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Treating periprosthetic joint infections as biofilms: key diagnosis and management strategies

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ABSTRACT

Considerable evidence suggests that microbial biofilms play an important role in periprosthetic joint infection (PJI) pathogenesis. Compared to free-floating planktonic bacteria, biofilm bacteria are more difficult to culture and possess additional immune-evasive and antibiotic resistance mechanisms, making infections harder to detect and eradicate. This article reviews cutting-edge advances in biofilm-associated infection diagnosis and treatment in the context of current PJI guidelines and highlights emerging technologies that may improve the efficacy and reduce costs associated with PJI. Promising PJI diagnostic tools include culture-independent methods based on sequence comparisons of the bacterial 16S ribosomal RNA gene, which offer higher throughput and greater sensitivity than culture-based methods. For therapy, novel methods based on disrupting biofilm-specific properties include quorum quenchers, bacteriophages, and ultrasound/electrotherapy. Since biofilm infections are not easily detected or treated by conventional approaches, molecular diagnostic techniques and next-generation antibiofilm treatments should be integrated into PJI clinical practice guidelines in the near future.

1. Introduction

Although infection following primary total joint arthroplasty remains relatively rare, occurring in ~1% of patients (Kurtz et al., 2008), postoperative periprosthetic joint infections (PJIs) nonetheless represent a serious concern for clinicians. These infections may place patients at greater risk for complications and often require costly treatments (Bozic and Ries, 2005). Further highlighting PJI's growing significance, the American Association of Orthopaedic Surgeons (AAOS) and the Infectious Diseases Society of America (IDSA) have released independent sets of PJI clinical practice guidelines within the past few years (Della Valle et al., 2010; Osmon et al., 2013). Of high priority for the next iteration of PJI guidelines is consideration of the role of microbial biofilms in PJI pathogenesis and treatment, which has been supported by increasing evidence in recent years. In this review, we evaluate cutting-edge advances in biofilm-associated infection diagnosis and treatment in the context of the current periprosthetic infection guidelines and highlight emerging technologies that may improve the efficacy and reduce the costs of identifying and managing PJI.

1.1. The biofilm paradigm

In most environments, including the human body, microbes preferentially exist as layers of aggregated sessile cells surrounded by extracellular biopolymer matrices, i.e., biofilms, rather than in free-floating planktonic form (Bjarnsholt et al., 2013). Biofilm formation occurs in several stages as motile cells gradually accrue on inorganic or organic surfaces. Importantly, cells within a biofilm become phenotypically different from their planktonic analogs (Fig. 1). In addition to reduced motility, bacteria in biofilms possess distinct gene transcription patterns and exhibit a spectrum of metabolic activity, with cells at the biofilm periphery growing more rapidly than the nutrient-deprived cells in the biofilm's inner layers (Bjarnsholt et al., 2013; Stoodley et al., 2011).

An estimated 80% of human infections can be attributed to biofilms, and nearly 3 decades ago, Gristina and Costerton (1984) promulgated the idea that many PJIs involve microbial biofilms, which has since been supported by direct and indirect observations. PJI often demonstrates key characteristics of biofilm-associated infections (Table 1). Moreover, the most common microbial causative agents of PJI, staphylococci, streptococci, and enterococci (Pandey et al., 2000), form biofilms in other types of infection, including jaw osteonecrosis and ureteric stent infections (Keane et al., 1994; Sedghizadeh et al., 2008). Additionally, a handful of studies have provided direct clinical evidence of biofilm formation on implants through electron or confocal laser scanning microscopy analysis of surgically removed infected prosthesis

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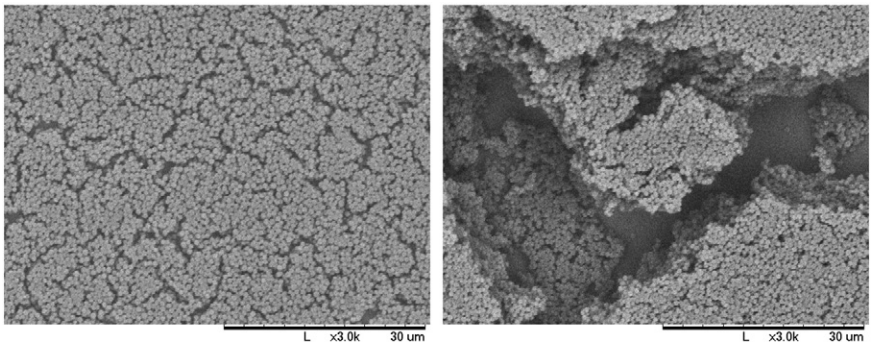

Fig. 1. Scanning electron micrograph of *S. aureus* (ATCC25923) biofilm growth on a Nunc coverslip in trypticase soy broth after 18 hours at 37 °C.

components (Neut et al., 2003; Stoodley et al., 2008; Tunney et al., 1998). Whether these studies represent outliers or the norm in PJI cases remains to be seen, but the collective evidence to date suggests that biofilms occur in at least a subset of PJI cases. Given that biofilm-forming microbes evade most conventional bacterial diagnosis and treatment strategies, it is surprising that biofilms do not factor more into the AAOS and IDSA guidelines for PJI.

2. Biofilm-associated PJI diagnosis

For initial assessment of patients with symptoms of possible PJI, such as wound drainage over the prosthesis and/or local and systemic inflammatory signs (Osmon et al., 2013), both AAOS and IDSA strongly suggest erythrocyte sedimentation rate (ESR) measurement and C-reactive protein (CRP) testing (Fig. 2). If abnormal ESR or CRP is detected, then arthrocentesis is highly recommended, with the aspirated fluid sent for white blood cell count and differential as well as aerobic and anaerobic microbiologic culture to determine treatment options (Della Valle et al., 2010; Osmon et al., 2013). Although these criteria may readily identify patients with early postoperative PJI (occurring within a few months), patients with late chronic PJI (occurring several months to years) may be difficult to distinguish from those with aseptic implant loosening, since both conditions may present simply as loose prosthesis accompanied by pain (Osmon et al., 2013).

Both the timing and the lack of systemic inflammation in chronic PJI may, in fact, indicate biofilm-associated infection (Table 1). Furthermore, given that most biofilm species escape detection by conventional culture-based methods, a large proportion of culture-negative infections may be misdiagnosed as aseptic loosening (Achermann et al., 2010; Tunney et al., 1998) and fail to receive appropriate treatment. Further complicating the issue is that many patients have previously received antibiotic therapy, which may eliminate the planktonic bacteria that is more easily detected by traditional approaches (Achermann et al., 2010; Peel et al., 2013). Hence, there is an urgent need for alternative, culture-independent methods of PJI detection.

Of great relevance are strategies based on molecular diagnostic methods. In addition to offering the ability to reveal dormant or metabolically inactive organisms, molecular detection methods can be completed in much less time than culture-based methods (hours versus days) (Cazanave et al., 2013; Costerton et al., 2011; Krimmer et al., 1999). These methods have great potential as PJI diagnostic tools (Table 2), especially in conjunction with improved culture methods such as implant sonication, which yield more sensitive culture results than tissue biopsy or synovial fluid sampling, prolonged culture incubation for up to 14 days to allow anaerobic microbial growth, and multisample collection from the infection site (Larsen et al., 2012; Trampuz et al., 2007).

2.1. Polymerase chain reaction (PCR)

PCR has routine clinical applications in genetic testing and in the detection of infectious agents including human immunodeficiency virus and *Mycobacterium tuberculosis* (Hamady and Knight, 2009; Moure et al., 2011). In PCR, target gene sequences undergo successive cycles of enzymatic amplification by DNA polymerase, as specified by a known pair of primers complementary to the sequence of interest. The 16S ribosomal RNA (rRNA) gene is the most common amplification target, as the gene comprises both highly conserved and hypervariable regions: the conserved regions serve as binding sites for universal bacteria primers, while the hypervariable regions can be probed by specific primers to identify bacterial taxa. Several studies have demonstrated that PCR of prosthesis sonicate fluid is at least as sensitive and specific as sonicate fluid culture (Cazanave et al., 2013; Gomez et al., 2012; Grif et al., 2012; Lévy and Fenollar, 2012; Rampini et al., 2011; Xu et al., 2012) and may have a higher PJI detection rate than culture for patients recently treated with antibiotics (Cazanave et al., 2013; Gomez et al., 2012; Grif

Table 1
Biofilm-like characteristics of chronic PJI.

Common characteristic of chronic PJI	Paradigmatic biofilm explanation	References
Infection local to device rather than systemic	Biofilm stationary on prosthesis surface	(Khoury et al., 1992; Stoodley et al., 2011)
Infection resolves after device removal	Biofilm removed along with prosthesis (substrate to which it is adhered)	(Osmon et al., 2013; Stoodley et al., 2011)
Infection occurs months to years postoperatively	Biofilm formed in a multistage process over time	(Khoury et al., 1992; Osmon et al., 2013)
Minimal inflammatory symptoms present	Biofilm evades host immunity, resulting in dampened inflammation	(Jensen et al., 1990; Khoury et al., 1992; Osmon et al., 2013)
Culture-negative infection indicated	Biofilm species not readily dislodged for sampling do not grow under laboratory conditions	(Berbari et al., 2007; Hall-Stoodley et al., 2012; Trampuz et al., 2007)
Infection resists antibiotic therapy	Biofilm highly antibiotic resistant through multiple mechanisms	(Bjarnsholt et al., 2013; Molina-Manso et al., 2013; Nishimura et al., 2006)