Microbiology and resistance in urogenital tuberculosis

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Abstract

Mycobacteria are less common than other infections but still represent a significant threat to patients. Their slow growing nature and the late appearance of symptoms of urogenital mycobacterial infections often result in a delayed diagnostic and more severe consequences. UGTB is mostly linked to an active or inactive lung tuberculosis, as a consequence a similar immune response is expected. Unfortunately, compared to TB, very little is known on specific response to urinary tract infection caused by MOTT, still knowledge from BCG instillation for bladder cancer treatment suggest a similar process as well. With respect to treatment and drug resistance, considering the late onset of symptoms, the potentially large populations of mycobacteria in some lesion and their mutation rate, monotherapy should be avoided. Such monotherapy would mostly lead to the emergence of resistant subpopulations. In addition, some studies focusing on persisters emphasize that at least PZA and RIF should be included in the treatment regimen as those drugs have shown some activity on persisters.

Summary of recommendations

Although very little data exist with respect to the diagnostic and treatment of *M. tuberculosis* and other mycobacterial urogenital infections a few recommendations can be considered useful:

- Because of the late appearance of some symptoms, patient showing repeated sterile pyuria or other symptoms (if any) should be screened for slow growing mycobacteria often missed in regular urine culture. Upon positive mycobacterial culture DST should be performed.
- Considering the potentially high population in some lesion and the mutation rate for drug resistance, monotherapy should be avoided for *M. tuberculosis* and other mycobacterial urogenital infections.
- As persisters are of major concern during the usually long treatment course of TB and MOTT infections, PZA and RIF should be included (if possible) in the regimen as those 2 drugs have shown some efficacy against such persisters.

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1 A brief introduction to mycobacteria

Mycobacteria are slow growing microorganisms with generation time of a few hours to a few days on appropriate microbiological medium [1], [2]. They are conventionally divided in tuberculous mycobacteria and mycobacteria other than tuberculosis (MOTT). The first ones are mycobacteria able to cause tuberculosis (or leprosy) as the latter are mycobacteria unable to cause tuberculosis (even if they can cause other related lung disease). The diagnosis of mycobacteria is difficult because of their slow growing nature. Indeed mycobacteria are also divided based on their growth rate. The slow growing mycobacteria are expected to form a colony on Lowenstein-Jensen medium in more than 7 days (typically 10–28 [1]) as fast growing mycobacteria are expected to produce a colony in less than 7 days. Still a culture for diagnosis might take up to 61 days to become positive (positive MGIT sample, or colony appearing on Lowenstein Jensen medium) [3], [4], [5], [6]. Most mycobacteria except for those appearing to be obligate pathogens (*M. tuberculosis*, *M. leprae*) are commonly found in soils, dust and water bodies. In addition some MOTT such as *M. smegmatis* are common inhabitants of the genitourinary tract [1], [7], [8], [9]. Mycobacteria are responsible for a significant number of urinary tract and urogenital infections. Among mycobacterial infection, *M. tuberculosis* is the main pathogen encountered. However, other species of mycobacteria can represent up to 35% of isolates (Table 1). These mycobacteria are often not linked to an active or inactive lung TB.

Table 1: Mycobacteria other than tuberculosis isolates from genitourinary infections or urine samples (non exhaustive list) (Table based on references [4], [5], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21]).

M. abscessus	*M. avium intracellulare*
M. gordonae	*M. bovis*
M. fortuitum	*M. smegmatis**
M. kansasii	*M. phlei*†
M. marinum	*M. scrofulaceum*
M. xenopi	*M. terrae*
M. chelonae	*M. simiae*
M. celatum	*M. haemophilum*
M. gastrii	*M. xenopi*
*Considered not pathogenic †Rarely causes diseases	

Urinary and urogenital mycobacterial infections are often diagnosed quite late as symptoms are usually not specific (see following sections/chapters) [22], [23]. Especially in urinary tuberculosis white blood cell count in urine is quite low compared to infection by MOTT [14]. This is also consistent with the physiology of mycobacteria in urine. Indeed mycobacteria have been shown to survive in human urine [19]. But, urine is a potent growth media for many microbes and mycobacteria can proliferate and thrive in it. Indeed mycobacteria have been shown to be able to growth in urine or in urine added with serum (growth conditions that mycobacteria could easily encounter in urinary tract, with or without lesions).

Such growth took place at a slow rate [24] with doubling time as long as 99 hours. Indeed, a slow growth is consistent with the late appearance of symptoms as well. If several studies have focused on urinary tuberculosis, UTI caused by other mycobacteria have been much neglected in the last years, therefore very few data are available.

2 The case of urogenital tuberculosis (UGTB)

In terms of number, 10.4 million new cases of tuberculosis and 1.4 million fatalities were attributed to tuberculosis in 2015 [25]. In addition to the 1.4 million people killed by tuberculosis, 400,000 died due to co-infection with HIV [25], [26]. Data for Germany suggest that extrapulmonary tuberculosis (EPTB) represent ca 20.7% of cases of tuberculosis and among those cases 12% are UGTB (i.e., 2.5% of the total cases of TB). However, urinary tuberculosis is often linked to an active or inactive lung tuberculosis [14], [27] thus emphasizing that the primary entry route of infection are the lungs. On the contrary, but not surprisingly, urinary tract infections caused by other mycobacteria is not linked to active or inactive TB (diagnosed by chest X-ray [14]).

3 Immune response to urogenital tuberculosis (UGTB)

As UGTB is mostly linked to an active or inactive lung tuberculosis, one can expect that immune response is mostly similar. In tuberculosis immune response acts as follows: Following interaction between the pattern recognition receptors (PRRs) and *M. tuberculosis* ligands, the microorganisms are phagocytized by antigen presenting cells (APCs). Upon phagocytosis, APCs migrate to the draining lymph nodes, initiating T-cell mediated immunity by priming naïve T lymphocytes. T-cell mediated immunity develops after two to three weeks of infection [28], [29], [30]. The phagosome inside the cells interacts with secreted proteins and developed to an endosome. The endosome processes the mycobacteria and presents fragments to the major histocompatibility complex (MHC) class II, which in turn will present the peptides on the APC surface to the T cell receptor (TCR) of $CD4^+$ T helper 1 cells. *M. tuberculosis* may also be killed by $CD8^+$ T cells, whereby mycobacteria in the phagosome are processed by protease enzyme and transported to the endoplasmic reticulum (ER) by transporter associated with antigen processing (TAP). The peptide is thereafter loaded and transported to the Golgi apparatus, whereby it is presented by the MHC I to the TRC on the $CD8^+$ T cells, which may exhibit cytotoxic effect against *M. tuberculosis*-infected cells [31], [32]. The $CD8^+$ T lymphocyte cells can directly kill *M. tuberculosis* using granulysin [33], [34]. During APC- and T-cell interaction, various pro-inflammatory cytokines such as IL-6, IL-12, TNF and interferon-gamma (IFN-γ) are produced. These cytokines play a central role by inducing macrophage activation and inducible isoform of nitric oxide synthetase (iNOS) expression [35]. Also, they enhance surface expression of MHC class II molecules and increase secretion of inflammatory mediators. Besides APCs, $CD4^+$ Th1 cells and $CD8^+$ T cells, other immune cells such as B cells, NK cells, neutrophils and regulatory T cells accumulate at the infectious focus [33], [36], [37], [38]. Due to a high production of IL-12 by APC, the immune response is largely polarized towards a Th1 type. At the infection side, the effector Th1 cells undergo functional maturation [39] and increase their production of effector cytokines and chemokines. These two markers attract new immune cells, amplifying local inflammatory and promote the formation of granuloma. It is presumed that the formation of granuloma represents a host strategy to contain the *M. tuberculosis* infection and limit dissemination of pathogen. However, individuals with latent TB infection and active TB patients both develop granulomatous response.

Although a lot is known on the immune response to lung TB, very little (not to say anything) is known on specific response to urinary tract infection caused by *M. tuberculosis* or MOTT. Studies on the use of BCG instillation for bladder cancer suggest a similar process [40], [41]. Still some variations have been noted in the proinflammatory cytokine profile in active kidney tuberculosis patients [42].

4 The problem of antimycobacterial resistance

Due to their extremely thick and multi-layered hydrophobic cell wall, mycobacteria have an intrinsic resistance to some antibiotics that cannot penetrate such permeation barrier. In addition mycobacteria [43], [44] and in particular *M. tuberculosis* developed many ways to counteract the effect of drugs including efflux pumps, modified targets, as well as overexpression of the drug target. Also mycobacteria produce efficient beta lactamases and other drug inactivating enzymes [43], [44]. Moreover, rate of emergence of resistance to antimycobacterial can be quite high. For *M. tuberculosis*, mutation rate leading to resistance against rifampin, isoniazid, streptomycin and ethambutol are $3.32x10^{-9}$, $2.56x10^{-8}$, $2.29x10^{-8}$, and $1.0x10^{-7}$ (expressed in mutation/bacterium/cell division), respectively. With an approximate number of 10^8 mycobacteria per lesion, it appears that monotherapy will surely result in the appearance of resistance [44], [45], [46]. This situation can be observed in lung cavities but also in kidney cavities thus advocating for multiple drug therapy. Also less data are available, similar finding were made with MOTT with mutation rate ranging from 10^{-5} to 10^{-9}. Among urinary tract pathogens *M. fortuitum* and *M. avium* were show to have the highest mutation rates for isoniazid and streptomycin, with 10^{-6} and 10^{-5} respectively [45]. Thus showing that such pathogens should also be considered carefully when initiating a treatment. This also emphasize that monotherapy should be avoided with MOTT as well in the context of urogenital infections with cavities containing large populations of mycobacteria.

From a more clinical point of view, delayed drug susceptibility results, inappropriate use of antimycobacterial compounds, interrupted treatment (due to drug shortage a state level, non compliance, or poor access from patient to drug caused by poverty), and presence of counterfeit drug lead to the appearance of these acquired resistance [44]. Further spread of the resistant strains combined with those bad practices lead to the appearance multiresistant TB strains. In 2015 MDR strains accounted for 4.6% of total TB cases (i.e., 480,000 case of MDR TB). Of these, 480,000 were primary infection/transmission of people having no previous TB history (i.e., likely transmission of an MDR strain). Only 21% (roughly 100,000) of these cases were found in individuals who received a successful TB treatments (i.e., likely acquired resistance link to previous drug treatment) [25], [47]. Finally it must be noted that within different countries the proportion of XDR TB within the MDR TB ranges from <1 to 11% (laboratory confirmed cases) and poses a major threat, especially considering that laboratory confirmed cases are probably highly underestimated [25]. As a result WHO considers that early initiation of appropriate drug treatment as well as avoiding transmission or acquisition of drug resistance is of critical importance [48].

5 Persistence in mycobacteria

Persisters are usually defined as a genetically identical subpopulation that is non-replicating or slow-growing and can survive bactericidal antibotics. They have a uninheritable phenotypic resistance (or tolerance) to antibiotics, but they daughter cells remains fully susceptible [49]. Persistence in *M. tuberculosis* and other mycobacteria, seems can be induced by many different factors such as pH, oxygen concentration, starvation for example. Indeed, in the urinary tract the nutrient, pH and oxygen concentrations are factors which can vary a lot and that could induce persistence. Still recent research show that the traditional view of persisters being non-replicating or slow growing might be wrong. Furthermore, persistence when mycobacteria are exposed to INH might be driven by pulsing KatG expression that activates INH (that is a prodrug) in still dividing microorganisms (in this study *M. smegmatis*). Therefore low-frequency pulsing of KatG might be beneficial and promote persistent lineages of mycobacteria [50]. Still mechanisms for other drug might be very different [51] [52]. Overall this emphasize that persisters should be considered a threat and must be taken into account when choosing a drug regimen. Indeed, this suggest again that monotherapy should be avoided and that regimen should include at least PZA and RIF that are the two drugs which have shown some efficacy against persisters. To our knowledge no studies have been conducted to evaluated the role of persisters in urogenital infection by *M. tuberculosis* or other mycobacteria.

6 Conclusions

Many aspects of the biology and pathology of mycobacteria (tuberculosis but also MOTT) and their role in UGTB have not been studied in detail yet. As such gap in knowledge impairs optimal treatment and patient management further study in the field of UGTB is indispensable. Also considering their rising importance MOTT should also be better studied. Finally, mechanisms of persistence are also crucial and need to be understood as well.

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