Introduction

The incidence of total knee arthroplasty (TKA) and total hip arthroplasty (THA) operations is increasing in the United States, along with the number of complications including periprosthetic joint infection (PJI) (1). Although the rate of PJI after total joint arthroplasty (TJA) is low, with a reported rate of 0.3–1.7% for TKA and 0.8–1.9% for THA, the rate is slowly increasing despite interventions (2).

Organisms responsible for PJI are often bacteria, which may spread from other parts of the body or may originate from the surgical wound itself. For example, organisms from the urogenital system, skin, gastrointestinal tract, and oral mucosa have all been found to cause PJI (3). The varieties of sources mirror the diversity of organisms that have the potential to cause PJI. Current literature identifies *Staphylococcus aureus* as the most common bacterial source of infection, followed by coagulase-negative *Staphylococcus*, beta-hemolytic *Streptococcus*, Enterococci and *Streptococcus viridans* (4). However, reports on PJI due to *S. viridans* are limited and are not commonly found in the literature. Additionally, results from a retrospective study demonstrated evidence of increasing incidence of *S. viridans* infection (2). Thus, the purpose of this review article is to discuss the prevention, diagnosis and treatment of *S. viridans* PJI.

*S. viridans*

*S. viridans* exists as an overarching group of organisms with common laboratory characteristics. They are visualized as gram-positive cocci with chaining morphology. These organisms do not grow on 6.5% NaCl or bile esculin agar. Laboratory measures show that they are catalase negative, pyrrolidonyl arylamidase negative, optochin resistant and not bile soluble. The *S. viridans* umbrella is further separated into five subfamilies: *S. mutans*, *S. salivarius*, *S. anginosus*, *S. sanguinis*, and *S. mitis* (5-7). All *S. viridans*
Organisms are found primarily in the oral cavity and *S. anginosus* can also be found in the gastrointestinal tract (6).

Each subfamily of the *S. viridans* group has additional identifying features. The *S. mutans* species ferment mannitol and sorbitol, hydrolyze esculin and has a positive Voges-Proskauer test. *S. salivarius* has a positive Voges-Proskauer test and hydrolyzes esculin. *S. anginosus* is able to hydrolyze arginine and esculin, and results in a positive Voges-Proskauer test. *S. sanguinus* can hydrolyze arginine and esculin. On the other hand, *S. mitis* cannot hydrolyze arginine or esculin, cannot ferment mannitol or sorbitol, and has a negative Voges-Proskauer reaction (5-7) (Table 1).

Although relatively rare and not seen often in the literature, organisms from almost each subfamily of *S. viridans* have been noted to cause PJI after primary TKA or THA. Researchers described either the specific subgroup—*S. mutans* (3,10), *S. anginosus* (11), *S. sanguinus* (12,13), or *S. mitis* (13-18)—or cited the overarching group *S. viridans* (3,18-31) as responsible for PJI in their patients. *S. salivarius* has not been specifically reported in the literature as the causative organism of PJI in TKA or THA.

**Prevention**

The best way to limit the consequences of PJI is to prevent the infection before it occurs. Although remote sources are considered to be a rare cause of PJI (32), specific subfamilies of *S. viridans* are thought to cause PJI due to spread from another part of the body. Specifically, *S. mutans*, which is normally found in the oral cavity (5,6,10), has the ability to spread hematogenously and infect a prosthetic joint. The literature on antibiotic prophylaxis prior to an oral procedure in patients with prosthetic joints is controversial. Prior to 1997, there was no consensus or professional recommendation on prophylactic measures. Some reports indicate a relationship between dental procedures and the onset of an *S. mutans* PJI (3,12,21,22,25). This relationship generated the idea of limiting the hematogenous spread from invasive oral procedures with preemptive antibiotic measures.

The American Academy of Orthopedic Surgeons (AAOS) and the American Dental Association (ADA) released a total of three joint statements regarding antibiotic prophylaxis in TJA patients prior to oral procedures. Additionally, the AAOS released a further individual statement on the practice (33-36). The first joint statement was released in 1997, and the report suggested that antibiotic prophylaxis prior to dental procedures was not routinely indicated in most patients. However, certain subpopulations were at higher risk for PJI and should be considered for prophylaxis. These included patients undergoing procedures that were at high-risk for hematogenous spread of infection, as well as immunocompromised patients, or patients with comorbidities with a high likelihood for infection that underwent TJA within two years of the oral procedure (34).

In 2003, the AAOS and ADA released the next update based on a combined literature analysis. The major difference was clarification of the recommendation based on the two-year postoperative time mark. Antibiotic prophylaxis was still recommended for high-risk dental procedures, but only as a routine measure for patients that underwent TJA within the last two years. In immunocompromised and comorbid patients, antibiotic prophylaxis was still recommended only before high-risk dental procedures, but with the added clarification that the duration since the index TJA should be disregarded.

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Source</th>
<th>Mannitol</th>
<th>Sorbitol</th>
<th>Esculin</th>
<th>Arginine</th>
<th>Voges-Proskauer</th>
<th>Optimal antibiotic sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. mutans</em></td>
<td>Oral cavity</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>Vancomycin</td>
</tr>
<tr>
<td><em>S. salivarius</em></td>
<td>Oral cavity</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>Penicillin, vancomycin</td>
</tr>
<tr>
<td><em>S. anginosus</em></td>
<td>Oral cavity, intestinal tract</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Penicillin, vancomycin, ceftriaxone, clindamycin</td>
</tr>
<tr>
<td><em>S. sanguinus</em></td>
<td>Oral cavity</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>Penicillin, vancomycin, ceftriaxone</td>
</tr>
<tr>
<td><em>S. mitis</em></td>
<td>Oral cavity</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>Vancomycin, clindamycin</td>
</tr>
</tbody>
</table>

Mannitol, fermentation of mannitol; sorbitol, fermentation of sorbitol; esculin, hydrolysis of esculin; arginine, hydrolysis of arginine; voges-proskauer, acetoin production from glucose (5-9).
(33,37). No antibiotic prophylaxis was recommended for all other patient groups: low risk dental procedures in immunocompromised or comorbid TJA patients, or TJA performed more than two years prior (33,37).

In the 1997 and 2003 statements, high-risk dental procedures were defined as dental extraction, periodontal procedures, dental implants, endodontic instrumentation beyond the tooth apex, subgingival placement of antibiotic fibers or strips, placement of orthodontic bands, intraligamentary local anesthetic injections and tooth cleaning with anticipated bleeding. Low-risk procedures include restorative dentistry, local anesthetic injections, intracanal endodontic treatments, placement of rubber dams, postoperative suture removal, placement of removable prosthetic or orthodontic appliances, taking oral impressions, fluoride treatments, oral radiographs, orthodontic appliance adjustment, and shedding of primary teeth. The risk stratification of high or low was based on likelihood of hematogenous spread of bacteria. Patients were considered immunocompromised if they had a history of rheumatoid arthritis, systemic lupus erythematosus, other inflammatory polyarthropathy, or drug or radiation induced suppression. Comorbid medical conditions include previous PJI, malnutrition, hemophilia, human immunodeficiency virus (HIV), type 1 diabetes mellitus or malignancy (33,34,37).

The AAOS released a solo information statement in 2009 regarding the practice of antibiotic prophylaxis before oral procedures in patients with a history of TJA. The AAOS recommended that prophylactic antibiotics be given to all patients before all oral procedures—regardless of time since surgery or risk of hematogenous spread (37). The new statement was without consultation of any dental professional organization and was ultimately unsuccessful at replacing the combined 2003 report (35).

The most recent and current joint AAOS/ADA recommendation was published in 2013. The report utilized evidence based medicine and literature reviews to create recommendations regarding oral dental procedures and PJI. The workgroup submitted a total of three recommendations regarding the relationship of bacteremic spread from the oral cavity and PJI in patients with a prosthetic joint implant. The first recommendation stated that health care professionals should consider discontinuing the use of antibiotic prophylaxis prior to invasive dental procedures. The recommendation was graded as “limited,” implying that the quality of evidence was unconvincing and that strong studies do not show a clear advantage from either practice. With this in mind, the paper stressed that each provider must decide what is in the best interest of the patient after consideration of the limited recommendation, personal clinical judgment, and the wishes of the patient. The second conclusion formed by the workgroup was that they were unable to recommend for or against the use of topical oral antibiotics in patients with prosthetic joint implants. This statement received an “inconclusive” grade and it was suggested that providers be cognizant of any future publications that may sway the debate in one direction. The final recommendation that received consensus support was that all patients with prosthetic joint implants maintain appropriate oral hygiene. The consensus was formed around the expert opinions of the members of the group, and not based on published data (36).

When antibiotic prophylaxis is indicated, the 1997 and 2003 combined reports provide suggested treatment regimens to be administered one hour before the oral procedure. First line antibiotic therapy is two grams of amoxicillin, cephradine or cephalaxin by mouth. If the patient is unable to tolerate oral medication, then 1 g of cefazolin or 2 g of ampicillin can be administered intravenously or intramuscularly. If the patient is allergic to beta-lactams, then 600 mg of clindamycin by mouth or intravenously is indicated (34,37).

**Diagnosis**

Studies suggest that history taking is the most effective way to determine the source of an infection (38). Although hematogenous seeding from a remote source infection is considered a rare cause of PJI (32), a thorough history will provide a complete medical picture for the clinician.

The current standard for diagnosing PJI is from the Musculoskeletal Infection Society (MSIS) criteria developed in 2011 (39). The criteria defined PJI if there was a sinus tract communicating with the prosthesis or if a pathogen was isolated via culture from two separate tissue or fluid samples. PJI was also diagnosed if 4 of 6 specific laboratory measures were met: (I) elevated serum erythrocyte sedimentation rate (ESR) and elevated serum C-reactive protein (CRP); (II) elevated synovial fluid leukocyte count; (III) elevated synovial fluid neutrophil percentage; (IV) presence of purulence in the affected joint; (V) isolation of microorganism in one culture of tissue or fluid; and/or (VI) greater than five neutrophils per high-power field in five high-power fields at ×400 magnification. However, the
statement did concede that a PJI may exist without meeting the criteria listed (39). Subsequent to the MSIS criteria, the International Consensus Group on PJI developed a new definition of PJI, which removed the criteria of purulence and added leukocyte esterase as another marker of infection (40).

Prior to the adoption of the standardized diagnostic criteria, there was a wide spectrum of diagnostic methods to establish the presence of a PJI. Specifically, the diagnosis of *S. viridans* joint infection was based on a multitude of factors. Many researchers utilized the presence of elevated serum inflammatory markers, specifically ESR and CRP, as signs of infection (13,14,16,18-20). Others relied on positive culture results from joint fluid aspiration or intraoperative tissue samples (10,13,16,18,19,21,24,27,28). To boost the sensitivity of the diagnosis, some researchers also incorporated the clinical picture of infection (19,28) and radiologic signs (19) in their assessment. However, since each study incorporated slightly different methods, it is difficult to provide a consensus on improved diagnostic reliability of *S. viridans*. The recent adoption and implementation of standard diagnostic criteria will help with the future analysis of PJI.

### Treatment

The treatment regimens for suspected or confirmed PJI can vary depending on severity and symptom duration. The gold standard for PJI treatment is two-stage resection arthroplasty with subsequent reimplantation (14,24,26,41,42). However, surgeons can also opt to treat with antibiotic suppression alone, debridement with component retention, or more rarely, resection arthroplasty, knee arthrodesis or amputation (26,30,41). These secondary options have fallen out of favor due to the increased rates of treatment failure and high morbidity/mortality, and are only reserved for specific circumstances (41-45).

While it is preferred to wait until an organism has been definitively identified before starting an antibiotic treatment, empiric coverage is an option for extremely ill patients. Standard empiric coverage generally includes antimicrobial activity against *Staphylococci* and gram-negative bacilli. However, once the diagnosis of *S. viridans* is confirmed, it is imperative to change treatment and start the appropriate antimicrobial agent.

Each subfamily of *S. viridans* demonstrates maximum susceptibility to different antibiotics. Literature suggests that *S. sanguinus* is most sensitive to ceftriaxone, *S. mitis* to clindamycin and *S. anginosus* to both ceftriaxone and clindamycin (8). Additionally, all *S. viridans* group organisms are highly responsive to vancomycin treatment (8,9) (Table 1). As is the situation with many organisms, *S. viridans* group organisms, and *S. mitis* specifically, have shown a growing and significant increase in its resistance to beta-lactams agents (5,9,46).

Unlike with other organisms, *Streptococcus* PJI does not have a standard or recommended therapy regimen (11). The absence of standardization may explain the lack of uniformity in treatment methods reported. In patients undergoing two-stage exchange arthroplasty, the most common antibiotics utilized in polymethylmethacrylate cement are vancomycin and tobramycin, as both antibiotics are heat stable and vancomycin is effective against *S. viridans* while tobramycin works synergistically with vancomycin (47). Postoperatively, dual antibiotic coverage often includes vancomycin and ceftazidime, linezolid, tobramycin, cefotaxime or gentamycin (14,18,19,23,28). One author suggested that *Streptococcus* species are more amenable to primary antibiotic suppression compared to other organisms (29). Alternatively, some surgeons have utilized oral rifampin and levofloxacin acutely, and then switched to amoxicillin for longer-term suppression (15). Antibiotic coverage for patients that undergo debridement surgery with component retention can receive either triple therapy of nafcillin, penicillin and gentamicin or dual coverage with penicillin and clindamycin (27,30).

### Conclusions

The incidence of TJA is predicted to increase in the United States, and the associated increase in PJI may result in more cases of *S. viridans*. Although *S. viridans* is a relatively uncommon cause of PJI, the current literature on *S. viridans* PJI is scarce and lacks a comprehensive review. Four of the subfamilies have been specifically identified as a cause of PJI: *S. mutans*, *S. anginosus*, *S. sanguinis* and *S. mitis*. Since *S. viridans* is known to live in the oral cavity, antibiotic prophylaxis may be used prior to invasive dental procedures, but should be reserved for TJA patients with high likelihood for developing PJI. There is no published standard treatment regimen for either *Streptococcal* or *S. viridans* PJI, likely due to the low incidence of *S. viridans* PJI. The preferred treatment for *S. viridans* PJI is identical to PJI from more common organisms, including two-stage resection arthroplasty with different primary antibiotic treatment based on each subfamily of *S. viridans*. 

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References


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