QUESTION 6: Does *Mycobacterium tuberculosis* form a biofilm on implants?

**Authors:** Parham Sendi, Giorgio Burastero, Georgios Komnos

**Response/Recommendation:**

Few data from experimental *in vitro* and *in vivo* studies and a limited number of case reports indicate that *M. tuberculosis* has a slow, albeit significant, ability to form biofilm on metal surfaces. The group suggests that management of *M. tuberculosis* implant-related infections should be treated using the same principles as that of other implant-related infections.

**Level of Evidence:** Strong

**Delegate Vote:** Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

**Post Meeting Rationale:**

A search of the English language literature on the question published during the period 1966–May 20, 2018 was conducted. The search strategy in PubMed used the terms *Mycobacterium tuberculosis* AND biofilm, and identified 177 articles. All articles were reviewed for the response to the question. The vast majority of articles were categorized as basic sciences articles focusing on the components for tubercular biofilm formation in vitro. There were no controlled clinical studies. A systematic review to answer the provided question is not meaningful. Hence, the response of the question is answered as a summary of a narrative review.

In the laboratory, *M. tuberculosis* (MTB) shows peculiar aggregated growth, or in other words, can form organized pellicle-like structures. The hallmark of biofilms is the self-production of the extracellular polymeric substance that holds the mycobacterial community together and confers phenotypic heterogeneity to the genotypically identical cells. Several studies have highlighted extracellular components within MTB aggregation, including mycolic acids, complex sugars, cellulose, proteins, lipids and DNA. In addition, MTB residing within organized pellicle-like structures exhibits drug tolerance to antitubercular agents. Thus, criteria used to define the structure of biofilms are present for TB aggregated growth. The vast majority of studies investigating MTB biofilms uses polystyrene plates. Ha et al. compared the adherence and the biofilm formation of *Staphylococcus epidermidis* with those of MTB on four types of metal segments. In contrast to *S. epidermidis*, MTB rarely adhered to metal surfaces and showed discrete biofilm formation. Similar results were reported by Chen et al. who compared *S. aureus* and MTB *in vitro* and *in vivo*. Adetunji V et al. analyzed MTB biofilm formations on cement, ceramic, or stainless steel coupons. The experimental settings in this study are difficult to transfer in an *in vivo* implant model (e.g., more biofilms were formed when media containing 5% liver extract was used). However, more biofilms were formed on cement than on ceramic and stainless steel coupons. Taken together, the few available data from *in vitro* and *in vivo* studies indicate that biofilm formation of MTB on metal segments is poor in comparison to *Staphylococcus* spp.

The clinical role of MTB biofilms in humans is not fully understood. Basaraba and Ojha provide convincing arguments that extracellular MTB likely grow as biofilms and may participate in the process of caseous necrosis and cavitation formation in lung tissue.
The majority of MTB periprosthetic infection cases reported in the literature describe patients with (delay) or late presentation with malfunctioning prostheses and hence prosthesis removal was performed with resultant cure. Based on this data the biofilm workgroup agreed that, MTB implant-related infections should be treated using the same principles as that of other implant-related infections. However, one of the original authors of this rationale (not present at the in person meeting) points out that, 13 of 66 (19.6%) cases reported by Veloci et al. were treated with antitubercular agents only. Hence, in these cases no surgical intervention was performed to reduce the mycobacterial load or to remove mechanically the biofilm adhering to the implant. One patient died because of far-advanced tuberculous meningitis, miliary tuberculosis of the lungs, femoral osteomyelitis and extended cold abscesses along the femoral shaft. In the other cases, no failure was reported. Though, only in 6 (50%) of 12 cases, a follow-up results of ≥18 months after the end of therapy was available. Treatment duration ranged from 6 to 18 months. These data indicate that tubercular biofilm eradication is possible using chemotherapy only and therefore there may be a place for a trial of medical therapy by clinicians with in experience managing musculoskeletal MTB prior to surgical intervention (if functionally necessary), particularly for susceptible isolates.
References: