

Diagnostic and Treatment Considerations for Prosthetic Joint Infections: Sonication and New Gram-Positive Agents

Julie E. Reznicek, DO^{1, *}
Angela Hewlett, MD, MS²

Address

^{1,2}Division of Infectious Diseases, Virginia Commonwealth University, Richmond, VA, USA

Email: Julie.reznicek@vcuhealth.org

²Division of Infectious Diseases, University of Nebraska Medical Center, Omaha, NE, USA

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Opinion Statement

Prosthetic joint infection (PJI) is a rare but serious and catastrophic complication of total joint arthroplasty (TJA). Culturing the causative microorganism can be difficult especially in the setting of biofilm formation or antibiotic exposure. In culture-positive cases, Staphylococcal species continue to be the most common organisms isolated. In this review, we will discuss the potential role of sonication to increase the yield of periprosthetic cultures as well as new treatment options for gram-positive organisms. As the percentage of patients who undergo TJA continues to grow, we must continue to optimize our diagnostic and treatment options of PJIs.

Introduction

Total joint arthroplasty (TJA) can dramatically improve the quality of life of patients with debilitating arthritis or other joint diseases. Prosthetic joint infection (PJI) is the most serious and catastrophic complication of TJA and may lead to multiple surgical procedures, prolonged courses of antibiotics, increased costs to the patient and the healthcare system, and significant functional

impairment and disability. Although PJI is a relatively rare complication of TJA with an incidence of around 1 % for primary arthroplasty, utilization of TJA has increased dramatically [1]. This trend is projected to continue, and by 2030, it is estimated that 4 million arthroplasty surgeries will be performed in the USA each year [2]. One study demonstrated that the lifetime risk of

receiving a primary total knee arthroplasty was 7.0% for males and 9.5 % for females [3].

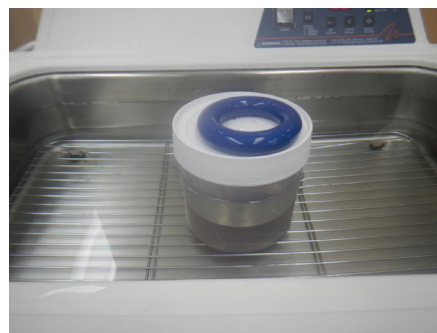
Prosthetic joint infections are notoriously difficult to manage, and diagnosis and treatment of these infections is challenging. This review will discuss the use of sonication, a method to enhance diagnostic capabilities, as well as newer treatment options for multi-drug resistant organisms often implicated in PJI.

Sonication

Microbiologic diagnosis of prosthetic joint infection can be problematic since standard culturing of periprosthetic tissue may not yield the offending organism. This occurs due to multiple factors, which include the lack of sensitivity and specificity of standard culture methods due to sampling limitations, the presence of biofilm on prosthetic material, difficult-to-culture organisms, and the prior receipt of antibiotics. Unfortunately, culture-negative PJI does occur and negative periprosthetic tissue cultures were found in 7 % of PJI cases at one large academic medical center [4]. The management of culture-negative prosthetic joint infections is fraught with problems, and empiric therapy is utilized since there is no positive culture result to guide antimicrobial therapy. Culture-negative PJI is a source of frustration for physicians in both orthopedics and infectious diseases since identification of the offending organism plays a great role in the choice of both the medical and surgical therapy for PJI.

Sonication was proposed as a technique to potentially enhance the yield of standard culture methods, thus decreasing the number of culture-negative PJIs. Sonication involves placing the explanted prosthesis in sterile fluid, then using an ultrasound bath to dislodge bacteria from a periprosthetic surface. The fluid is then cultured using standard microbiologic methods (Fig. 1). A 2007 study demonstrated increased sensitivity of sonication when compared to conventional culture methods of periprosthetic tissue, especially in patients who had recently received antibiotics [5]. This study stimulated interest in sonication as an adjunct method to diagnose PJI and has been replicated in several other studies [6, 7]. Sonication is now utilized in multiple centers as an adjunct diagnostic modality for PJI.

Since the initial 2007 study, centers have been working to enhance the sonication method further by adding other diagnostic modalities to the sonication protocol. A 2012 study assessed the utility of broad-range PCR on sonicate fluid but did not find a difference in the



(a) prosthetic knee in ultrasound bath



(b) removal of fluid for culture

Fig. 1. Selected steps from the sonication procedure. **a** Prosthetic knee in ultrasound bath. **b** Removal of fluid for culture.

proportion of patients with PJI detected with sonicate fluid PCR or sonicate fluid culture. However, subgroup analysis did indicate a trend towards higher sensitivity of PCR in patients who received antibiotics within 2 weeks of surgery [8]. A recent prospective multicenter study evaluated PCR (without sonication) for the diagnosis of PJI and demonstrated a low sensitivity of 73 % [9]. The advantages of PCR (rapid turn-around time, possible enhanced sensitivity with prior antimicrobial use) must be weighed against the disadvantages (false-positive results due to contamination, high cost, difficulty with polymicrobial cultures) when considering implementation into a PJI diagnosis protocol.

A 2013 study evaluated the usefulness of prolonged incubation time in cultures of sonicated orthopedic implants and found that extending the incubation time to 14 days did not add more positive results when compared with a standard 7-day incubation period [10]. Another study involving prolonged incubation demonstrated that sonication detected pathogens more rapidly than traditional tissue cultures [11].

A 2015 study evaluated sonication in combination with incubation in BD Bactec bottles for diagnosis of PJI

and demonstrated a higher yield of microorganisms compared with synovial fluid incubated in BD Bactec bottles without sonication. However, coagulase-negative Staphylococci was frequently detected in this study from the patients with aseptic failure (no evidence of infection), indicating that this method may enhance the isolation of contaminant organisms [12].

A meta-analysis of 12 studies on sonication showed a pooled sensitivity of 80 % and a specificity of 95 % for diagnosis of PJI [13]. A subgroup analysis was performed and demonstrated that alterations in sonication technique like adding centrifugation and using 400–500 ml of solution for containers may improve sensitivity and/or specificity. This analysis was, however, limited by the relatively small number of prospective studies available for analysis, as well as variation of PJI diagnostic criteria and sonication methods utilized.

Sonication of implants other than the primary prosthesis has been studied. A small, single-center study of 36 patients in 2014 sought to evaluate if sonication of antibiotic spacers in two-stage revisions improved the sensitivity of intraoperative cultures and also if positive sonication results were predictive of implant failure. The researchers found that sonication of antibiotic spacers did improve the sensitivity of cultures alone and also were more likely to predict reinfection after two-stage reimplantation for PJI [14].

Although multiple studies have demonstrated that it is feasible to implement sonication as an adjunct method for diagnosis of PJI, the sensitivity of sonication remains low (<80 % in most studies). The reported sensitivity is also dependent on the criteria used for diagnosis of PJI, and different criteria were utilized in the various studies. Implementation of the sonication protocol also necessitates the purchase of laboratory equipment along with specialized training of laboratory technicians. The addition of other techniques, including PCR and prolonged incubation, may not increase the sensitivity of sonication alone and add additional costs and steps in the laboratory.

All of these issues must be taken into account prior to implementation of sonication for diagnosis of PJI. It may also be useful to evaluate the sensitivity of the microbiology laboratory at a center prior to consideration of the addition of any additional procedures like sonication or PCR, as this determines whether new procedures will add to the yield of the current microbiologic methods.

Antimicrobial Agents for Infections Due to Resistant Gram-Positive Organisms

Gram-positive organisms continue to be the primary bacterial pathogens associated with prosthetic joint infections. The causative microorganism often correlates with the timing of the infection, with *Staphylococcus aureus* seen more in early-onset infections (<3 months) and less virulent organisms, such as coagulase-negative staphylococci seen in delayed and late-onset infections. Together, *Staphylococcus aureus* and coagulase-negative staphylococci are responsible for approximately half of all prosthetic joint infections (PJI) [15–17]. Other gram-positive organisms, including enterococci and beta-hemolytic streptococci, comprise a much small proportion (<10 %) [18].

Since penicillin resistance in *Staphylococcus aureus* was first identified in 1945, the decreasing susceptibility of this organism has been a significant concern [19]. It was a less than two decades later that methicillin resistance emerged in both *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE) [20]. Increasing numbers of infections due to healthcare-associated MRSA (HA-MRSA) occurred in the 1970s–1990s. MRSA infections then began to occur in patients without traditional risk factors for HA-MRSA and became known as community-associated MRSA (CA-MRSA) infections [21]. Epidemiologic studies indicate that about 60 % of invasive infections due to *S. aureus* are methicillin-resistant *Staphylococcus aureus* (MRSA), and approximately 80 % of coagulase-negative staphylococci isolates are methicillin-resistant *Staphylococcus epidermidis* (MRSE) [22, 23].

Antibiotic-resistant staphylococci are a significant concern in patients with PJI given the severity of infection and propensity to form biofilm on the implant. These infections generally necessitate an aggressive and often complex management strategy utilizing antimicrobial agents that specifically target resistant staphylococci along with appropriate surgical management. Table 1 shows the various antimicrobial agents utilized to manage resistant gram-positive infections, which are further discussed in the review below.

Since its introduction in 1958, Vancomycin, a glycopeptide, has been the mainstay in treatment for serious infections caused by resistant staphylococci. Vancomycin usage increased significantly due to the increasing incidence of MRSA infections which led to the development of staphylococcal strains with decreased susceptibility to vancomycin [24]. Fortunately, infections due to *Staphylococcus aureus* that are fully resistant to

Table 1. Antimicrobial agents for the treatment of drug-resistant gram-positive infections

Drug name	Year introduced	Route of administration	FDA-approved indications
Vancomycin	1958	Intravenous (oral for treatment of <i>Clostridium difficile</i> colitis or <i>S. aureus</i> enterocolitis only)	Endocarditis, bloodstream infection, bone infections, lower respiratory tract infections, skin and skin structure infections
Daptomycin	2003	Intravenous	Complicated skin and skin structure infections, <i>Staphylococcus aureus</i> bloodstream infection, right-sided endocarditis
Ceftaroline	2010	Intravenous	Acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia
Tigecycline	2005	Intravenous	Complicated skin and skin structure infections, community-acquired bacterial pneumonia, complicated intra-abdominal infection
Linezolid	2000	Intravenous or oral	Nosocomial pneumonia, complicated skin and skin structure infections, community-acquired bacterial pneumonia
Tedizolid	2014	Intravenous or oral	Acute bacterial skin and skin structure infections
Telavancin	2009	Intravenous	Complicated skin and skin structure infections, hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia caused by <i>Staphylococcus aureus</i>
Dalbavancin	2014	Intravenous	Acute bacterial skin and skin structure infections
Oritavancin	2014	Intravenous	Acute bacterial skin and skin structure infections

vancomycin (VRSA) continue to be a rare occurrence. Vancomycin is, however, associated with toxicities, complex dosing regimens and laboratory monitoring, and continued concerns for emerging resistance. The antimicrobial agents outlined below offer additional options for the treatment of resistant gram-positive microorganisms.

Daptomycin is a bactericidal lipopeptide antibiotic that was introduced in 2003. The once daily weight-based dosing is simplified compared to vancomycin's dosing nomogram. It is not indicated for pulmonary infections, because it binds to alveolar surfactant leaving it inactivated. Daptomycin has been associated with asymptomatic creatinine phosphokinase (CPK) elevations and serious myopathy and rhabdomyolysis; therefore, weekly CPK monitoring is recommended. Lastly, daptomycin-induced acute eosinophilic pneumonitis is a rare but potentially fatal adverse drug reaction that can present with fever, cough, hypoxemia, and new pulmonary infiltrates [25].

Ceftaroline is a fifth-generation cephalosporin that was approved for use in 2010. It has a broad spectrum

of activity, including some gram-negative organisms and resistant gram-positive organisms. Ceftaroline is generally well-tolerated, with a side effect profile similar to other cephalosporins (e.g., hypersensitivity reactions, gastrointestinal effects, hematological abnormalities) [26].

Tigecycline is a derivative of minocycline and was the first member of the glycylicyclines to be approved in 2005. It has a broad spectrum of activity including resistant gram-positive organisms and gram-negative organisms. Concerns about the pharmacodynamics of tigecycline have limited its use. The FDA also issued a warning regarding increased mortality in patients who received tigecycline. The initial alert in 2010 was specifically in patients treated with tigecycline for ventilator-associated pneumonia, which is not an FDA-approved indication. Analyzation of additional data in 2013 prompted the FDA to expand its warning to include FDA-approved indications [27].

Linezolid was approved in 2009 and was the first member of the oxazolidinones to be marketed. It has excellent bioavailability, allowing for oral therapy and the avoidance of risks associated with long-term

intravenous catheters (e.g., deep vein thrombosis (DVT) and bacteremia). Use is often limited because of cost and significant drug interactions. Linezolid can inhibit monoamine oxidase (MAO), increasing the risk of serotonin toxicity when it is given concomitantly with drugs that increase the levels of serotonin in the central nervous system, such as the commonly prescribed selective serotonin reuptake inhibitors (SSRIs) [28]. Linezolid is also associated with reversible myelosuppression, peripheral neuropathy, and optic neuropathy.

Tedizolid, also an oxazolidinone, has a similar spectrum of activity as linezolid (e.g., MRSA, vancomycin-resistant enterococci (VRE)) but has the added advantage of efficacy against emerging linezolid-resistant strains. Long-term tedizolid data is lacking, but it appears to have less potential for myelosuppression and MAO inhibition [29].

Telavancin, dalbavancin, and oritavancin are all semisynthetic lipoglycopeptides, with telavancin being

the first to gain FDA approval in September 2009. All three have activity against methicillin-resistant staphylococci, but they have varying activity against vancomycin-resistant staphylococci and resistant enterococci [30]. These drugs are promising, especially in the outpatient arena because they have very long half-lives, allowing for once weekly dosing with dalbavancin and oritavancin.

Although the antimicrobial agents discussed above are utilized for the treatment of various complicated bone and joint infections due to resistant staphylococci, only vancomycin is currently FDA approved for the treatment of osteomyelitis. Further studies on the pharmacodynamics properties and clinical applications of these agents are ongoing, and obtaining this data is important in order to ensure that these newer agents provide opportunity for the optimal antimicrobial management of complicated bone and joint infections due to resistant gram-positive organisms.

Conclusion

As more people undergo total joint arthroplasty, even a relatively rare complication like prosthetic joint infection will continue to become more common in the population. It is imperative that methods to enhance our ability to accurately diagnose and to effectively treat these catastrophic infections are developed. Preoperative evaluation and reduction of infection risk through modification of known risk factors is also an important area of focus that deserves significant attention. Although strides have been made in all of these arenas, there is much work to be done. Large, multicenter trials are necessary to effectively evaluate the use of newer diagnostic and therapeutic agents for the treatment of infections in prosthetic joints as well as other complicated bone and joint infections. These will only occur through collaborative efforts involving multiple centers, and the provision of adequate funding mechanisms is vital in order to conduct these important trials.

Compliance with Ethical Standards

Conflict of Interest

Julie E. Reznicek declares that she has no conflict of interest.

Angela Hewlett declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the author.

References and Recommended Reading

- Namba RS, Inacio MC, Paxton EW. Risk factors associated with deep surgical site infections after primary total knee arthroplasty: an analysis of 56,216 knees. *J Bone Joint Surg Am.* 2013;95:775.
- Kurtz S, Ong K, Lau E, et al. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am.* 2007;89:780–85.
- Weinstein AM, Rome BN, Reichmann WM, et al. Estimating the burden of total knee replacement in the United States. *J Bone Joint Surg Am.* 2013;95(5):385–92.
- Berbari EF, Marculescu C, Sia I, et al. Culture negative prosthetic joint infection. *Clin Infect Dis.* 2007;45(9):1113–9.
- Trampuz A, Piper KE, Jacobson MJ, et al. Sonication of removed hip and knee prostheses for diagnosis of infection. *N Engl J Med.* 2007;357:654–63.
- Piper KE, Jacobson MJ, Cofield RH, et al. Microbiologic diagnosis of prosthetic shoulder infection by use of implant sonication. *J Clin Microbiol.* 2009;47(6):1878–84.
- Bogut A, Niedzwiadek J, Koziol-Montewka M, et al. Sonication as a diagnostic approach used to investigate the infectious etiology of prosthetic hip loosening. *Pol J Microbiol.* 2014;63(3):299–306.
- Gomez E, Cazanave C, Cunningham SA, et al. Prosthetic joint infection diagnosis using broad-range PCR of biofilms dislodged from knee and hip arthroplasty surfaces using sonication. *J Clin Microbiol.* 2012;50(11):3501–08.
- Bemer P, Plouzeau C, Tande D, et al. Evaluation of 16S rRNA gene PCR sensitivity and specificity for diagnosis of prosthetic joint infection: a prospective multicenter cross-sectional study. *J Clin Microbiol.* 2014;52(10):3583–89.
- Esteban J, Alvarez-Alvarez B, Blanco A, et al. Prolonged incubation time does not increase sensitivity for the diagnosis of implant-related infection using samples prepared by sonication of the implants. *Bone Jt J.* 2013;95-B:1001–6.
- Portillo ME, Salvado M, Alier A, et al. Advantages of sonication fluid culture for the diagnosis of prosthetic joint infection. *J Infect.* 2014;69:35–41.
- Shen H, Tang J, Wang Q, et al. Sonication of explanted prosthesis combined with incubation in BD Bactec bottles for pathogen-based diagnosis of prosthetic joint infection. *J Clin Microbiol.* 2015;53(3):777–81.
- Zhai Z, Li H, Qin A, et al. Meta-analysis of sonication fluid samples from prosthetic components for diagnosis of infection after total joint arthroplasty. *J Clin Microbiol.* 2014;52(5):1730–36.
- Nelson CL, Jones RB, Wingert NC, et al. Sonication of antibiotic spacers predicts failure during two-stage revision for prosthetic knee and hip infections. *Clin Orthop Relat Res.* 2014;472:2208–14.
- Hidron AI, Edwards JR, Patel J, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention: 2006–2007. *Infect Control Hosp Epidemiol.* 2008;29:996–1011.
- Brause BD. Infections with prosthesis in bones and joints. In: Mandell G, Bennett J, Dolin R, editors. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases.* 7th ed. Philadelphia: Elsevier Churchill Livingstone; 2009. p. 1469–74.
- Del Pozo JL, Patel R. Infection associated with prosthetic joints. *N Engl J Med.* 2009;361(8):787–94.
- Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. *N Engl J Med.* 2004;351:1645–54.
- Spink WW, Ferris V. Quantitative action of penicillin inhibitor from penicillin-resistant strains of *Staphylococci*. *Science.* 1945;102:221–3.
- Barrett FF, McGehee Jr RF, Finland M. Methicillin-resistant *Staphylococcus aureus* at Boston City Hospital. Bacteriologic and epidemiologic observations. *N Engl J Med.* 1968;279:441–8.
- Shinefield HR, Ruff NL. Staphylococcal infections: a historical perspective. *Infect Dis Clin N Am.* 2009;23:1–15.
- National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control* 2004; 32(8):470.
- Diekema DJ, Pfaller MA, Schmitz FJ, et al. Survey of infections due to *Staphylococcus* species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific region for the SENTRY Antimicrobial Surveillance Program, 1997–1999. *Clin Infect Dis.* 2001;32 Suppl 2:S114.
- Howden BP, Davies JK, Johnson PDR, et al. Reduced vancomycin susceptibility in *Staphylococcus aureus*, including vancomycin-intermediate and heterogeneous vancomycin-intermediate strains: resistance mechanisms, laboratory detection, and clinical implications. *Clin Microbiol Rev.* 2010;23(1):99–139.
- Miller BA, Gray A, LeBlanc TW, et al. Acute eosinophilic pneumonia secondary to daptomycin: a report of three cases. *CID.* 2010;50(11):e63–8.
- Beresford E, Biek D, Jandourek A, et al. Ceftaroline fosamil for the treatment of acute bacterial skin and skin structure infections. *Expert Rev Clin Pharmacol.* 2014;7(2):123–35.
- FDA drug safety communication: FDA warns of increased risk of death with IV antibacterial Tygacil (tigecycline) and approves new Boxed

- Warning. <http://www.fda.gov/Drugs/DrugSafety/ucm369580.htm>. Accessed 31 Aug 2015.
28. Lawrence KR, Adra M, Gillman PK. Serotonin toxicity associated with the use of linezolid: a review of postmarketing data. *CID*. 2006;42:1578–83.
29. Rybak JM, Marx K, Martin CA. Early experience with tedizolid: clinical efficacy, pharmacodynamics, and resistance. *Pharmacotherapy*. 2014;34(11):1198–208.
30. Zhanel GG, Calic D, Schweizer F, et al. New lipoglycopeptides a comparative review of dalbavancin, oritavancin and telavancin. *Drugs*. 2010;70(7):859–86.