As a result of the increasing number of total joint arthroplasties (TJAs) being performed annually, the number of complications necessitating revision surgery is increasing. \(^1\,^2\) Periprosthetic joint infection (PJI), one of the major complications and etiologies of implant failure after TJA, is associated with substantial financial burden on the healthcare system and significant physical and psychological morbidity for patients. \(^3\,^4\) Despite the relatively low incidence of PJI, the annual US hospital cost for revision surgery because of infection increased from $320 million to $566 million from 2001 to 2009, and it is estimated that the cost will exceed $1.62 billion by 2020. \(^3\)

Management of PJI is challenging because infecting organisms have the ability to form a biofilm on the surface of the prosthesis and cross the cell membrane of osteoblasts. These capabilities provide the infecting organisms with the advantage to easily evade the host immune system in spite of antibiotic administration. Future efforts to curb PJI need to consist of strategies that can deprive the infecting organisms of these survival advantages.

**Pathophysiology**

The pathogenesis of PJI begins with the adherence of bacteria to the implant. \(^5\) Two distinguishable phases of attachment, reversible (nonspecific) and irreversible (specific), occur during bacterial adhesion to the surface of the implant. \(^5\) Nonspecific physical and
Biofilms play an important role in the pathogenesis of PJI. Biofilm is a complex structure consisting of microorganisms enveloped in macromolecules of glycocalyx and other protective films. The attachment of bacteria to the surface of the implant and then a cell-to-cell bacterial adhesion, which is associated with pluristratification of bacteria onto the artificial surface, are both important steps in biofilm formation. Evidence suggests that the internalization of staphylococci is a mechanism that contributes to pathogenesis of PJI and resistance to treatment. According to this concept, staphylococci can invade and live inside host cells. Intracellular adaptation may facilitate long-term persistence of the microorganism in bone, thereby avoiding exposure to antibiotics and immune system responses. Small colony variant strains, which have mutations that impair the electron transport pathway, are particularly skilled in invading and living inside host cells.

### Table 1

<table>
<thead>
<tr>
<th>Factors</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Hemoglobin $A_g &lt; 7$</td>
</tr>
<tr>
<td></td>
<td>Strict perioperative glucose control $&lt; 200$ mg/dL</td>
</tr>
<tr>
<td>Obesity</td>
<td>Body mass index $&lt; 40$ kg/m$^2$ before elective surgery</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Total lymphocyte count $&gt; 1,500$ cells/µL</td>
</tr>
<tr>
<td></td>
<td>Albumin $&gt; 3.5$ g/dL</td>
</tr>
<tr>
<td></td>
<td>Transferrin $&gt; 200$ mg/dL</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>Delay surgery if symptoms of obstruction; positive urinalysis $&gt; 10,000$ cells/mL</td>
</tr>
<tr>
<td>Antirheumatic drugs</td>
<td>See Table 2</td>
</tr>
<tr>
<td>Anemia</td>
<td>Preoperative iron plus erythropoietin if hemoglobin $&lt; 13$ g/dL</td>
</tr>
<tr>
<td></td>
<td>Tranexamic acid</td>
</tr>
<tr>
<td></td>
<td>Lower transfusion triggers to avoid allogeneic blood</td>
</tr>
<tr>
<td>Methicillin-resistant</td>
<td>Positive test: 5 days mupirocin nasal ointment, 5 days chlorhexidine showers,</td>
</tr>
<tr>
<td>Staphylococcus aureus screening</td>
<td>preoperative vancomycin plus cefazolin sodium</td>
</tr>
<tr>
<td><strong>Intraoperative</strong></td>
<td></td>
</tr>
<tr>
<td>Prophylactic antibiotics</td>
<td>First-generation cephalosporin weight-adjusted dosing</td>
</tr>
<tr>
<td>Preoperative preparation</td>
<td>Alcohol-based chlorhexidine or povidone-iodine solution</td>
</tr>
<tr>
<td></td>
<td>Preoperative shaving with clippers before surgery</td>
</tr>
<tr>
<td>Minimize operating room traffic</td>
<td>Diminishes turbulent flow in operating room and reduces number of bacterial</td>
</tr>
<tr>
<td></td>
<td>colony-forming units</td>
</tr>
<tr>
<td>Antibiotic cement</td>
<td>Administer to high-risk patients</td>
</tr>
</tbody>
</table>

### Prevention

Several strategies are known to be effective in PJI prevention. These strategies can generally be categorized as optimizing the host and optimizing the surgical and perioperative environment (Table 1). This section focuses on the most common modifiable patient risk factors for PJIs.

### Diabetes

Diabetes is associated with multiple comorbid health conditions; therefore, patients with diabetes have demonstrated higher complication rates and chemical characteristics of the bacteria as well as biomaterial and surrounding joint fluid play a role in reversible adhesion. In contrast, irreversible adhesion depends on more specific bacterial structures and receptors.
longer hospital stays after surgery.\textsuperscript{14} Marchant et al\textsuperscript{15} reported that patients with uncontrolled diabetes (as defined on the basis of International Classification of Diseases-version 9 codes) had a 2.8 times increased risk of infection after TJA.

The role of hemoglobin A\textsubscript{1C} in patients with diabetes undergoing TJA remains controversial.\textsuperscript{16,17} Hemoglobin A\textsubscript{1C} is a marker of long-term glucose control and may take 3 months to change. Ideally, patients with optimal blood glucose control should have a hemoglobin A\textsubscript{1C} level less than 7% before surgery. Perioperative hyperglycemia is associated with an increased risk of postoperative infection, and some physicians believe that this may be of more importance than an assessment of hemoglobin A\textsubscript{1C}.\textsuperscript{18} Postoperatively, blood glucose should be maintained between 110 to 180 g/dL.\textsuperscript{19} Patients with diabetes may require frequent blood glucose monitoring postoperatively, and it has been shown that a standard diabetic algorithm can minimize the risk of hyperglycemia after surgery.\textsuperscript{20}

Obesity
Obesity has reached epidemic proportions in the United States. Patients who are obese are at high risk for osteoarthritis and, therefore, increasingly require TJA. With regard to functional improvement and longevity, most outcomes data for TJA in the obese population are comparable to data for TJA in the nonobese population.\textsuperscript{21,22} However, patients who are obese are susceptible to increased risk of infection secondary to longer surgical times, greater surgical dissections, poorly vascularized subcutaneous tissue, a high-calorie poor nutritional diet, inadequate prophylactic antibiotics not adjusted for weight, and a pathologic relationship with type 2 diabetes.\textsuperscript{23,24}

Several studies have shown that patients with obesity have an increased risk of deep infection after TJA.\textsuperscript{25-27} Namba et al\textsuperscript{25} showed that when compared with a nonobese population, patients who are obese had a 6.7 times higher risk for infection after total knee arthroplasty. Another study demonstrated that patients with a body mass index greater than 40 kg/m\textsuperscript{2} had a 3.3 times increased odds for the development of infection. When the body mass index increased to 50 kg/m\textsuperscript{2}, the odds of infection development increased to 21 times greater than the risk for a nonobese patient. In addition, Winiarsky et al\textsuperscript{27} showed a 22% wound complication rate in the patients who were morbidly obese compared with a 2% wound complication rate in a control group. To diminish the risk for infection, it is critical that a patient’s weight is optimized through education, counseling, and, occasionally, surgical intervention.

**Urinary Tract Infection**
The association between a preoperative urinary tract infection and the development of a postoperative infection is unclear; however, all patients should be asked about symptoms of a urinary tract infection in their preoperative workup. Initial screening should include a urine white blood cell (WBC) count. Pyuria (WBC count >10,000 cells/mL) should prompt an evaluation of urine bacteria. In general, it is acceptable to proceed with surgery if the patient has bacteriuria (WBC count >10,000 cells/mL) without symptoms or if symptoms are present and the WBC count is less than 10,000 cells/mL.\textsuperscript{28} These patients can generally be treated with a standard oral antibiotic. It is recommended that surgery be postponed in any patient who shows signs of a urinary pathway obstruction or has a symptomatic urinary tract infection and WBC count greater than 10,000 cells/mL.\textsuperscript{29,30}

**Inflammatory Arthropathies**
Patients with inflammatory arthropathy are known to have two to three times greater risk of postoperative infection.\textsuperscript{31} Many of these patients are being treated with complex drug routines that affect wound healing and infection. There is no substantial evidence in the literature on how to handle these medications around the time of surgery. Therefore, practical guidelines must be established for patients to minimize their risk of infection and allow for appropriate control of inflammatory arthropathy postoperatively. The International Consensus Group recently published a practical guideline for the discontinuation of antirheumatic drugs in consultation with the treating rheumatologist before TJA\textsuperscript{32} (Table 2).

**Preoperative *Staphylococcus aureus* Screening**
Molecular DNA studies have shown that most infecting strains of *S. aureus* are part of the patient’s resident nasal flora. These rates can be as high as 85% in an at-risk patient population.\textsuperscript{33,34} A study by Kim et al\textsuperscript{35} evaluated the role of a prescreening program for the detection and eradication of methicillin-resistant *S. aureus* in patients undergoing elective orthopaedic surgery. Patients were identified using a rapid polymerase chain reaction–based screening of nasal swabs and were treated with intranasal mupirocin and chlorhexidine showers before surgery. Patients showed a colonization rate of 22.6% for *S. aureus* and 4.5% for methicillin-resistant *S. aureus*. 

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
Inflammatory Arthropathy & Screening Method \\
\hline
Psoriatic Arthritis & \textit{Staphylococcus aureus} \textsuperscript{+} \\
\hline
Rheumatoid Arthritis & \textit{Staphylococcus aureus} \textsuperscript{-} \\
\hline
Systemic Lupus Erythematosus & \textit{Staphylococcus aureus} \textsuperscript{+} \\
\hline
Osteoarthritis & \textit{Staphylococcus aureus} \textsuperscript{-} \\
\hline
\end{tabular}
\caption{Preoperative Screening for *Staphylococcus aureus* in Inflammatory Arthropathies}
\end{table}
This prescreening and decolonization program reduced the surgical site infection rate by 59%. In a study by Rao et al,26% of the patients were identified as carriers of S. aureus prior to undergoing orthopaedic surgery. The patients were treated with a 5-day course of mupirocin and chlorhexidine baths, which reduced surgical site infection from 2.6% to 1.5% and resulted in an institutional savings of $231,000.

### Diagnosis

The accurate diagnosis of PJI is imperative because treatment is fundamentally different from that of an aseptic etiology. The diagnosis of PJI continues to be challenging because no single test can reliably confirm it or rule it out in all cases. However, with the publication of the American Academy of Orthopaedic Surgeons’ clinical practice guideline on the diagnosis of PJI in 2010, some firm recommendations have been established that provide the practicing surgeon with a framework for evaluation.37,38

Assessment should begin with a thorough patient history and physical examination to identify if the diagnosis of PJI is probable. Plain radiographs help identify entities such as loosening but rarely help in specifically identifying PJI. However, it should be assumed that early osteolysis seen around an implant is related to PJI and not to bearing-surface wear if seen within the first few years postoperatively. Likewise, early implant loosening should raise the clinical suspicion for infection.

The next step in the diagnosis is obtaining the erythrocyte sedimentation rate and the C-reactive protein level; these screening analyses should be performed in all patients who are either indicated for a revision procedure or who have a painful hip or knee arthroplasty and PJI is suspected. The erythrocyte sedimentation rate and C-reactive protein level are good screening tools because they are easily obtained in virtually all practice settings with little risk to the patient, they are relatively inexpensive, and numerous studies have shown a very high sensitivity for these tests with respect to PJI.39 The serum WBC count has been shown to be of little value, and its use has been abandoned in most centers.40

If the erythrocyte sedimentation rate and/or C-reactive protein level are abnormal or if the clinical suspicion for PJI is high, joint aspiration is recommended. Joint aspiration provides the clinician with three separate data points: a synovial fluid WBC count, a differential (specifically the percentage of neutrophils), and a culture. Based on the available literature, the International Consensus Group determined the optimal cutoff values for the diagnosis of chronic and acute PJI.41 In cases of chronic PJI (>6 weeks), the threshold for the synovial fluid WBC count was determined to be 3,000 cells/μL and 80% for the differential. In cases of acute PJI, the threshold for the synovial fluid WBC was determined to be 10,000 cells/μL and 90% for the differential.41

In cases where an attempted aspiration yields no fluid, it is recommended that aspiration be repeated at another time and/or by another physician. If fluid is still not obtained, the options include either an indium In-111–labeled leukocyte scan (typically combined with a sulfur colloid bone marrow scan to correct for marrow packing artifact) or diagnostic confirmation at the time of surgery with intraoperative testing. Given their expense and poor performance in terms of accuracy when compared with other interventions such as joint aspiration, nuclear medicine studies have a limited role in contemporary practice. There currently is no role for CT or MRI in the diagnosis of PJI, and technetium Tc-99m bone scintigraphy is not specific for PJI.

### Table 2

**International Consensus Group Recommendations for the Discontinuation of Antirheumatic Drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>No stress dose: Less than 7.5 mg/d or treatment at any dose for less than 3 weeks</td>
</tr>
<tr>
<td></td>
<td>Stress dose: 7.5 mg/d for duration more than 3 weeks; should be dosed with 50 to 100 mg of hydrocortisone on the day of surgery and then resume normal regimen</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Do not discontinue before surgery; may continue in the perioperative period</td>
</tr>
<tr>
<td>Sulfasalazine/azathioprine</td>
<td>Withhold for 1 week prior</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Withhold for 2 weeks prior</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Continue therapy up to and including day of surgery</td>
</tr>
<tr>
<td>Biologic response modifiers (etanercept, infliximab, anakinra, rituximab, adalimumab, certolizumab pegol)</td>
<td>Withhold one dosing cycle before surgery based on half-life of medications; resume 1 to 2 weeks after surgery after wound healing</td>
</tr>
</tbody>
</table>

Orthopaedic Medicine and Practice
Several intraoperative tests are available in cases where PJI has not been definitively confirmed or ruled out before revision surgery. In the past, Gram stains have been used, but they have been shown to have poor sensitivity, and routine use should be discouraged. Frozen section analysis is selectively recommended and can be useful if performed by a skilled pathologist. Frozen section analysis is subjective by nature, subject to sampling error, and controversial in defining PJI; however, most pathologists believe that an average of 5 to 10 neutrophils in a high-power field is considered consistent with PJI.

Although still considered the gold standard for diagnosis, cultures are plagued by both false-positive and false-negative results. In general, the most suspicious areas identified intraoperatively should be cultured, and tissue cultures are preferred over swabs. Multiple cultures should be obtained (typically three to five) to aid in their interpretation; for example, one of five positive cultures is a very different scenario than four of five positive cultures yielding the same organism.

**Surgical Treatment**

Worldwide debate continues regarding the effectiveness and the benefits of one-stage versus two-stage treatment of infection. Two-stage exchange is preferred by most surgeons in North America; however, several studies have demonstrated reasonable results with one-stage exchange (Table 3). One of the most important aspects of surgical intervention for PJI relates to the efficiency and thoroughness of removing the infection or bioburden. Thus, the success of any surgery largely depends on surgical débridement.

Surgical management of PJI begins with a thorough débridement (including the removal of all components) and the placement of a spacer with antibiotic-laden cement, followed by a few weeks (6 weeks in the practice of this chapter’s authors) of intravenous antibiotics via a central catheter. Reimplantation is performed when infection is believed to be controlled. As recommended by several authors, the spacers should contain high concentrations of antibiotics. One of this chapter’s authors (KRB) prefers to use 3.6 to 4.8 g of tobramycin or gentamicin and 3.0 to 4.0 g of vancomycin per 40 g unit of cement, whereas another author (CDV) prefers to use less antibiotics (a total of 4 to 6 g of antibiotics per 40 g unit of cement). This chapter’s authors prefer articulating spacers consisting of cement mixed with the high concentration of antibiotics as described and endorsed by the International Consensus on Periprosthetic Joint Infection.

**The Knee**

Both static and articulating spacers are effective for eradicating infection (Tables 4 and 5); however, articulating spacers promote greater range of motion, preserve bone,
facilitate reimplantation, and may enhance functional recovery.⁴⁹,⁵⁵,⁸¹ Commencing at the start of the case, the femoral and tibial molds for the knee are separately prepared. Two disposable injection nozzles are used to mold intramedullary dowels, which will enhance delivery of antibiotics into the femoral and tibial canals. The tibial component mold depth is fabricated based on the thickness of the metal and polyethylene that was removed while striving for minimal thickness (Figure 1). The femoral mold is massaged to eliminate air spaces and keep the anterior flange somewhat thin so the patellofemoral articulation is not overstuffed. After the cement cures, the molds are removed. The spacers may be contoured, as needed, with a high-speed burr to reduce bulkiness and facilitate motion. After all components and cement are removed, using care to ensure minimal bone loss, the wound is copiously and thoroughly irrigated with several liters of pulsatile lavage. The spacers are intentionally implanted with poor cement technique by applying a small amount of doughy cement into a bloody wound after tourniquet release to reduce adherence and allow for easier removal at the time of reimplantation.

In a multicenter retrospective study, 60 infected knees were treated with the same cement-on-cement, high-dose antibiotic-laden spacer. At a minimum 24-month and average 35-month (range, 24 to 51 months) follow-up, seven knees were reinfected for a success rate of 88%. Four of these recurrent infections were caused by a different organism than that identified during the first two-stage treatment. One spacer broke between stages, but no additional bone loss was noted, and it did not require any specific treatment. Range of motion improved an average of 11° between the predebridement examination and final follow-up.⁸¹

### The Hip

The femoral stem and head molds for the hip are, like the knee molds, prepared separately. Cement is injected into the distal opening of the reinforced femoral stem mold; when the mold is completely filled, the opening is capped, excess cement is cleared, and it is submerged into a warm saline bath to facilitate cement curing. The reinforced femoral head mold is then filled with cement, capped, and submerged in the saline bath. After the cement has cured, the silicone molds are removed.

After all components and cement are removed, using care to ensure minimal bone loss, the wound is copiously and thoroughly irrigated with several liters of pulsatile lavage. The stem is then inserted and impacted into the femoral canal in a press-fit fashion. A large head and modular neck trial are then placed,
the hip is reduced, and stability and leg length are assessed. A corresponding metallic neck-length adaptor is inserted into the molded, cement-encapsulated femoral head, and the construct gently is impacted onto the femoral stem. The hip is reduced and closed in standard fashion.

Between 1996 and 2009, this chapter’s authors retrospectively reviewed 205 consecutive infected hips treated with two-stage exchange. Thirteen patients were lost to follow-up. In the remaining patients, the average follow-up was 53 months (range, 24 to 180 months). Fourteen patients (7%) died before the second-stage procedure; and two more were deemed too ill for the second-stage procedure. Of the 189 hips that underwent a second-stage exchange, 83% (157 hips) achieved infection control. The success rate dropped to only 76% when mortality associated with the two procedures and failure from recurrent infection were included.

Both static and articulating spacers are effective for eradicating infection. Articulating spacers are beneficial because they prevent soft-tissue contracture, promote range of motion, and facilitate antibiotic delivery. The success rate of two-stage treatment of PJI with antibiotic spacers is between 76% and 88% at a minimum 24-month follow-up.

**Summary**

PJI is a devastating complication of TJA that is challenging to diagnose and treat. Rigorous attention to preventive measures and optimization of a patient’s status before surgery can reduce the risk of infection. Persistent pain, early loosening, or radiographic signs of osteolysis around the implant should raise the suspicion of subtle infection, even in the absence of other manifestations. If PJI is suspected, a thorough workup, including an erythrocyte sedimentation rate and C-reactive protein level, followed by aspiration of the joint for assessment of the synovial fluid WBC count, differential, and cultures, is routine. Treatment should be tailored to each patient depending on comorbidities, functional status, the timing of the infection, and the virulence of the pathogen. Chronic infections require prosthesis removal, meticulous débridement, and reimplantation in one or two stages. With appropriate treatment, good clinical outcomes can be expected, with infection eradication rates that reach 90%.

**References**

14. Marchant MH Jr, Viens NA, Cook C, Vail TP, Bolognesi MP: The impact of glycemic control and diabetes mellitus...


