habitat of the causative organisms (soil, dung, other)
  - Risk factors environmental factors
  - Role of endemic co-infections such as schistosomiasis
  - Genetic predisposition.

Diagnosis and Care - To discover & develop effective diagnostics & treatments:

- Serological tests for use at point-of-care; need for identification of specific antigens
- Oral, heat resistant treatment which is effective in humans, affordable and available and that can be given in rural areas.

1 Similar to the Product Development Partnership (PDP) or innovative model such as how DNDi works on other neglected diseases, with in kind contributions from key stake holders such as pharmaceutical companies, academics etc.
Some key dates on mycetoma treatment and research:

**Eumycetoma** is a chronic, specific, granulomatous, fungal disease which often affects the foot. *Mycetoma pedis* is also known as **Madura foot**. Most of the basic lab research has been done in the past ten years. Next step: clinical studies in field conditions for treatments.

- **Madura foot** was originally described in Sanskrit in the Vedic texts from India². The first English language accounts occurred much later in Madras (aka Chennai).
- **1694:** First description of the disease in western literature (thesis in Leiden university) by Kaempfer.
- **1842:** First description in English literature by Dr. Gill.
- **1860:** First time the disease is called “mycetoma” by Vandyke Carter.
- **1955:** First large epidemiological survey to determine the amount of cases seen in Sudan, by Abbott. He found 1231 cases.

1960’s, 1970’s, 1980’s - Over three decades of little action or progress.

- **1991:** Mycetoma Research Centre set up, Khartoum, Sudan: highest number of patient intake.
- **2002:** Laboratory research really begins, Prof. Ed Zijstra links Khartoum Mycetoma Centre to Erasmus Univ. of Rotterdam. Lab research by Dr. Wendy van de Sande shows that fungi causing mycetoma respond well to newer treatments (azoles: voriconazole, posaconazole). Next step: clinical trials, but need consent from companies.
- **2013** – Creation of Mycetoma Consortium a result of first global mycetoma meeting.
- **2013** – July - First official description of mycetoma on WHO web page.

Other mycetoma references:

http://www.who.int/neglected_diseases/en/ WHO on Neglected Tropical Diseases (NTDs)
http://www.who.int/neglected_diseases/diseases/en/ Mycetoma –18th on WHO NTD list?
http://www.mycetoma.edu.sd/ Sudan site. Prof. Fahal, Director and leading global expert
http://www.mycetoma.edu.sd/academic/gallery/index.html More pictures from Sudan
http://www.dndi.org/about-us/business-model.html DNDi and not for profit R&D model
http://en.wikipedia.org/wiki/Eumycetoma

² Sanskrit references made in some papers (e.g. Mycetoma, McGinnis, Dermatol Clin, 1996, volume 14, pages 97-104). The first case was named a skeleton from the byzantine period. (300 BC).
What is being done to move mycetoma up the global agenda?

February 1, 2013, a first meeting was held in Geneva: Mycetoma: why is it still neglected? This resulted in the creation of an informal group of experts, known as the “Mycetoma Consortium”, supported by the Drugs for Neglected Diseases initiative (DNDi), is now pushing for new treatments and recognition of the disease at an international level.

In May 2013, during the World Health Assembly (WHA), the Federal Minister of Health Sudan, HE Bahar Idriss Abu Garda, hosted a dinner meeting to address mycetoma and invited various Ministers of Health and technical experts from WHO and around the world.

In July 2013 WHO posted the first official web-page on mycetoma, listed under ‘Other Conditions’ which includes snakebite, podoconiosis and strongyloidiasis. This is an important first step to formally list or recognize mycetoma. WHO in Khartoum is supporting the process. http://www.who.int/neglected_diseases/diseases/mycetoma/en/

Ideally mycetoma will become the 18th neglected disease to be added to the WHO NTD list (see below). http://www.who.int/neglected_diseases/diseases/en/index.html

Mycetoma today is at a similar stage to where Buruli ulcer was ten years ago, when few people had heard of or understood the disease. Today Buruli ulcer is on the global agenda and progress is being made. http://www.who.int/topics/mycobacterium.ulcerans/en/

The Mycetoma Consortium is also pushing for a WHA resolution + work plan. http://www.who.int/neglected_diseases/WHA_66_seventh_day_resolution_adopted/en/index.html

The ultimate goal is to find a better more affordable treatment for patients, to get access to promising treatments from pharmaceutical companies for clinical trials so that patients can be treated with an affordable, short course, oral treatment.

After decades of neglect, there is new hope for patients suffering from mycetoma and multiple amputations.

Where is the Mycetoma Research Centre in Sudan? Can media go?

The Mycetoma Research Center was established in 1991 under the umbrella of the University of Khartoum. It is the main referral centre for mycetoma in Sudan and aims to eradicate mycetoma, as a life-mutilating disease, through the advancement of medical care, research, education and disease prevention. To date they have registered 6,500 patients.

The Center was set up at Soba University Hospital and is recognized globally as a world leader and an authoritative advisor in mycetoma management and research. Prof. Fahal is the Director at the Center and a leading expert. http://www.mycetoma.edu.sd/

The mycetoma project in Khartoum can arrange visits to the Centre this and the Minister of Health has given his personal guarantee that visas will be issued quickly. WHO is also supportive and helpful to journalists in Khartoum.
More about mycetoma in Mexico:

Mycetoma is mainly caused by bacteria - aerobic actinomycetes (around 97%). Patients present late due to poor understanding of the disease and its treatment and cost of treatment. Control efforts are almost non-existent and there is a lack of basic knowledge of the disease within the health systems.

However, in recent years, there is an increasing level of research on new drugs for treatment of actinomyctoma performed by Dr. Lucio Vera et al. and on the immune response of the host by Dr. Mario Cesar Salinas-Carmona. Dr. Oliverio Welsh developed combination treatment with cotrimoxazole and amikacin for severe and recalcitrant cases with promising results; in the few cases where there is no response they combine different aminoglycosides, carbapenems and other antimicrobials.

Mycetomas are evaluated and treated in the Department of Dermatology of the UANL University Hospital in Monterrey where there is a very active clinical and basic research team led by Dr. Oliverio Welsh, Dr. Lucio Vera-Cabrera and Dr. Mario Cesar Salinas-Carmona. One of their research lines is mycetoma with emphasis on the pathogenesis and treatment of actinomycetoma.

Numerous articles on the physiopathogenia of actinomycetoma, molecular studies of *N. brasilensis*, and the treatment of complicated and difficult cases can be found in PubMed.gov.

There are 10 more dermatology centers and mycology laboratories in Mexico that study and treat patients with mycetoma. They are located in Mexico City, Guadalajara, San Luis Potosi, Merida, and other cities.

**Mycetoma Consortium – working group contacts:**

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- UK - Prof M. Goodfellow - michael.goodfellow@newcastle.ac.uk,
Other useful mycetoma contacts:

- WHO / NTD - Dept of Control of Neglected Tropical Diseases – Director, Dr L. Savioli, Dr. Jean Georges Jannin, contacts on: http://www.who.int/neglected_diseases
- WHO / TDR (Tropical Disease Research) - Dir. John Reeder http://www.who.int/tdr/en
- The mycetoma working group by the International Society of Human and Animal mycoses – contact, Dr. W. van de Sande, w.vandesande@erasmusmc.nl
- Eisai - Dr. Frederick P. Duncanson, Infectious Diseases, Eisai. Frederick_duncanson@eisai.com. Telephone: (201) 949-4653.
- Pfizer - Christopher Gray, Global Institutions - Chris.Gray@pfizer.com

What does WHO require to be in the Neglected Tropical Disease (NTD) list? How does mycetoma fit? http://www.who.int/neglected_diseases/diseases/en/index.html

A proxy for poverty and disadvantage ✓ NTDs have an enormous impact on individuals, families and communities in developing countries in terms of disease burden, quality of life, loss of productivity and the aggravation of poverty as well as the high cost of long-term care. They constitute a serious obstacle to socioeconomic development and quality of life at all levels.

Affect populations with low visibility and little political voice ✓ This group of diseases largely affects low-income and politically marginalized people living in rural and urban areas. Such people cannot readily influence administrative and governmental decisions that affect their health, and often seem to have no constituency that speaks on their behalf. Diseases associated with rural poverty may have little impact on decision-makers in capital cities and their expanding populations.

Do not travel widely ✓ Unlike influenza, HIV/AIDS and malaria and, to a lesser extent, TB, most NTDs do not spread widely, and so present little threat to the inhabitants of high-income countries. Distribution is restricted by climate and its effect on the distribution of vectors and reservoir hosts; in most cases, there appears to be a low risk of transmission beyond the tropics.

Cause stigma and discrimination, especially of girls and women ✓ (though tends to affect boys more). Many NTDs cause disfigurement and disability, leading to stigma and social discrimination. In some cases, their impact disproportionately affects girls and women, whose marriage prospects may diminish or who may be left vulnerable to abuse and abandonment. Some NTDs contribute to adverse pregnancy outcomes.

Have an important impact on morbidity and mortality morbidity ✓ The once-widespread assumptions held by the international community that people at risk of NTDs experience relatively little morbidity, and that these diseases have low rates of mortality, have been comprehensively refuted. A large body of evidence, published in peer-reviewed medical and scientific journals, has demonstrated the nature and extent of the adverse effects of NTDs. (Lancet is now reviewing the first joint publication by these experts, though others have published)

Are relatively neglected by research ✓ Research is needed to develop new diagnostics & medicines, and to make accessible interventions to prevent, cure and manage the complications of all NTDs.

Can be controlled, prevented and possibly eliminated using effective and feasible Solutions ✓ The five strategic interventions recommended by WHO (preventive chemotherapy; intensified case management; vector control; the provision of safe water, sanitation and hygiene; and veterinary public health) make feasible control, prevention and even elimination of several NTDs. Costs are relatively low.

ENDS