Diagnosis and Management of Infected Total Knee Arthroplasty[§]

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Abstract: Infection following total knee arthroplasty can be difficult to diagnose and treat. Diagnosis is multifactorial and relies on the clinical picture, radiographs, bone scans, serologic tests, synovial fluid examination, intra-operative culture and histology. Newer techniques including ultrasonication and molecular diagnostic studies are playing an expanded role. Two-stage exchange arthroplasty with antibiotic cement and 4-6 weeks of intravenous antibiotic treatment remains the most successful intervention for infection eradication. There is no consensus on the optimum type of interval antibiotic cement spacer. There is a limited role for irrigation and debridement, direct one-stage exchange, chronic antibiotic suppression and salvage procedures like arthrodesis and amputation. We examine the literature on each of the diagnostic modalities and treatment options in brief and explain their current significance.

Total knee arthroplasty (TKA) is a common surgery for end-stage knee arthritis that is associated with significant improvements in pain, function and quality of life. Outcomes following TKA are excellent in the majority of the patients. Perhaps the most challenging complication following TKA is periprosthetic infection (PPI). PPI occurs in 1-2 % of primary TKAs and 3-5 % of revision TKAs [1]. It is also possible that certain aseptic TKA failures may actually not be truly aseptic but secondary to undiagnosed periprosthetic infections. An improvement in our ability to diagnose TKA infections with more sensitive diagnostic algorithms and tests could reveal more PPI than currently estimated [2]. In this paper, we review the current literature regarding diagnosis and management of PPI in TKA.

DEFINITION, CLASSIFICATION AND PATHO-PHYSIOLOGY

There is currently no clear consensus on the definition of PPI in TKA. A commonly accepted definition was proposed by Ghanem *et al.* as meeting one of the following three criteria:

1. abscess or sinus tract communicating with the joint space;

2. a positive pre-op culture of aspirate on solid medium ;

3. ≥2 positive intra-op culture of same organism, or one positive culture on solid medium <u>plus</u> gross intracapsular purulence <u>or</u> abnormal histological findings (>5 PMNs/HPF) [3].

Based on the timing of the TKA infection, Cui *et al.* [4] classified TKA infections into four types: (1) acute post-operative (≤4 weeks post-op); (2) late chronic (indolent infection >4 weeks post-operative); (3) acute hematogenous (acute onset at the site of a previously well-functioning prosthetic joint); and (4) positive intra-operative culture (clinically unapparent infection with two or more positive intra-operative cultures).

TKA infections, like other PPI, are mediated by the formation of biofilms on the implant surfaces. Biofilm is an aggregate of microorganisms in which cells are adherent to each other and/or to a surface. Bacteria secrete extracellular polymeric substance (EPS) which forms the basic architecture of biofilms [5]. These adherent bacterial cells are frequently embedded in small clusters within the EPS matrix, often forming favorable environments which can be very heterogeneous in the same biofilm. EPS isolates bacteria from the surrounding environment and help bacteria survive in the biofilm. EPS also protects bacteria from host defenses resulting in an ineffective inflammatory response, which in turn causes more damage to the host and aids the growth of bacteria by providing additional nutrients from damaged cells [6, 7]. Antibiotics are ineffective in the non-physiologic environment of the biofilm due to poor penetration. The biofilm itself is responsible for many of the challenges underlying diagnosis & management of PPI in TKA [8, 9].

CLINICAL FEATURES OF INFECTED TKA

Infected TKA can present acutely with obvious signs and symptoms of joint infection or more insidiously, especially beyond the early post-operative period. The clinical signs and symptoms of infected TKA include persistent pain, swelling, erythema, local warmth or drainage after TKA.

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Examination findings include tenderness and limitation of range of motion and/or painful range of motion of the joint that is new or disproportionate to the expected recovery from the surgery. However, PPI in TKA can present with few, if any, of these symptoms and signs.

DIAGNOSIS OF INFECTED TKA

The presentation of PPI in TKA can be varied and the diagnosis challenging. Because there is no single test that can diagnose PPI in TKA, the diagnosis is typically based on a combination of clinical, serologic, imaging and laboratory findings.

SEROLOGICAL TESTS

The peripheral leukocyte count is frequently normal in TKA infections and affords little diagnostic help. Erythrocyte sedimentation rate (ESR) is a nonspecific indicator of inflammation that peaks 5-7 days after TKA surgery and usually returns to baseline in 3 months to 1 year. Continued elevation of ESR after TKA is suggestive of infection. With an abnormal level defined as >30 mm/hr 3 months to 1 year after TKA, ESR has a sensitivity of 82% and specificity of 87% in diagnosing TKA infections [10]. Based on receiver operating curves, a cutoff level of 22.5 mm/hr 3 months to 1 year after TKA would have sensitivity of 93% and specificity of 83%. However, ESR is elevated in both inflammatory conditions and infections in locations other than infected TKA (10), and thus specificity is low.

C - reactive protein (CRP) is an acute phase reactant produced by hepatocytes in response to infection, inflammation or acute injury. CRP levels peak 2-3 days after surgery and return to baseline in 14-21 days. With an abnormal level defined as >10 pg/mL 14-21 days after TKA, CRP has sensitivity of 93% and specificity 83% [10]. Based on receiver operating curves, a cutoff level of 13.5 pg/ml 14-21 days after TKA, would have sensitivity of 91% and specificity of 86% [10].

A new investigational test used in the diagnosis of PPI in TKA is serum interleukin-6 (IL-6) level. IL-6 is cytokine that stimulates the liver cells to produce acute phase reactants like CRP. Serum IL-6 levels can be measured by a simple ELISA test. IL-6 levels peak 6-12 hrs after surgery and return to baseline in 48-72 hrs. With a cut-off defined as <10 pg/mL, IL-6 level has a sensitivity of 100% and a specificity of 95% in diagnosing TKA infections [11]. However, more studies are needed to examine its clinical utility. Other conditions causing elevated serum IL-6 are chronic inflammatory diseases like rheumatoid arthritis, previous antibiotic treatment prior to surgery, multiple sclerosis, Pagets disease of bone and acquired immune deficiency syndrome. IL-6 may prove to be useful in early post-operative diagnosis of infection and pre-operative diagnosis prior to revision total knee arthroplasty [11].

IMAGING MODALITIES

Several imaging modalities are available to assist surgeons in diagnosing PPI in TKA. Radiographs showing periosteal new bone formation, scattered foci of osteolysis and subchondral bone resorption are highly suggestive of infection, but are typically late findings. Periprosthetic radiolucency may be unrelated to a septic process and serial radiographs help rule out other conditions like wear, osteolysis or fracture.

Nuclear medicine tests may be helpful in the diagnosis of PPI in TKA, because their results are not impacted by the presence of metallic implants. Triple-phase technetium-99 bone scan (TPBS) is a simple, widely available test which is quite sensitive in detecting bone remodeling changes around TKA components; however, it cannot distinguish between aseptic loosening and TKA infection [12]. TPBS does have a high negative predictive value, however, making it a useful initial screening test [13, 14].

WBC imaging with indium-111 is more sensitive than TPBS, but has low specificity. Combining an indium[111] WBC scan with a technetium 99m bone scan improves the accuracy for detecting deep infection up to 95% [15].

Fluro-deoxyglucose positron emission tomography (FDG-PET) scans have been recently evaluated for diagnosis of PPI in TKA. Inflammatory cells express more glucose transporters, resulting in intracellular accumulation of deoxyglucose which cannot be metabolized by the cell and can be identified by PET imaging. One study found 91% sensitivity and 72% specificity for diagnosis of TKA infections [16]. The advantages of a PET scan are that only one injection is required and the results are available within 4 hrs. However, it is not widely available, is expensive and can produce false positives secondary to uptake of FDG in aseptic inflammation around implants [17].

In their meta-analysis, Reinartz *et al.* reported that the accuracy of the TPBS, WBC imaging, and FDG-PET scan was 81%, 84% and 83% respectively [17].

JOINT FLUID AND TISSUE ANALYSIS

Knee aspiration is a simple test recommended in every case of suspected PPI in TKA. The knee aspirate should be sent for cell count and differential, culture and crystal analysis. Use of antibiotics prior to aspiration can lead to false-negative results. In the setting of a 2-stage exchange arthroplasty, studies have shown that delaying knee aspiration at least 4 weeks from the discontinuation of antibiotic therapy can significantly lower the false-negative rate [18, 19]. The synovial fluid (SF) leukocyte count and differential are two helpful parameters to examine. With an abnormal value defined as >1100 WBC/ml, the SF leukocyte count has a 91% sensitivity and 88% specificity in diagnosing PPI in TKA [3]. With an abnormal value defined as >64%, SF neutrophil percentage is 95% sensitive and 94% specific in diagnosing TKA infection [3]. If both SF leukocyte count and neutrophil percentage, are below their cutoff values, then infection is highly unlikely (NPV= 98.2%). If both tests are above their cutoff values, then the likelihood of infection is 98.6 % (PPV= 98.6%) [3]. When SF neutrophil percentage and the C-reactive protein level are less than the cutoff values of 64% and 10 mg/L, respectively, the presence of periprosthetic infection is very unlikely [3].

Intra-operative frozen section looking for neutrophils in tissue obtained from the joint capsule or periprosthetic membrane has been used to help intra-operative decision making. The exact histologic critera used for diagnosis of infection are not yet uniform [2]. However, one commonly

quoted study [20] found that with abnormal frozen section defined as >5 neutrophils /5 separate high power fields (500x), excluding surface fibrin and inflammatory exudates, the sensitivity is 25% and specificity is 95%. Frozen section is less sensitive at the time of reoperation than in the setting of primary arthroplasty [20].

Gram staining of intra-operative specimens is not very helpful. Morgan *et al*. [21] found that intra-operative Gram staining has poor sensitivity (27%) and a poor negative predictive value, and its results did not alter the treatment of any patient undergoing revision TKA because of a suspected infection.

Intra-operative cultures have traditionally been considered the gold standard for PPI diagnosis. However, nearly 10 % of infections may be culture-negative. Conventional culture results may be delayed for 2-5 days and contamination of samples causes false positive results [2].

It is recommended that pre-operative antibiotics be withheld until cultures are obtained, multiple cultures including anaerobic cultures be obtained from different sites during surgery, fluid be injected directly into culture tubes instead of using swabs [22], strict aseptic protocol be maintained, and only > 2 positive cultures of same organism be regarded as a positive result [2].

MOLECULAR DIAGNOSTIC TESTS

Molecular diagnostic techniques are new tools in the armamentarium for diagnosis of PPI. Polymerase chain reaction (PCR) amplifies strains of bacterial DNA to allow detection of infectious bacteria. PCR can detect non-viable bacteria that do not grow on culture as well as bacteria lysed by ultrasonication, with results within 12-13 hrs. Results of the PCR are unaffected by the administration of antibiotics. However, PCR is exquisitely sensitive; co-amplification of contaminating DNA causes false positives mandating strict aseptic measures. The specific nature of infection can only be identified by comparing DNA sequences with global sequence databases and PCR results are not dependable in polymicrobial infections [23, 24].

FISH (Fluorescent In Situ Hybridization) utilizes fluorescent- labeled oligonucleotide probes that hybridize to their intracellular targets permitting single-cell identification and quantification by either epifluorescence microscopy or flow cytometry. Complex cell envelopes of some bacteria may inhibit penetration of the probes. Autofluoresecence of some organisms make interpretation difficult [24].

Immunofluorescence microscopy can give results within 2-3 hrs [24]. The technique is relatively inexpensive (excluding the microscope itself) and does not require strict aseptic protocol. Immunofluorescence microscopy can distinguish between biofilm organisms (large aggregates) and contaminants (single dispersed cells/ small aggregates) by direct visualization.

Biofilm cells of S. aureus and S. epidermidis produce a surface epitope (SSPA). SSPA-ELISA test can detect antibodies to this epitope. This is a very sensitive and specific test in the detection of staphylococcal biofilms (p < 0.001) [25].

Biofilms are known to be tenacious and difficult to dislodge by scraping. Ultrasonication uses ultrasound energy to mechanically disrupt biofilm on retrieved implants in revision surgery. This increases the number of bacteria isolated on culture or other techniques enabling the detection of bacteria that would have been missed by conventional tissue culture [5, 26]. Sonicate cultures have 78.5% sensitivity and 98.8% specificity as compared to 60.8% and 99.2% for tissue culture. Improvement in sensitivity is particularly notable in patients who have been on antibiotics within 2 weeks of surgery [5, 26].

Ultrasonication for a longer time (30 min) can lyse the bacteria and make them non-viable on cultures. PCR can be used to detect these lysed bacteria thereby further improving microbiological diagnosis from retrieved implants [5, 26].

MANAGEMENT OF INFECTED TOTAL KNEE ARTHROPLASTY

Treatment of infected TKA is complex, expensive, requires more surgical and inpatient time than non-infected revision TKA, and is more prone to failure. The goal of treatment is eradication of the infection and maintenance of a pain-free, functional joint [27].

Treatment options include irrigation and debridement with component retention (with or without polyethylene exchange), one-stage or two-stage exchange, antibiotic suppression, resection arthroplasty and rarely arthrodesis or amputation.

Irrigation and debridement with component retention (with or without polyethylene exchange), is suitable for selective cases where infection occurs within the first 4-6 weeks of primary TKA or in the setting of acute hematogenous Gram positive infection with stable implants [28, 29]. Polyethylene liner exchange is preferred as it allows better debridement of the posterior synovium and eliminates biofilm on the polyethylene [30]. Success of open debridement with polyethylene exchange is limited (23 to 28% success rate) by persistence of organisms on retained implants, cement and dead bone [31]. Factors associated with success include early debridement, absence of sinus formation, multiple debridements rather than a single debridement, gram positive infection, and use of 4-6 weeks of sensitive systemic antibiotics [32-34].

Two-stage exchange arthroplasty, first described by Insall, has been the most successful treatment alterantive for infected total knee arthroplaty (91% success rate for eradicating infection) [35]. The first stage involves removal of all total knee components and cement, thorough debridement and irrigation followed by implantation of an antibiotic cement depot in the joint. The antibiotic cement depot releases antibiotics locally at high concentrations helping to eradicate the infection. This is supplemented by intravenous antibiotics per sensitivity for six to eight week period. If there are no clinical signs of infection and the sedimentation rate and CRP levels are declining, a decision for second stage reimplantation is made. A more extensile approach like quadriceps snip, VY-quadricepsplasty or tibial tubercle osteotomy may be necessary because of scarring between stages [36]. The second stage involves removal of the cement depot, thorough debridement and irrigation and

implantation of appropriate new total knee components with antibiotic-impregnated cement.

Use of antibiotic-impregnated cement has greatly improved the chances of success in treatment of infected arthroplasties [37]. Antibiotics suitable for this purpose should be heat- stable, broad-spectrum, bactericidal at low concentrations, at low risk of allergy /delayed hypersensitivity, and available in powder form with low serum binding, which facilitates release from the spacer at high concentrations for prolonged periods. Antibiotics in common usage for this purpose are gentamycin, vancomycin, tobramycin and cefuroxime.

Antibiotic elution from PMMA depends on the antibiotic dose, the combination of antibiotics used, and the type of cement [38]. The recommended doses of antibiotics are 2-5 times higher for therapeutic use than for prophylactic use [27]. Most antibiotics have a high initial release followed by a reduced, constant, elution over the next several days.

A higher dose of gentamicin or tobramycin will increase the amount of antibiotic initially released and prolong the duration of the bactericidal level of the antibiotic. However, higher doses of vancomycin may not increase the *in vivo* elution characteristics [39, 40]. Tobramycin may synergistically increase the release of vancomycin in the cement mix by "passive opportunism"- a phenomenon that one antibiotic dissolves, resulting in increased porosity, it allows increased elution of the other antibiotic [39]. Tobramycin elutes better from Palacos cement (Heraceus Medical, Hanau, Germany; marketed by Zimmer Inc., Warsaw, IN) than from Simplex cement (Stryker, Kalamazoo, MI). Premixed antibiotic cements have low dose of antibiotics [41]. Hand mixing without a vacuum results in increased porosity, which increases antibiotic elution.

There is an on-going controversy over the optimal type of antibiotic spacer to be used. Static spacers, first described by Cohen, [42] were historically preformed in the shape of a hockey puck that was inserted loosely in the joint space after the cement was polymerized. This technique was associated with spacer subluxation and secondary bone loss and erosion of quadriceps mechanism. This led to the development of the molded arthrodesis block. In this technique cement is placed in the knee joint in a doughy state so that it conforms to the shape of the bone ends and stabilizes the knee joint by interdigitation. Static spacers have infection eradication rates approximating 88% [43-47]. Static spacers restrict knee movement between stages, distract & preserve the joint space, provide stability to the limb and give rest to the infected joint. Problems with static spacers include contracture of the extensor mechanism, collateral ligament shortening, arthrofibrosis, tibial and femoral bone loss (incidence-60%) and potential difficulty with secondary exposure for reimplantation [45,48].

Articulating spacers maintain joint motion between stages and cause less periarticular scarring resulting in easier surgical exposure at reimplantation. They result in marginally better post-operative ROM and function as compared to static spacers, though statistical significance is not reached [49]. Infection eradication rates with articulating spacers approximate 92% [44, 45, 49-57].

Articulating spacers can be metal on polyethylene (new components or recycled components) or cement on cement. Cement on cement articulating spacers can be pre-formed or manufactured in the operating room with cement molds or can be hand-made. Articulating spacers reduce bone loss as compared to static spacers [45, 48]. Problems with articulating spacers include risk of cement fracture, spacer dislocation, and potential problems with wound healing [38].

Cement on cement spacers [45, 49-52] have more surface area for antibiotic elution, though these are expensive, take more OR time and are prone to cement fracture and formation of cement debris [49]. Preformed cement spacers (Interspace Knee, Exactech, Gainesville, F) deliver a lower dose of single antibiotic [36]. The prosthesis of antibiotic loaded acrylic cement (PROSTALAC) (Depuy, Warswaw, IN) includes a bicompartmental metal femoral component articulating with a polyethylene tibial component. This has a 91% infection eradication rate but has not yet been approved by the US Food and Drug administration [53, 55]. Metal on polyethylene spacers [44, 53-57] use a new or recycled femoral component and polyethylene insert for articulation. This provides an inexpensive articulation that can be custom fitted to each patient. However, there is a lower surface area for antibiotic elution as compared to cement on cement spacers

One-stage exchange involves explantation of all total knee components, thorough debridement, copious irrigation and reimplantation of new appropriate total knee components with antibiotic impregnated cement followed by 6-12 weeks of systemic antibiotic therapy. This is primarily indicated in high morbidity patients unsuitable for multiple operations who are infected with susceptible organisms. Advantages of one-stage exchange include abbreviated recovery and decreased cost and morbidity due to avoidance of a second operation. There are few studies published with this technique with an average success rate of 81% [58]. One of the studies with a higher (89%) success rate [59] found that factors associated with success are absence of sinus formation, Gram positive infection, use of antibiotic cement in reimplantation and 12 weeks of antibiotic therapy. Another online publication of 1,000 septic knee revisions at the Endo-Klinik in Hamburg over the past 25 years using the one-stage revision procedure, the success rate with the one-stage revision procedure was reported to be 75% (http://www.cementinguniversity.com/centres-of-excellence/endo-klinik/technique/therapy/).

Antibiotic suppression alone is considered only under special circumstances because the prognosis for infection eradication is poor with only 6% success rate [60]. It may be considered if the implant is stable, the microorganism has low virulence and is susceptible to oral antibiotics, and the patient has a high anesthesia risk [61, 62]. Long term antibiotic suppression has a risk of antibiotic related adverse effects and emergence of resistant bacteria [62].

Resection arthroplasty is suitable for low demand patients after failure of other treatments in patients with polyarticular rheumatoid arthritis. This eradicates infection at the cost of stability and function of the knee [63].

Arthrodesis is indicated for infected TKA with deficient extensor mechanism and in cases with highly resistant

organisms or salvage after failed treatments. Mabry [64] found that arthrodesis by intramedullary nailing has a union rate of 96% as compared to 67% with external fixation. However, the risk of recurrent infection associated with IM nailing is 8.3% as compared to 4.9 % with external fixation. Infection eradication rates with arthrodesis approach 94%, though the complication rate is also very high (40%) [64].

Above knee amputation is considered for life-threatening systemic sepsis or persistent local infection combined with massive bone loss and intractable pain [30]. The prognosis for amputation is poor as more than half of the patients become wheelchair-bound [65]. Fortunately, less than 5 % of patients with TKA infections need amputation [66]. Arthrodesis should be considered early in the treatment of persistent infection as multiple revision surgeries may ultimately require amputation [67].

CONCLUSIONS

Periprosthetic TKA infections remain difficult to diagnose and treat. Diagnosis is based on a combination of clinical findings, serologic tests, and imaging and laboratory findings. Knee aspiration for cell count and neutrophil differential can be very helpful. Ultrasonication of retrieved implants in combination with molecular diagnostic techniques is improving our ability to diagnose infections. Two stage exchange utilizing antibiotic cement has better success at infection eradication than direct exchange. Use of an articulating spacer preserves motion between stages and reduces scarring and bone loss, with potential improvements in ROM, function, and second-stage exposure. Two stage exchange with an articulating spacer is the most accepted treatment option.

GRANT SUPPORT

POTENTIAL FINANCIAL CONFLICT:

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