Diagnostic Target Product Profile for mycetoma diagnostics

Mycetoma is a chronic granulomatous infection which causes tumorous lesions in the subcutaneous tissue. Most of the infection can be found in the feet, followed by the hand, legs and back [1, 2]. Characteristic of this disease is that the causative agent will organise itself in granules called grains which can be secreted through sinuses.

Epidemiology

Mycetoma can be caused by at least 70 different micro-organisms, either of fungal or bacterial origin [1]. Fungal mycetoma, or eumycetoma, is most often caused by the fungi *Madurella mycetomatis, Scedosporium boydii* and *Falciformispora senegalensis.* Bacterial mycetoma, or actinomycetoma, is most often caused by *Actinomadura madurae, Streptomyces somaliensis, Actinomadura pelletieri, Nocardia brasiliensis* and *Nocardia asteroides [1].* Although mycetoma is reported in 102 countries the aetiology differs per region[1, 3]. *M. mycetomatis, S. somaliensis* and *A. pelletieri* were highly prevalent in Africa and Asia but hardly found in South-America . In South-America, *N. brasiliensis* was by far the most common causative agent. However this species was very rarely encountered in the rest of the world. Only *A. madurae* was found to be prevalent on all continents [1].

Hallmark of mycetoma is that the causative agent organises itselve in granules called grains. The colour of the grain is dependent on the causative agent. Eumycetoma causative agents form in general black (*M. mycetomatis, F. senegalensis*) or white (*S. boydii*) grains [4], while actinomycetoma causative agents can cause white (*Nocardia* spp, Actinomadura madurae), yellow (*Streptomyces* spp) or red (Actinomadura pelletieri) grains [4].

Clinical Course and Treatment

Although mycetoma is divided in actinomycetoma and eumycetoma based on the causative agent, the clinical presentation is virtually identical with only minor differences. In both cases the infection starts with a small nodule. This is usually the site where the micro-organism was is introduced into the subcutaneous tissue via a minor trauma such as a thorn prick. With time, this painless nodule will grow into a larger subcutaneous mass. Sinuses will occur which discharge grains, purulent or seropurulent material [2]. In advanced lesions, the bone will also be invaded by the micro-organism [2]. In general actinomycetoma can be more aggressive and destructive and invades the bone earlier than eumycetoma.

Treatment of mycetoma is dependent on the causative agent. Actinomycetoma is usually treated with a combination of antibiotics. Most often trimethoprim/sulfamethoxazole (TMP/SMX) plus amikacin is used, however other drug combinations are also in use [5]. In general actinomycetoma caused by *Nocardia brasiliensis* seems to respond better to these drugs than actinomycetoma caused by *Actinomadura madurae.* Eumycetoma is treated with a combination of antifungal therapy and surgery. Itraconazole is used most often, followed by terbinafin [5].

Available Diagnostic Tools

At the moment, the diagnosis mycetoma is often made clinically. The identification of the causative agent is most often done by a combination of histology and culturing [6]. For this a deep-seated biopsy is recommended, as the grains secreted from open sinuses are often non-viable [4]. With histology, the grain can be easily seen inside the infected tissue and discrimination between actinomycetoma and eumycetoma can be made. However identification to the species level is not possible [4]. With culturing, the isolate can be grown and species identification can be done. However, it can take up to six weeks to have a positive culture and misidentifications have been common [7]. Molecular diagnostic tests such as PCR are commonly used in research settings but only rarely in the endemic regions [4]. Furthermore not for all causative agents species specific molecular assays are available.

WHO Neglected Tropical Diseases and the Diagnostic Technical Advisory Group

In 2016 mycetoma was added to the list of Neglected Tropical Diseases (NTD) of the World Health Organisation and as such the disease has been added in the 2021-2030 road map for neglected tropical diseases [8]. For mycetoma the core strategic intervention planned in the 2021-2030 is case managment by developing differential rapid diagnostic tests and effective treatment, establishing surveillance for case detection and reporting, developing a standardized field manual for diagnosis and treatment, ensuring proper training of health care workers and providing access to affordable diagnosis and treatment [8].

Since the case management is heavenly dependent on proper diagnosis, the Diagnostic Technical Advisory Group (DTAG), an advisory group from the Department of Control of Neglected Tropical Diseases, included mycetoma in its portfolio. To ensure that diagnostic assays will be made which are needed by the clinical staff in the endemic regions, DTAG recommended the development of Target Product Profiles (TPP) for mycetoma.

Purpose of the TPP

As indicated in the 2021-2030 and by experts in the field, the mycetoma field urgently needs point-of-care diagnostic tests to improve early detection at primary health care level. This assay should not only detect mycetoma but also differentiates between actinomycetoma and eumycetoma to allow the initiation of the appropriate therapy. Furthermore since currently it is not apparant when treatment can be stopped a point of care test of cure is also needed.

Literature

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