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on

Periprosthetic Infection in a Nutshell

Total joint arthroplasty (TJA) is an effective means of improving function and decreasing morbidity in patients with degenerative arthritis. However, deep periprosthetic infection (PPI) remains one of the major complications of TJA,[1] even though incidence has dropped significantly, from 10% during the early era of joint replacement[2] to the current rate of approximately 1%[3,4] after primary TJA and up to 7% after revision surgery.[5,6] This decrease occurred because of the introduction of laminar flow and body exhaust systems and, more important, the administration of prophylactic antibiotics within 30 to 60 minutes of incision.[7]

Although the incidence of PPI appears small, there are massive economic and psychological burdens associated with this complication given the large number of joint replacements being performed.[8] Further, the extension of indications to perform TJA in patients with medical comorbidities and immunocompromised status is likely to lead to an increase in PPI incidence. Many challenges are associated with this infection. The major challenge is to correctly diagnose PPI before or during surgery and to implement effective treatment regimens capable of eradicating the inciting organism.

"...the extension of indications to... patients with medical comorbidities...is likely to lead to an increase in PPI incidence."

Classification

Patients with infected arthroplasties may present at various times after surgery and have differing symptoms. The type of PPI and time of presentation affect treatment and prognosis.[9,10] Acute postoperative infections are thought to result from the direct seeding of the organism from the operative field, overlying skin, or postoperative drainage.[11] Patients present within 4 to 6 weeks after surgery with acute onset of pain, local signs of infection (erythema, cellulitis, drainage), and/or systemic toxicity (fever, chills, night sweats). However, late chronic infections are more commonly encountered and usually develop after the 4- to 6-week threshold,[3] which gives adequate time for the inciting organism to proliferate and induce indolent symptoms. The third group is the acute hematogenous infections that result in seeding of the implant by an organism found at a remote site.[12] Patients often report a history of recent dental, genitourinary, or gastrointestinal procedures.[7]

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Preoperative Workup

History and Physical Examination

A thorough clinical evaluation, including detailed history taking, must be performed before progressing with the diagnostic workup. Presence of a draining sinus tract, fever, chills, and/or a history of persistent postoperative drainage with concomitant painful range of motion can be used to accurately diagnose infection in 25% of cases.[13] Therefore, a rigorous algorithm consisting of additional preoperative and intraoperative tests must be performed for these patients either to rule out or confirm the presence of PPI.[14]

Serologic Tests

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are traditional serologic markers used as part of the diagnostic workup in patients with a possibly infected TJA. An ESR arbitrary cutoff of 30 mm/hr has often been used to denote an abnormal finding indicative of possible PPI.[15] CRP is an acute-phase reactant; plasma levels in healthy people are present in trace amounts undetected by standard laboratory techniques and are often reported as less than 0.5 mg/L.

Many conditions, including inflammatory arthropathies, metastatic disease, and chronic conditions such as renal failure, can lead to elevated ESR.[16] CRP is also nonspecific and can be elevated in several infective and traumatic conditions, including surgery,[17] and in inflammatory diseases, especially rheumatoid arthritis.

After TJA, CRP peaks at 48 hours postoperatively[18] and then returns to normal within 3 weeks.[19,20] ESR lags behind CRP, peaks during postoperative days 5 to 7, and takes 6 weeks[19,21] to 3 months[22] to return to baseline values.

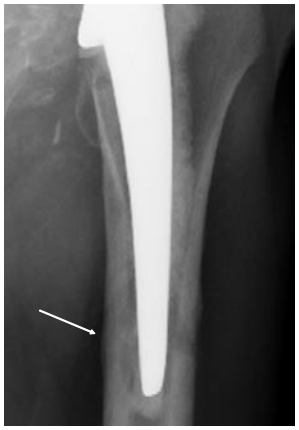

Figure 1. Plain x-rays of an infected total hip arthroplasty show changes specific for periprosthetic infection, including areas of focal osteolysis and periosteal reaction.

Therefore, CRP can detect infection in a joint arthroplasty sooner than ESR can, and earlier detection allows for earlier treatment. In the absence of the confounding factors listed earlier, ESR elevations that persist for more than 3 months after surgery and CRP elevations that persist for more than 3 weeks are cause for alarm about possible PPI.

In a recent retrospective study[15] that included patients with inflammatory disorders, results were similar using ESR of more than 30 mm/hr (sensitivity, 63%; specificity, 55%) and CRP of more than 1 mg/dL (sensitivity, 60%; specificity, 63%) to diagnose PPI in revision total knee arthroplasty (TKA). In an older, prospective study of revision total hip arthroplasty (THA) that excluded patients with inflammatory arthropathy, Spangehl and colleagues[23] concluded that ESR of more than 30 mm/h had sensitivity of 82% and specificity of 85% in determining infection. Compared with ESR, however, CRP of more than 1 mg/dL was a better indicator of infection (sensitivity, 96%; specificity, 92%). Although ESR and CRP are not diagnostic of infection when used individually, Spangehl and colleagues concluded that, when both ESR and CRP are below their respective cutoff values, then PPI can be reliably excluded from the differential.

Another serologic test that has shown promising results is interleukin 6 (IL-6), a cytokine that is produced by monocytes and macrophages and induces the production of acute-phase proteins, including CRP.[24] IL-6 levels peak during the first 12 hours after surgery and return to preoperative baseline within 3 days.[25] Therefore, serum IL-6 levels can be used to detect early postoperative infections and to monitor treatment response, which is not possible with the other commonly used serologic markers. Di Cesare and colleagues[26] showed that a cutoff of 12 pg/mL had adequately high sensitivity (100%), specificity (95%), positive predictive value (PPV, 89%), and negative predictive value (NPV, 100%) to diagnose PPI.

Joint Fluid Analysis

Aspirated joint fluid can be analyzed for cell counts and differentials. Although it is generally accepted that aspirate of a nonreplaced joint with a white blood cell (WBC) count of 50,000 cells/μL or more and a polymorphonuclear neutrophil percentage (PMN%) of 75% or more is highly suggestive of infection,[27] these values are not applicable to PPI. In a retrospective study of 440 revision TKAs, investigators identified 86 patients with possible PPI and determined that cutoffs of 2500 cells/mL and 60% PMN yielded sensitivity of 98% and specificity of 95% for the diagnosis of PPI.[28]

Receiver operating curves were first used by Trampuz and colleagues[29] in a prospective study of 133 TKAs, of which 34 were revised for PPI. The optimal cutoffs for fluid cell count (1700 cells/μL) and PMN% (65%) were defined, and the areas under the curve were compared. PMN% was a significantly better diagnostic modality than absolute leukocyte count (area under the curve, 0.997 vs 0.96; $P = .02$) and had both higher PPV (94% vs 73%) and higher NPV (99% vs 98%). In a recent study of 168 TJAs, Parvizi and colleagues,[14] using receiver operating curves, found similar cutoffs for fluid WBC count (1760 cells/μL) and PMN% (73%). The fluid cell count had slightly higher PPV compared with PMN% (99% vs 96%) and slightly lower NPV (88% vs 91%).

The cutoffs used for fluid cell count and differential in native joints to determine infection are too high and have no clinical application in TJA.[14] From a practical standpoint, leukocyte count of more than 2000 cells/μL and PMN% of more than 70% can be used to assess for infection in patients with artificial knee or hip joints.

Joint Fluid Culture

Aspirated fluid can be cultured for aerobic and anaerobic organisms. As demonstrated,[30] the PPV of culture fluid can be enhanced by using the test to confirm infection rather than to randomly screen patients. Patients with high clinical suspicion of PPI and negative aspiration culture should be reaspirated, as the sensitivity of the test is increased by repeating the procedure.[30]

Knowledge of the antibiotics sensitivities and resistance profiles of the culprit organism can facilitate preoperative administration of suitable treatments and allow efficacious antibiotics to be combined with cement. It is generally accepted practice to withhold all oral or intravenous (IV) antibiotics during the 2 weeks before aspiration to maximize culture yield.[30]

X-Rays

Plain x-rays can disclose important information about the mode of TJA failure (Figure 1). Certain changes, such as focal areas of osteolysis, osteopenia, and endosteal and periosteal reactions, are consistent with PPI,[31] and early implant loosening points to the possibility of an underlying dormant infection.[32] Although these changes can be used to determine PPI, they seldom manifest in infected joint arthroplasties,[33] and therefore the role of x-rays is in ruling out other aseptic etiologies.

Radionuclide Modalities

The technetium-Tc99m (^{99}Tc) isotope bone scan, which detects areas of increased metabolic activity is often used

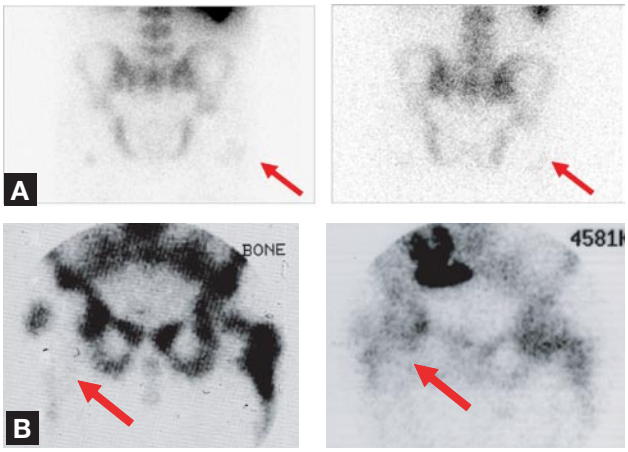

Figure 2. **(A) Uptake of both technetium (left) and indium-111 labels (right) in concordant areas around the hip implant indicate an aseptic etiology. (B) There is lack of uptake of technetium (left) and increased uptake of indium-111 labels (right).**

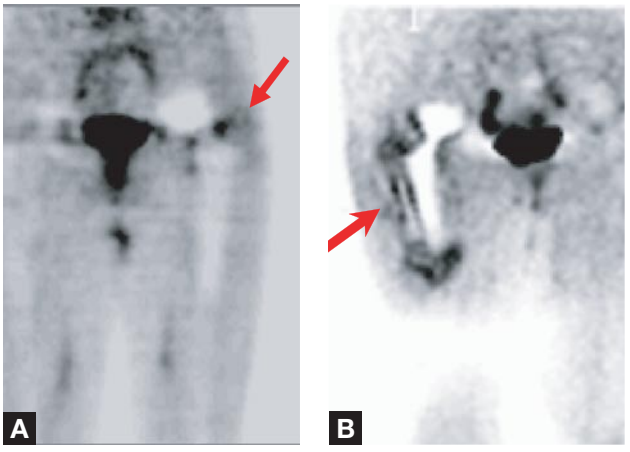

Figure 3. **(A) Uptake around proximal portion of the total hip arthroplasty indicates aseptic loosening. (B) Involvement of distal aspect of the stem is specific for periprosthetic infection.**

by many surgeons as part of the initial workup for PPI. This modality has been reported to have high NPV[34] and poor specificity (because of the high rate of false-positives), which allow it an important role in screening and ruling out infection. Indium-111, an isotope used to label leukocytes, is another important test that has produced slightly higher sensitivity (77%) and NPV (95%) compared with bone scan.[35]

Bone scan and indium-111 have been combined to reduce false-positive cases and improve specificity. The technetium scan is injected into the patient and accumulates in areas of high metabolic activity, including bone turnover, and in areas of increased blood flow.[36] Leukocytes are then obtained from the patient, labeled with indium-111, and reinjected to delineate areas of inflammation. Increased uptake of both the technetium and the indium-111 labels indicates that aseptic changes are occurring near the TJA, whereas lack of congruence in spatial distribution (ie, increased uptake with indium-111 but no uptake with technetium) indicates infection (Figures 2A, 2B).[37]

Some centers are implementing fluorodeoxyglucose positron emission tomography (FDG-PET) as part of the preoperative evaluation for PPI (Figures 3A, 3B). This test detects increased glucose uptake by macrophages and neutrophils, especially in areas of inflammation and infection.[14] Love and colleagues[37] noted that combined technetium/indium-111 scans had higher specificity compared with FDG-PET scans, but other centers have reported superior results for PET scans in terms of sensitivity and specificity.[35,38] In a recent prospective study, Pill and colleagues[39] compared FDG-PET with combined technetium/indium-111 in 89 patients with 92 painful THAs, of which 21 cases had confirmed PPI. The authors concluded that FDG-PET has far higher sensitivity (95% vs 50%) compared with technetium/indium-111 and is a useful diagnostic tool, with promising ability in differentiating PPI from aseptic etiologies. However, false-positives still plague FDG-PET, especially in areas of particle-induced inflammation where macrophages accumulate.[40] Although FDG-PET has shown adequate sensitivity (90%) and specificity (89%) for diagnosing infection around a THA, its ability to confirm PPI in TKA (specificity, 72%) is far inferior because of the large number of false-positives.[41]

Intraoperative Diagnostics

Many thorough preoperative workups fail to reach a conclusive diagnosis of infection. Although isolation of an organism from intraoperative culture remains the gold standard for diagnosing infection,[11,23] one drawback is that the PPI diagnosis is made 3 to 4 days after surgery. However, surgeons can use a multitude of other intraoperative diagnostic modalities, including frozen section of periprosthetic tissue and gram stain, to either confirm or refute the PPI diagnosis.

Frozen Section

Frozen section of periprosthetic tissue is a useful intraoperative test for PPI diagnosis (Figures 4A, 4B). Acute inflammation, as indicated by more than 5 neutrophils per high-power field, may implicate PPI.[28] However, the histologic criteria and neutrophil cutoff values used to diagnose infection have varied among clinicians.[42-44]

With 2 early studies, Mirra and colleagues[44,45] began the clarification of the histologic criteria used to diagnose infection. They documented the presence of more than 5 neutrophils per high-power field in 5 separate high-power fields in samples taken from sites of acute inflammation with confirmed positive cultures. In both original articles, however, histologic analysis was performed under a magnification of x500, which may influence results when applying the criteria to the more commonly used x400 microscope. Lonner and colleagues[43] attempted to validate these criteria in a prospective study of 175 consecutive patients. They reported sensitivity and specificity of 84% and 96%, respectively, when implementing the aforementioned recommended criteria using x400 magnifica-

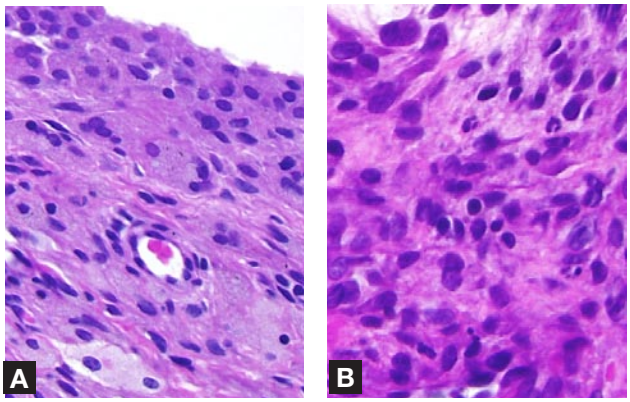

Figure 4. **(A)** Macrophages and giant cells containing particle debris are found in tissues retrieved around aseptically loose implants. Note absence of neutrophils. **(B)** Presence of numerous neutrophils indicates acute inflammation.

tion. However, specificity improved to 98% when using the more stringent criteria of more than 10 neutrophils per high-power field in more than 5 high-power fields.

In another prospective study, of 106 TKAs and revision THAs, Athanasou and colleagues[46] compared histologic criteria (>5 inflammatory cells including neutrophils, lymphocytes, and plasma cells per high-power field in >10 high-power fields) to the gold standard of intraoperative culture, which yielded adequate sensitivity (90%) and specificity (96%). On the other hand, in a large retrospective study of 617 revision TJAs, Pandey and colleagues[47] considered the presence of 1 inflammatory cell per high-power field in at least 10 fields to be consistent with infection. The histologic criteria that they used were in concordance with a clinical diagnosis of infection in 97.8% of the cases of septic failure.

Gram Stain

Gram stain of periprosthetic tissue samples has had poor results in various studies. Sensitivity has ranged from 15% to 30%, depending on the criteria used as a standard for PPI diagnosis,[14,23, 48] and therefore it cannot detect infection consistently. Although specificity and PPV, which have ranged from 98% to 100%,[14,23] can confirm PPI when a smear is found to be positive, gram stain remains an ineffective tool for detecting PPI.

Intraoperative Culture

Isolation of an organism from intraoperative fluid or periprosthetic tissue—the current gold standard—has some shortcomings. False-positive (ie, contaminant) or false-negative intraoperative cultures can occur, and these limit the absolute accuracy of the test.[14,32] However, the test has high specificity (97%-100%) and high PPV (98%-100%) in confirming PPI.[14,47,48] Although agreement of culture and PPI diagnosis is excellent, an organism may not be isolated in 10% to 12% of cases of confirmed infection.[47]

The exact number of samples that must be obtained to confirm PPI, while adjusting for false-positives caused by contamination, has been studied extensively. Atkins and colleagues[48] constructed a mathematical model based on multiple criteria for infection. This model proposes taking 5 or more samples for accurate diagnosis of PPI. However, for practical purposes, including cost-effectiveness, the authors indicated that use of 3 samples or more can have similar sensitivity (65%) and specificity (99.6%). Similarly, Pandey and colleagues[47] reported that infection can be confirmed in 89% of cases when an organism is isolated from 3 specimens or more.

Molecular Techniques

Polymerase chain reaction (PCR), which relies on amplification of bacterial DNA, has been used for PPI diagnosis.[49,50] The major problem with PCR is its excessively high rate of false-positives. Refinements (eg, use of bacteria-specific primers and sequencing) may improve the sensitivity of this test. Although PCR can detect a significant number of infected joint arthroplasties, its diagnostic value is depreciated by its high false-negative rate.[51] However, a recent study applied PCR technology to dry reagent dipsticks, which can detect different pathogens within a few hours.[52]

During recent years, other molecular techniques, such as microarray, have been tested. Deirmengian and colleagues[53] demonstrated that WBCs in the synovial fluid of patients with PPI express a "signature" gene. Among the genes found to be differentially expressed were interleukin 1, chemokine ligands CCL3 and CCL4, and intercellular adhesion ligands ICAM1.

Treatment Modalities

Eradicating infection and maintaining a functional prosthesis and extremity are the primary goals of treatment. Multiple factors, including infection type and patient comorbidity, must be considered when selecting treatment for PPI. Indications for the various treatment techniques vary, and therefore treatment must be tailored to the many confounding factors to produce the most satisfactory results.

Two-Stage Resection Arthroplasty With Delayed Reimplantation

In the United States, the treatment of choice is 2-stage exchange arthroplasty, which involves resection arthroplasty and insertion of an antibiotic-impregnated cement spacer supplemented with 6 weeks of IV antibiotics followed by reimplantation arthroplasty at an appropriate time. Even though a delay of 6 to 8 weeks is used as the threshold for reimplantation, the optimal point for spacer removal remains debatable.[54] After treatment, resolution of infection is confirmed by clinical assessment, serologic tests (ESR, CRP), and, in some cases, joint aspiration.[55]

Reimplantation with cementless components has shown promising outcomes and infection-free survivorship. Hart and Jones[56] recently successfully eradicated infection in 88% of infected TKAs by a mean of 4 years after surgery. Similarly, a review of 29 chronically infected TKAs revealed an 83%

treatment success rate.[57] Resection arthroplasty with delayed reimplantation of 44 infected THAs successfully eradicated infection in 98% of cases at a minimum follow-up of 2 years.[58] However, with evolving bacterial resistance to newer generation antibiotics, existing treatment protocols for virulent and resistant organisms have been questioned. In a review of 46 TJAs with deep PPI, Volin and colleagues[59] found similar reinfection rates among methicillin-resistant and non–methicillin-resistant staphylococci. However, TKAs infected with resistant organisms have significantly worse survivorship compared with TKAs infected with less virulent bacteria.[60]

Some investigators have advocated using preformed articulating cement spacers to allow for moderate joint motion and ease of subsequent reimplantation.[28,61] Emerson and colleagues,[62] who compared articulating cement spacers and static block spacers in 46 infected TKAs, found similar reinfection rates at 3-year follow-up. Use of articulating spacers (vs static block spacers) allowed patients an additional 16° of range of motion after reimplantation. Another investigator devised articulating spacers made of resected components enveloped by antibiotics-impregnated cement.[63] These spacers proved to be as efficacious as others[61] in eradicating infection but had the advantages of improved function and decreased pain after reimplantation.

Single-Stage Exchange Arthroplasty

Single-stage exchange arthroplasty entails resection of components, thorough débridement, and same-stage reimplantation followed by 6 weeks of IV antibiotics.[64] The rate of recurrent infection has been reasonably similar to that reported in the literature for 2-stage resection arthroplasty.[64] However, some studies comparing the survivorship of the 2 procedures have shown significantly better results and lower failure rates for 2-stage revision arthroplasty.[65,66]

Irrigation and Débridement

An infected joint arthroplasty can be successfully managed with débridement and component retention in a select group of cases.[67] This procedure is recommended for sick, elderly patients who have a well-fixed prosthesis and for whom 2-stage exchange arthroplasty is not feasible.[68-70] Success with this intervention has varied according to health status, type of infecting organism, and duration of follow-up.[71-73] Recently, Marculescu and colleagues[74] reported a 40% failure rate at 2-year follow-up of 99 infected TJAs treated with débridement and retention of components. Several risk factors for failure have been identified: presence of sinus tract, old age, and prolonged time between symptom onset and treatment,[71,74,75] among others. Multiple attempts at débridement and retention of components of infected TKAs can decrease the overall failure rate and preserve components.[76]

Chronic Antibiotics Suppression

Serious comorbidities, poor bone stock, and other situations may preclude use of 2-stage resection arthroplasty, in which case long-term suppressive antibiotics treatment becomes a viable option.[7,57,77] Rao and colleagues[77] reported favorable results in 86% of 36 infected TJAs at a mean follow-up of 5 years. However, 8% of these patients developed complications (most notably, diarrhea) related to chronic use of antibiotics. Other investigators were able to salvage the prosthesis in a similar percentage of patients (63%-83%) through use of long-term antibiotics.[78,79] However, another study found very poor short-term survivorship (23%) of 13 infected THAs at a mean follow-up of 3 years.[80]

Authors' Disclosure Statement

The authors report no actual or potential conflict of interest in relation to this article.

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This paper will be judged for the Resident Writer's Award.