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B6: Does *Mycobacterium tuberculosis* (*M. tuberculosis*) form a biofilm on implants?

Response and 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)

Premeeting rationale

Methods

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 *M. 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. 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.

Narrative Literature Review and Discussion

It is important to differentiate between *M. tuberculosis* and non-*M. tuberculosis* mycobacterium. This review focusses only *M. tuberculosis*.

M. Tuberculosis Forms Biofilms

In the laboratory, *M. tuberculosis* shows peculiar aggregated growth, or in other words, can form organized pellicle-like structures [1]. 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 [2]. Several studies have highlighted extracellular components within *M. tuberculosis* aggregation, including mycolic acids [3], complex sugars [4], cellulose, proteins, lipids and DNA [5,6]. In addition, *M. tuberculosis* residing within organized pellicle-like structures exhibits drug tolerance to antitubercular agents [3]. Thus, criteria of a structure to what is interpreted as biofilms are given.

TABLE 1. Clinical data —PJI due to *Mycobacterium tuberculosis* is treated a mitubercular agents without surgery

Author/Year	Joint	Age/ Gender	Reported Risk Factors or Previous Clinical Hx	Preoperative Dx	Time Elapsed from Arthroplasty to Joint Infection	Time Elapsed from Joint Infection to Dx or Medical Therapy	Concomi- tant Infe- ctions	Instrumental Examina- tions	Histological Examinations	Micro-biological Dx	Other Sites	Medical Therapy (Duration in Months)	Surgery	Time Eliged from Start of Medical Therapy to Surgery	Follow-up from end of Therapy
Wray1987	Knee	61/M	None	Osteoarthritis	Postoperatively	NR	Rx	Chronic granulomatous inflammation	NR	NR	Lung	INH, RIF (12)	None	NR	18 months
Present work, case 2	Knee	61/M	None	Osteoarthritis	Postoperatively	3 years	Rx, Scint	Chronic granulomatous inflammation	Arthrocentesis cultures	None	None	INH, RIF (18), PZA (2)	None	NR	1 month
Tekin Koruk2013	Knee	55/M	None	Osteoarthritis	15 days	1 month	Rx	Chronic granulomatous inflammation	Arthrocentesis microscopy and cultures	None	None	INH, RIF (12), PZA, EMB(2)	None	NR	NR
Kadakkai; 2007	Knee	84/F	None	Traumatic fracture	1 month	3 months	Rx	NR	Arthrocentesis cultures	Lung	INH, RIF, PZA, EMB (6)	None	NR	NR	NR
Cansu2011	Hip	46/F	None	Dislocation	4 months	NR	Rx, CT	NR	Arthrocentesis cultures	None	None	INH, RIF, EMB(16), PZA(3)	None	NR	72 months
Marshall; 2007	Knee	46/M	AIDS	Osteoarthritis	6 months	3 months	Rx, MRI	NR	Arthrocentesis microscopy, PCR and cultures	Lung, CNS	INH, PZA, EMB(1), MOX(1/2), RIF(1/2)	None	NR	NR	Died during therapy
Present work, case 1	Knee	34/F	None	Rheumatoid arthritis	8 months	4 years	Rx, MRI, ILS, PET	Chronic inflammation	Arthrocentesis cultures	None	None	INH, RIF (18), PZA, EMB(2)	None	NR	24 months
Jhoson2019	Hip	51/F	Hip TB 41 yrs ago	Osteoarthritis consequent TB	13 months	NR	Rx	NR	Arthrocentesis cultures	None	None	INH, RIF, EMB(on therapy)	None	NR	On therapy when published
Shanbhag 2007	Hip	59/F	None	Osteoarthritis	14 months	2 months	Rx, MRI	Chronic granulomatous inflammation	Arthrocentesis cultures	None	None	RIF, PZA, EMB(12)	None	NR	18 months
De Nardo2012	Hip	61/F	None	NR	16 months	3 months	CT, LLC	Chronic active inflammation	Arthrocentesis PCR	Proas muscle, adrenals	INH, RIF (on therapy), PZA, EMB (3)	None	NR	NR	On therapy when published
Lee2012	Hip	61/M	None	Fracture	8 years	NR	Rx, US, CT	Chronic active inflammation	Intraoperative microscopy and cultures	None	None	INH, RIF, PZA, EMB (6)	None	NR	24 months
Neogi2009	Knee	73/F	None	Osteoarthritis	14 years	2 months	Rx	Chronic granulomatous inflammation	Arthrocentesis PCR	None	None	INH, RIF (18), PZA (7), EMB (4)	None	NR	36 months
Egues Dubuc2014	Knee	77/F	Anti-TNF therapy	Rheumatoid arthritis	NR	1 year	US, Scint	NR	Arthrocentesis PCR	Lung, small intestine	INH, RIF, PZA(on therapy)	None	NR	NR	On therapy when published

M. Tuberculosis Biofilms in Humans

The clinical role of *M. tuberculosis* biofilms in humans is not fully understood. Basaraba and Ojha [7] provide convincing arguments that extracellular *M. tuberculosis* in necrotizing lesions likely grows as biofilms. Hence, mycobacterial biofilms may participate in the process of caseous necrosis and cavitation formation in lung tissue [5–7].

M. Tuberculosis Biofilms on Metal Surface

The vast majority of studies investigating *M. tuberculosis* biofilms uses polystyrene plates [8]. Ha et al. [9] compared the adherence and the biofilm formation of *Staphylococcus epidermidis* (*S. epidermidis*) with those of *M. tuberculosis* on four types of metal segments. In contrast to *S. epidermidis*, *M. tuberculosis* rarely adhered to metal surfaces and showed discrete biofilm formation. Similar results were reported by Chen et al. [10] who compared *S. aureus* and *M. tuberculosis* in vitro and in vivo. Adetunji et al. [11] analyzed *M. tuberculosis* 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 [11]. Taken together, the few available data from in-vitro and in-vivo studies indicate that biofilm formation of *M. tuberculosis* on metal segments is poor in comparison to *Staphylococcus* spp.

Among the 66 cases reported by Veloci et al. [12], 13 (19.6%) 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 [13]. In the other cases, no failure was reported. Though only in 6 (50%) of 12 cases, 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 with chemotherapy only. Whether this is due to poor biofilm formation on metal implants or due to effective anti-biofilm activity of antitubercular agents cannot be assessed.

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