Current Reviews in Musculoskeletal Medicine (2018) 11:409–419
https://doi.org/10.1007/s12178-018-9503-2

PROSTHETIC JOINT INFECTION (S NODZO AND N FRISCH, SECTION EDITORS)

Low-Virulence Organisms and Periprosthetic Joint Infection—Biofilm Considerations of These Organisms

K. Keely Boyle[1] · Stuart Wood[2] · T. David Tarity[3]

Published online: 30 June 2018

Abstract

Purpose of Review The purpose of this manuscript is to provide a critical review of peer-reviewed literature over the last 5 years related to low virulent organisms associated with periprosthetic joint infection (PJI). We evaluated the most common organisms, the diagnostic challenges, and the novel tools available in the perioperative workup of PJI as well as the current understanding of how biofilm potentiates the indolent clinical presentation and explore a possible shift in the surgical management of these patients.

Recent Findings Biofilm actively prevents macrophage phagocytosis by suppressing proinflammatory activity through the recruitment of myeloid-derived suppressor cells. Given the appropriate host and organism conditions, increased utilization of one-stage exchange arthroplasty in the surgical treatment of these low virulent infections may be on the rise.

Summary Biomarkers and molecular techniques offer encouraging results to diagnose low virulent organisms and future research focused on the disruption of biofilm may ultimately give rise to improved treatment strategies.

Keywords Periprosthetic infection · Low-virulent organisms · Biofilm

Introduction

Infection after total joint arthroplasty (TJA) is a devastating and unfortunate complication that brings significant challenges to the patient, treating surgeon, and healthcare system. Periprosthetic joint infection (PJI) is associated with technically difficult revision procedures, extensive therapeutic treatments including long-term antibiotics, often unpredictable or poor patient outcomes and substantial economic burden. A multidisciplinary team approach is required for optimizing the success of these complex treatment regimens for PJI as well as minimizing patient morbidity. PJI is the most common reason for total knee arthroplasty (TKA) revisions and is a major reason for total hip, total shoulder, total elbow, and total ankle arthroplasty revisions [1, 2••, 3–5, 6•]. In 2010, the estimated annual incidence was over one million TJAs performed in the USA with a cost of $18.75 billion [7]. Our aging population desires to remain physically active and improve their quality of life, ensuring that there will be an exponential increase in the numbers of total joint arthroplasty in the USA. The demand for total hip and total knee arthroplasties is projected to increase by 174 and 673% respectively by the year 2030, with an estimated 572,000 total hip arthroplasties (THA) and 3.48 million TKAs being performed annually by 2030 [8]. The growth rates of upper extremity arthroplasty procedures have been reported to be between 7 and 13% annually, with total shoulder arthroplasty rates projected to increase by more than 150% by the year 2020 [9]. With these projections, there is growing concern for an exponential increase in the number of PJI cases with significant fiscal implications to the patient, hospital, and healthcare system.

The rates of PJI after primary TJA have been reported between 1.55 and 2.5%, with hospital costs previously estimated at $566 million annually [10–13]. The cost of treating a case of PJI in the hip and knee is on average 2.8–4.8 times higher than a primary TJA, with a projected rise in annual costs to $1.6 billion by 2020 [11, 14]. The cost disparity noted

This article is part of the Topical Collection on *Prosthetic Joint Infection*

✉ K. Keely Boyle
kkboyle@buffalo.edu

[1] Department of Orthopaedics, Erie County Medical Center, State University of New York at Buffalo, 462 Grider, Street, Buffalo, NY 14215, USA

[2] Infectious Disease Clinic Keesler Medical Center, 301 Fisher Street, Keesler AFB, MS 39564, USA

[3] Orthopedic Surgery Clinic Keesler Medical Center, 301 Fisher Street, Keesler AFB, MS 39564, USA

between primary arthroplasty and management of PJI is largely driven by the complex algorithms associated with successful treatment of PJI including longer operative times with multiple procedures, extended lengths of stay (LOS), higher complication rates, subsequent hospitalizations with higher inpatient charges, administration of long-term antibiotics, and more outpatient visits to various providers [15]. Management of PJI employs significant morbidity on patients and may even increase the risk of mortality [16]. Various definitions of success have been proposed, but there remains no uniform definition for success or failure of treatment in the PJI literature. Success in PJI treatment is multifactorial and includes infection control, functional outcomes, patient satisfaction, cost effectiveness, and minimization of complications. There is continued debate in the orthopedic community regarding the ideal management for PJI, as failure rates, defined as reinfection by the same or different organism(s), continue to range from 0 to 24% [17, 18, 19••, 20••].

Identification of the causative organism is critical for timely, targeted, and appropriate treatment. This may be especially challenging in the case of low virulent organisms, such as *Propionibacterium acnes* (*P. acnes*), as the clinical presentations and utility of classic diagnostic tools may not be as efficacious in establishing the presence of PJI. Previously, some of these low virulent organisms were thought to be culture contaminants when isolated, largely due to their presumed indolent nature, as well as presence on normal skin flora and role in maintenance of the human microbiome. These low virulent bacteria are now recognized as true pathogens and infecting organisms of PJI. The two most common organisms isolated from intraoperative cultures from upper extremity arthroplasty procedures are *P. acnes* and coagulase-negative staphylococci (CoNS), both of which are low virulent organisms [21, 22]. For lower extremity arthroplasty procedures, the most common isolated organisms are CoNS and methicillin-susceptible *Staphylococcus aureus* [23, 24•]. Cultures fail to isolate an infecting organism in up to 50% of PJI cases [25–27, 28•]. Culture-negative patients that meet the Musculoskeletal Infection Society (MSIS) Criteria for PJI (Table 1) are difficult to treat and have been associated with 4.5 times increased risk of reinfection when compared to those patients where an organism was identified by culture [29, 30]. In a recent study, culture-negative patients who met criteria for MSIS infection underwent next-generation sequencing and an organism was identified in 81.8% of samples with the majority being low-virulent organisms [31••]. Low-virulent organisms pose a unique challenge to successful diagnosis and treatment of PJI and due to their widespread nature as causative organisms. It is important to continue to try and understand the behavior patterns, tailor management protocols, and closely observe patient outcomes.

Table 1 Musculoskeletal Infection Society (MSIS) Diagnostic Criteria: 2013–2018 [15]

Major criteria (1 required)	Minor criteria (3 of 5 required)
Sinus tract communicating with the affected joint	Elevated ESR and CRP
	Elevated synovial fluid white blood cell count
Two positive periprosthetic cultures with phenotypically identical organisms	Elevated synovial polymorphonuclear neutrophil percentage (PMN%) or ++ change on leukocyte esterase test strip
	Positive histological analysis of periprosthetic tissue
	A single positive culture

One major criterion and/or 3 of 5 minor criteria must be present for the diagnosis of PJI according to the MSIS Diagnostic Criteria

ESR, erythrocyte sedimentation rate; *CRP*, C-reactive protein

Clinical Presentation: Low-Virulent Organisms and Diagnostic Tools

There are many challenges surrounding the management of patients who present clinically with concern for PJI. Perhaps one of the most difficult aspects is promptly and accurately establishing a definitive diagnosis of PJI with identification of the causative organism(s). Low-virulence organisms, such as *P. acnes*, pose a unique challenge to successful diagnosis of PJI. The clinical presentation is often indolent without the characteristic signs of infection and can lead to delayed treatment and increased associated costs.

Inflammatory Markers and Preoperative Aspiration

Classic nonspecific inflammatory markers, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), as well as preoperative synovial fluid aspirations used in many diagnostic algorithms are often unreliable [32, 33, 34•]. Synovial fluid aspirations often produce scant amounts of fluid where cell counts may not be elevated and cultures may be negative, especially in the shoulder [35•]. Histological findings at time of surgery are often negative, especially with certain low-virulent organisms and in the setting of chronic infection [36•]. Identifying PJI in the setting of low-virulence organisms largely depends on intraoperative findings and tissue culture results [37]. Some organisms have extended culture growth times, including *P. acnes*, which can take up to 14–21 days to grow on certain media [38]. There are concerns with holding cultures for two to three times longer than standard institutional protocols, including an increased risk of contamination [38]. In some instances, cultures remain negative for a multitude of reasons, including prior antibiotic use and laboratory protocols. A major risk factor for culture-negative PJI is postoperative wound drainage and the use of

vancomycin and cephalosporins [39••]. Due to these diagnostic challenges, enhanced effort has been placed on various techniques for rapid and accurate detection of PJI and identification of an infecting organism for determination of appropriate treatment, predicting prognosis and cost containment.

Biomarkers

With this growing need for improved diagnostic methods for PJI, synovial fluid biomarkers have demonstrated potential and may be a valuable addition to the diagnostic armamentarium. Previous work has shown synovial fluid biomarkers to have a high accuracy in establishing the presence of PJI, even in the setting of patients with systemic inflammatory disease and ongoing antibiotic treatment. Many synovial fluid biomarkers have previously been assessed with a recent meta-analysis evaluating the diagnostic accuracy and highest diagnostic odds ratio of eight index tests: leukocyte count, percent polymorphonuclear leukocytes (PMN%), CRP, alpha-defensin, leukocyte esterase, IL-6, IL-8, and culture. The overall sensitivity of the eight markers was 85%, and each marker showed sensitivity greater than 80%, except culture. All markers showed a specificity of greater than 90% with alpha-defensin demonstrating the highest log diagnostic odds ratio [40••]. Alpha-defensin has also shown to respond to a wide spectrum of organisms having consistent results for all organism types, Gram type, species, or virulence of the organism [41]. The rapid and accurate diagnosis of PJI may be established with the assistance of synovial fluid biomarkers, but it is critical to promptly identify the organism and tailor treatment options.

Sonication

Sonication of components that have been explanted in the setting of PJI with culture of the sonication fluid is utilized to enhance diagnostic sensitivity [42, 43]. A clinically significant percentage of patients undergoing a presumed aseptic revision have been shown to have positive sonicate cultures, with the most common isolated organisms being CoNS and *P. acnes* [24•]. Culturing fluid from sonicated implants is an adjunctive tool when diagnosing PJI, especially when considering the presence of biofilm. Sonication has been shown to mechanically disrupt biofilm from implants, increasing the number of bacteria available for culture. Certain organisms are harbored and protected within the complex structure and matrix of biofilms, and the use of sonication can theoretically allow for identification of species otherwise not detected on standard culture. The use of sonication continues to evolve with multiple studies demonstrating varying results. A recent study showed that regular use of implant sonication culture for presumed aseptic revisions may improve the accuracy of diagnosing PJI by detecting low-virulence organisms [24•]. Whereas, another report concluded that implant sonication of fluid culture in revision shoulder arthroplasty showed no significant benefits over standard intraoperative cultures in diagnostic utility for PJI [44•].

Molecular Techniques for Diagnosing PJI

Multiplex polymerase chain reaction (PCR) has been used previously to isolate organisms to aid in the diagnosis of PJI. However, PCR raised concerns as this particular technique revealed a false-positive rate up to 88% in prior literature [45, 46]. The overall performance of PCR has been shown to be comparable to culture, although a recent study demonstrated that PCR was superior for detection of low-virulent bacteria, such as *Cutibacterium* species and CoNS, when compared to synovial fluid culture [47••]. Multiplex PCR can produce results within 5 h, whereas cultures can take several days for growth, identification, and speciation. Broad-range PCR has not proved to be advantageous over traditional culture and has limitations including the inability to detect multiple organisms at one time and lower sensitivities ranging from 67.1 to 73.3% [26, 48].

Next-generation sequencing (NGS), also known as high-throughput sequencing, is a term used to describe multiple modern techniques used for rapidly sequencing all DNA and RNA present in a sample, thus allowing for a more complete microbial profile. A recent study investigated the utility of next-generation sequencing in PJI and found that next-generation sequencing was able to identify an organism in almost 90% of patients with PJI as defined by the MSIS criteria, with a large percent classified as polymicrobial. NGS was found to be more sensitive, but less specific than culture. This study also discovered that this technology detected a potential pathogen in about 80% of culture-negative PJIs and had an 88.2% correlation with culture. When reviewing the patients who underwent aseptic revisions, next-generation sequencing found microbial DNA in 25% of cases, with the most predominant organism being *P. acnes* [31••].

Low-Virulent Organisms Associated with PJI

Though most microbes are capable of establishing PJI, in clinical practice only, a select few are frequently identified. While virulent organisms, such as *Staphylococcus aureus* and gram-negative aerobes, are frequently seen as an acute presentation of PJI often occurring in early-onset following total joint arthroplasty, low-virulent organisms such as CoNS, *P. acnes*, enterococcus, and actinomyces should be considered with indolent and delayed onset PJI. Many low-virulent organisms are gram-positive in nature and are able to form biofilm of abiotic surfaces [49, 50]. The microbiological features, many virulence factors, some biofilm properties, and commonly used antibiotics are outlined in Table 2 [33, 51, 52, 54].

Table 2 Low-virulent organism profiles

Organism	Characteristics	Virulence properties	Biofilm properties	Antibiotics commonly used*
Coagulase-negative Staphylococci [51] *S. epidermidis* *S. lugdunensis* *S. saprophyticus* *S. haemolyticus* *S. capitis* *S. caprea*	Gram-positive cocci, aerobe, or facultative anaerobe; common on normal skin flora and mucous membranes	Biofilm production, immune system avoidance, antimicrobial tolerance, adherence to host proteins or biomaterials, toxin production—injury to host cells, exoenzymes—skin and wound colonization and destruction of host tissue	PIA—polysaccharide intracellular adhesion; Aap—accumulation of biofilm cells; Bhp—accumulation; DNA—structure of biofilm/nutrient/ gene transfer; ica—locus important for biofilm creation	Beta-lactams (oxacillin), vancomycin
Propionibacterium acnes [33]	Gram-positive rod, facultative anaerobe, nonsporulating; common on normal skin flora	Biofilm production, bacterial seeding, modification and manipulation of host immune response, host tissue-degrading enzymes, cell adhesion, inflammation, cohemolytic activity—cytotoxic to macrophages, beta-hemolytic activity—lysis RBCs	Slime/capsular polysaccharide, PIA—polysaccharide intracellular adhesion; lipoglycan—adherence to skin tissue/biofilm, increased lipase activity—neutrophil lysis, ExoA, glycosyltransferases	Beta-lactams, penicillin, doxycycline, rifampin
Enterococcus [52] *E. faecalis* *E. faecium*	Gram-positive; inhabits oral cavity and gastrointestinal flora	Strong biofilm production, antibiotic multi-resistance, gelatinase, cytolysin, extracellular superoxide	Esp—enterococcal surface protein, hydrophobicity, aggregation substance, fsrB gene (locus)	Ampicillin, vancomycin, daptomycin
Actinomyces [53]	Gram-positive rod, filamentous, branching, microaerophilic or facultative anaerobe, nonsporulating	Capable of crossing tissue planes with no respect to anatomical boundaries or divisions.	EPS—exopolysaccharides, polysaccharide deacetylase, Spo0J containing ParB-like nuclease domain, TransRDD family protein	Penicillin, doxycycline

*Commonly used antibiotics are representative of methicillin-sensitive CONS

RBCs, red blood cells

Coagulase-Negative Staphylococcus

There are currently over 40 species of CoNS identified and these species are closely related to *Staphylococcus aureus*, but are differentiated by their inability to produce free coagulase [51]. CoNS are members of native skin flora and mucous membranes. Historically, these bacteria have rarely caused disease and were frequently considered contaminants in microbiological cultures. CoNS have recently been recognized as true pathogens and an important cause for PJI due to ability to colonize prosthetic material as well as produce biofilm. CoNS demonstrate many virulent properties, the most important of which is the ability to produce a highly structured, tenacious biofilm [55]. Though a common cause for early-onset PJI, these organisms are also one of the most common causes for delayed or late-onset PJI largely due to the formation of a robust biofilm causing antibiotic tolerance and host defense evasion [51, 56]. *Staphylococcus epidermidis* is the most frequently identified PJI-associated coagulase-negative staphylococcus, though other staphylococci have been reported as the inciting organism in PJI to include *Staphylococcus saprophyticus*, *Staphylococcus haemolyticus*, and *Staphylococcus lugdunensis*. Of these, *Staphylococcus lugdunensis* may be the most virulent with multiple cases documenting acute and aggressive infection mimicking that of *S. aureus* [57]. Although, it has been our clinical experience that a more indolent presentation may occur as well.

Propionibacterium acnes

P. acnes may be the most quintessential low-virulence organism to cause PJI and is the most common isolated organisms during revision shoulder arthroplasty [4]. There is joint specificity with regard to how patients present with *P. acnes* PJI. A recent study found that inflammatory markers, including ESR, CRP, and synovial fluid white blood cell count, were significantly higher in the knee and hip groups compared to the shoulder group [58••, 59•]. Patients typically have a slowly evolving clinical course with pain likely being the only manifestation of infection [38, 60]. Extended culture incubation up to 21 days is utilized to enhance detection of *P. acnes* and may be indicated for identification of indolent PJI. There is a need for long hold anaerobic culture protocols up to a minimum of 14 days to be able to accurately identify *P. acnes* as the causative organism, especially in the setting of TKA [59•]. Given the ubiquity of *P. acnes* as common skin flora, differentiating infection from contamination may be difficult to determine. Genomic studies have isolated distinct phylotypes of *P. acnes* with type IB being frequently associated with orthopedic infections [61]. There are various adaptive virulence properties throughout each of the phylotypes that have been shown to contribute to the pathogenic potential of the bacterium. These virulence properties include the ability to degrade and invade host cells, produce an enhanced host inflammatory response, demonstrate antibiotic resistance, and form biofilms [33, 62, 63]. Christie-Atkins-Munch-Petersen (CAMP) factor serves as a toxin to host cells and is found in the *P. acnes* genome [62]. CAMP may be associated with virulence properties such as beta-hemolytic activity. Certain strains of *P. acnes* that have been clinically correlated with true infection have demonstrated beta-hemolytic activity through their phenotypic expression of hemolysis [64] (Figs. 1 and 2). Hemolytic strains of *P. acnes* have also been associated with increased antibiotic resistance patterns, especially to clindamycin [65••] (Fig. 3).

Enterococcus

Though seen in 17% of patients with early-onset PJI, enterococcus typically presents as part of a polymicrobial infection, where a delayed presentation can be seen with monomicrobial PJI [66]. In a review of 50 cases of enterococcal PJI, the median length of time between joint implantation and diagnosis of PJI was 36 months with median duration of symptoms before PJI diagnosis of 164 days [53]. Clinical presentation was consistent with a low-virulence organism, where patients presented with pain and loosening of the prosthesis with minimal systemic features.

Actinomyces

Actinomyces are a rare cause of monomicrobial anaerobic PJI with a typical indolent presentation and histology showing signs of chronic infection typical of a low-virulence organism [67]. Actinomyces remains a rare cause of PJI with dental work, IV drug use, and intrauterine device use believed to increase risk for infection. This genus of bacteria is capable of crossing tissue planes with no adherence to anatomical

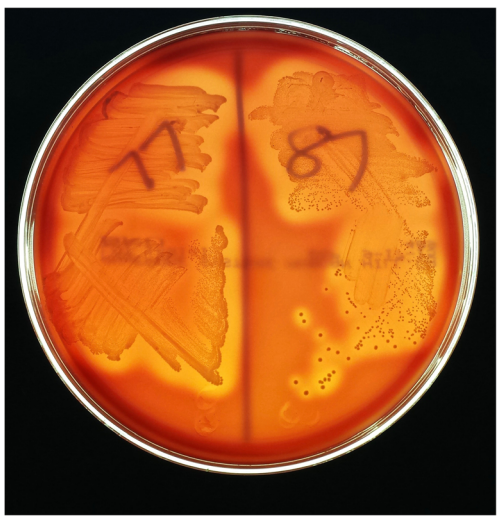

Fig. 1 *P. acnes* strains 77 and 87 on Brucella Blood Agar plates demonstrating the hemolytic phenotype as defined by greater than 2 mm of clearance surrounding the bacteria

Fig. 2 *P acnes* strains 83 and 84 on Brucella Blood Agar plates not demonstrating the hemolytic phenotype as shown by no evidence of clearance around the bacteria

boundaries and has the ability to form a robust mesh-like biofilm structure, especially in the oral cavity setting [68].

Biofilm Considerations

Biofilm is a complex three-dimensional structure that adheres to surfaces and describes monomicrobial or polymicrobial bacterial organisms residing in a self-produced matrix comprised of proteins, polysaccharides, and extracellular DNA [56, 69, 70]. Research has demonstrated Staphylococcal biofilms establish chronic infections by actively preventing macrophage phagocytosis and by a penchant for suppressing proinflammatory activity through the recruitment of myeloid-derived suppressor cells [71•, 72]. *S. epidermidis*, in particular, produces a thick biofilm matrix with extensive polysaccharide network to assist in host immune avoidance in addition to minimal toxin production as compared with more virulent organisms such as *S. aureus* [71, 73]. Figures 4 and 5 demonstrate the differences in biofilm architecture between *S. epidermidis* and methicillin-resistant *Staphylococcus aureus*. Biofilm allows bacteria to thrive by providing a potent defense against both host immune system responses and antimicrobial pharmacologic agents. Multiple mechanisms for antibiotic recalcitrance have been described depending on the organism and type of antibiotic administered for treatment [74, 75]. Research continues to better understand the complex pathogenesis of biofilm and the unique characteristics offending organisms elicit. Future strategies will be aimed toward optimizing current treatment strategies and developing innovative techniques for managing biofilm associated PJI.

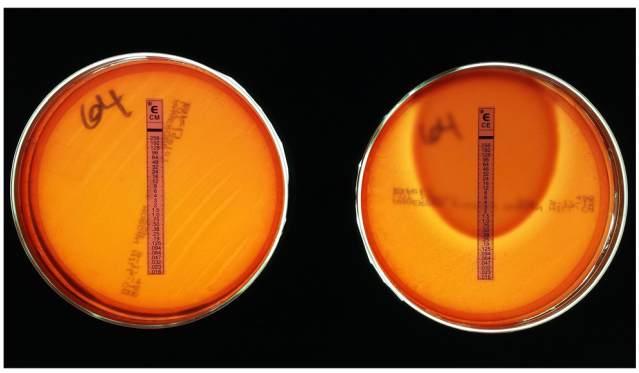

Fig. 3 *P. acnes* strain 64 on the left demonstrating resistance to clindamycin by showing the bacteria growing up to the e test strip at the highest minimum inhibitory concentration (MIC). *P. acnes* strain 64 on the right showing an MIC of 0.25 for cephalothin (first-generation cephalosporin), which is considered susceptible based on EUCAST (European Committee on Antimicrobial Susceptibility Testing) standards

Treatment of PJI Caused by Low-Virulent Organisms

The goals of PJI treatment are to eradicate the infection, reconstruct the joint to restore pain-free motion, improve the quality of life, and minimize the treatment-related morbidity and mortality for the patient. Surgical treatment options for PJI include open debridement without complete removal of the prosthesis, the so-called debridement antibiotic implant retention (DAIR) with an exchange of modular components, one-stage exchange arthroplasty, two-stage exchange arthroplasty, arthrodesis, and amputation. Medical managements with antimicrobial-targeted treatment based on organism sensitivity

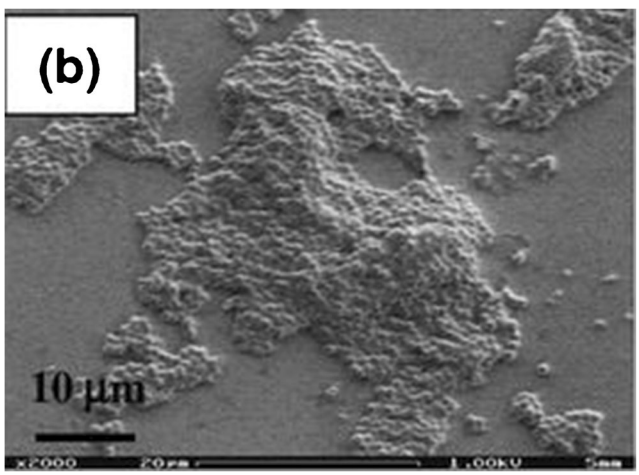

Fig. 4 *S. epidermidis* biofilm formation when evaluating microfluidic devices for studying growth and detachment of *S. epidermidis* biofilms. Reprinted with permission from Lee, JH., Kaplan, J.B., and Lee, W.Y. *Biomed Microdevices* (2008) 10: 489. https://doi.org/10.1007/s10544-007-9157-0. Please note that this photo originally appeared in a multi-paneled figure. The "(b)" on the image is not relevant to this review

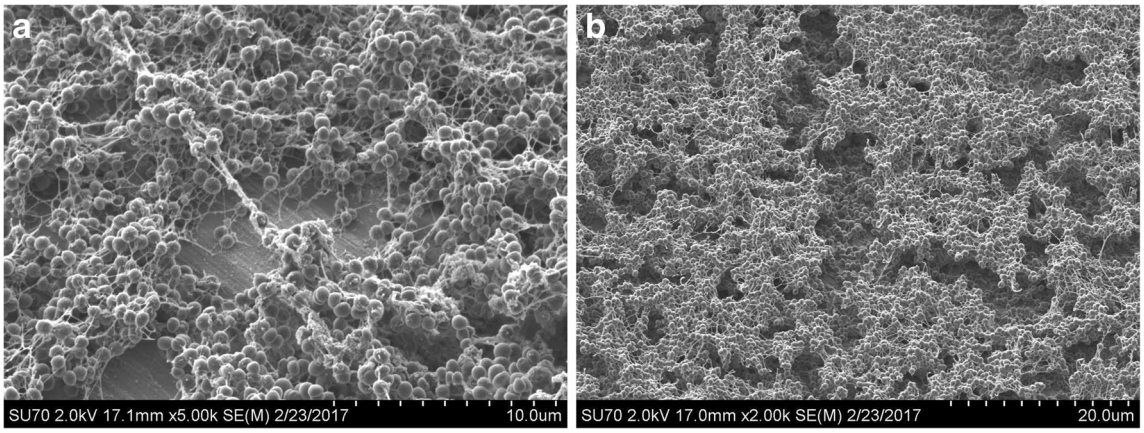

Fig. 5 **a**, **b** MRSA (clinical isolate NRS70) biofilm image by scanning electron microscope (SEM) grown on titanium in vitro. Courtesy of Caelen Clark, PhD University at Buffalo

or long-term suppression therapy with or without surgery are possible strategies to treat PJI. While two-stage exchange arthroplasty is the most accepted treatment for PJI in the USA, centers in Europe have reported results of single-stage revision for hip and knee PJI that are nearly similar to results of two-stage revision [76–78]. There has been a renewed interest in one-stage exchange arthroplasty, particularly for treating PJI associated with low-virulent offending organisms driven by decreased patient morbidity and increased function with decreased cost compared to two-stage exchange [79, 80, 81••]. Prior to one-stage exchange, we recommend considering the conclusions drawn by the international consensus group of arthroplasty surgeons and researchers from the meeting held in July 2018. Patient comorbidities that predispose to infection such as diabetes, obesity, immunosuppression, renal disease, smoking, severe cardiac disease, and metastatic carcinoma or compromised soft tissue envelope are likely to negatively impact the results of one-stage revision [15]. Further, as recently summarized by Jiranek et al., and based on the work from a 2013 international consensus group, we suggest a patient may be considered for one-stage exchange arthroplasty if they do not have generalized sepsis, the offending low-virulent organism without antibiotic resistance is identified in the preoperative setting, and the host is medically optimized without sinus tract or severe soft tissue compromise over the joint [81••, 82].

Conclusion

PJI is a devastating complication that requires sound clinical judgment and decision-making, as well as an algorithmic approach to preoperative workup including the use of biomarkers and molecular testing. The primary goal in the early stage of diagnosing PJI is to identify the offending organism and antibiotic susceptibility. A co-management approach between surgeons, infectious disease specialists, and ancillary professional staff to successfully eradicate infection and restore maximal functional and satisfaction of the patient is recommended. Coupled with a burst of novel peer-reviewed research focused on PJI in general over the last several years, there has been a particular recognition and acceptance of low virulent organisms as a cause for failure in total joint arthroplasty. Research continues to provide incremental answers on how to best define and manage this problem while sparking new questions as we learn more about the complex nature of low virulent organisms and the dynamic role between host and pathogen.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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