REVIEW ARTICLE

Periprosthetic Joint Infections: Current Concepts

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Editor KJO

Article Info

Keywords
periprosthetic joint infections
revision arthroplasty

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Source of funding
Nil

Conflict of interest
The author(s) declare that they have no conflicting interests.

Available online at
http://www.kjoonline.org/

Quick response code

Abstract

Periprosthetic joint infection(PJI) is a disaster, the most dreaded complication of any arthroplasty. Different series mention different rates of infection ranging from 1.6% to 7% across primary and revision TJA's. Single institutions with precise diagnostic criteria for PJI report lower incidences. As more shoulders and elbows are getting replaced, these have revealed infection rates with relative similarity to hips/knees. Cost implications apart, the impact on the quality of life of the patient is serious, with the conflict sometimes being deciding between aggressive attempts to achieve eradication versus conservatively keeping things quiescent.

Cite this paper as: Girish Gopinath. Periprosthetic Joint Infections: Current Concepts. *Kerala Journal of Orthopaedics* 2018;30(1–2):22–32.

Majority of PJIs occurring within one year of surgery are initiated through the introduction of microorganisms at the time of surgery. An important factor here is the lower inoculum needed to establish infection in the setting of a prosthesis. Animal models have shown that roughly 10^2 times lesser number of microbes can establish infection in the setting of a prosthesis than when there is no implant. The other mechanism of initiation is by contiguous spread from an adjacent site, either early on when the superficial planes are still healing, or later when the contiguous tissue planes are disrupted from trauma/surgery. The prosthesis also remains at risk of hematogenous seeding throughout the life of the arthroplasty.

The first step in pathogenesis of a PJI is bacterial adherence to implant surfaces. This happens in two phases, an initial non-specific reversible one driven by physical forces and chemical reactions, and a more specific irreversible one which involves specific enzymatic reactions and receptors.

The complex biofilm, which is an envelope of glycocalyx and other macromolecules, provides the invading bacteria an impregnable defence wall against antibiotics and macrophages. The formation of this biofilm is classically seen as a four-step process:

i. initial attachment of bacterial cells;
ii. cell aggregation in multiple layers;
iii. matrix elaboration and film maturation; and
iv. detachment of cells in a planktonic state to initiate the process elsewhere.

The biofilm may be monomicrobial or polymicrobial, and even a monomicrobial biofilm may consist of sub-populations of the same organism with different genotypic/phenotypic characteristics. They are therefore differentially hit by anti-microbial agents and this is significant not only in treatment but also in diagnosis of these PJIs. Biofilm explains how a normally harmless pathogen becomes troublesome in the setting of a prosthesis. Certain agents like rifampicin may be able to penetrate the biofilm.

Evidence also suggests that some organisms develop the ability for intracellular internalization and thus persist internally. This can also contribute to pathogenesis of PJI and resistance to treatment.

Microbiology

Majority of PJI's are caused by Gram-positive cocci (*Staphylococcus aureus* and coagulase-negative Staphylococcus), but Gram-negative bacteria and fungi may also be encountered. A good number of PJIs can be polymicrobial. There are differences in the relative frequencies of a causative organism between early and late infections, and also between different joints. For egs. S. aureus has a lesser frequency than coag-neg Staph in hip and shoulder infections compared to knees where the two are relatively equal in frequency. Anaerobic organisms are more frequent in the hip than in knee. Shoulder PJIs are much more commonly caused by *P. acnes* than PJIs of other joints.

A good number of patients, about 11–26% across series, are culture-negative PJIs. These patients have purulence, or positive histopathology, or communicating sinus tracts without any identifiable causative organism. This maybe due to prior antibiotic therapy, or due to an inability to identify the pathogen with currently available techniques. The median period of presentation of a culture-negative PJI is 31/2 years from index surgery, and the median duration of symptoms before diagnosis is usually around 100 days.

Classification

There are various classification schemes for PJIs. The first is based on the time to infection and includes early, delayed, and late onset. Early is less than three months from surgery, believed to be from intraoperative contamination by relatively virulent organisms. Delayed-onset PJI are those occurring after 3 months but before 12-24 months. These are caused by less virulent organisms and therefore do not present early within three months. Late-onset PJI are those occurring greater than 12-24 months after surgery. These are frequently hematogenous but may also be due to extremely indolent infection acquired at surgery.

Tsukuyama Classification

According to this, there are four categories. i. positive intra-op cultures in aseptic failures; ii. early post-op infection in the first month; iii. late post-op infection after the first month; and iv. acute haematogenous infection.

McPherson staging system:

This is similar to the Cierny-Mader system for osteomyelitis which incorporates patient's physiological status into the staging. Here, there are three grades which include I. early post-op, II. haematogenous and III. late chronic. The host status is graded as A (uncompromised), B (compromised), or C (significant compromise), based on several factors, including the presence of neutropenia, low CD4 T-cell count, or age of >80 years. Finally, the local extremity is graded as 1 (uncompromised), 2 (compromised), or 3 (significantly compromised), based on the presence of local chronic active infection, soft tissue loss, or the presence of a fistula/subcutaneous abscess. This system allows more individualized treatment decisions and prognostication, even though some studies have shown that this does not directly correlate to prediction of recurrence.

Definition of Periprosthetic Joint Infection

The new definition for periprosthetic infection defines it as being present when:

i. a sinus tract communicates with the prosthesis; or

ii. a pathogen is isolated from at least two separate tissue or fluid samples from the prosthetic joint; or

iii. four of the following six are present:

   (a) elevated ESR/CRP

   (b) elevated synovial WBC

   (c) elevated synovial neutrophil percentage

   (d) isolation of microorganism in one culture of periprosthetic fluid/tissue

   (e) purulence in the joint

   (f) greater than five neutrophils per hpf in five high power fields at ×400 magnification on histologic analysis.

PJI may also be present if fewer than four of these criteria are met and clinical suspicion is high.

Diagnosis

The diagnosis of infection after TJA should begin with a careful history and physical examination. The timing of an infection can have a profound effect on the outcome of its treatment. Any patient with consistent pain in a previously pain-free, well-functioning arthroplasty should be worked up to rule out infection. A history of subjective swelling, erythema, or prolonged wound drainage may or may not be present. Early PJI usually presents with acute joint pain, redness, warmth, effusion and reduced mobility. Sinus tract and purulent drainage may be present too. Late PJI may present with chronic joint pain and loosening.

Table 1. From Diagnosis and management of prosthetic joint infection MatthewsPC, BerendtAR, McNallyMA, ByrenI. BMJ 2009;338:b1773.

	IV Antibiotic	Oral Antibiotic
Gram Positive		
C-negative Staph	Glycopeptide	Rifampicin plus cipro, fusidic
MSSA	Flucloxacillin/Cefalosporin	acid, trimethoprim, or
MRSA	Glycopeptide	doxycycline, according to sensitivities; Linezolid
Streptococcus	Penicillin or Cefalosporin	Amox or Cefalosporin
Enterococcus	Penicillin/Glycopeptide ± Aminoglycoside	Amox or Linezolid
Diphtheroids (Corynebacteria, Propionibacteria)	Glycopeptide	Rifampicin combination, or Ampicillin
Gram Negative		
Enteric bacilli	Cefalosporin ± Aminoglycoside	Ciprofloxacin
Pseudomonas spp	Cefalosporin ± Aminoglycoside	Ciprofloxacin
Others		
Anaerobes 1–8%	Carbapenem	Clindamycin/Metronidazole
Mycobacteria	Rifampicin Combination	
Fungi	Amphotericin/Itraconazole	
Polymicrobial	Co-amoxiclav, or on basis of sensitivity	
Culture Negative PJI	Glycopeptide with or without carbapenem or cephalosporin	Combination, such as rifampicin plus ciprofloxacin

Peripheral Blood Tests

The markers studied for their their sensitivity, specificity, and positive and negative predictive values in diagnosing PJIs include CRP, ESR, WBC count, Interleukins and procalcitonin.

With *ESR* and *CRP*, a serial measurement is more helpful than a one-off value. CRP reaches a 50% higher peak after TKR compared with THR. This peak occurs in both procedures 48 to 72 hours postoperatively and returns to normal within about 3 weeks.

The *serum interleukin-6* level has been found to be a reliable indicator of infection affecting hip or knee arthroplasty, with 100% sensitivity and 95% specificity. Levels rapidly return to normal shortly after joint arthroplasty, peaking the same day, with a mean half-life of only 15 hours, compared to a half-life of 62 hours for CRP. However, due to lack of consistent data, in addition to its less widespread availability than ESR and CRP tests, the IL-6 test is not currently part of standard clinical practice.

Determination of *serum procalcitonin* levels has shown utility in other infections. In PJIs, different studies have shown high specificity (98%) but low sensitivity (33%). It is more widely available than the IL-6 test and it may be useful in patients thought to have elevated ESR and CRP values from non-infectious causes. Further definitive data is needed before it can be recommended.

Blood for culture should be taken before patients with suspected acute infection are started on antibiotics, although cultures are usually negative. However, it may be impossible to take deep cultures before starting antibiotics in patients with systemic sepsis or rapidly evolving local infection.

Synovial Fluid Analysis

Preoperative joint aspiration is the second step of evaluation for suspected PJI following examination, CRP and ESR tests, and performance of plain radiography. Synovial fluid aspiration of a knee arthroplasty is easy but hip aspiration may require image intensifier guidance. Synovial fluid is sent for estimating white cell counts, neutrophil differential and for bacterial culture. A few other direct or indirect infection markers are being investigated but are not widely used at this time. Aspiration remains the standard for diagnosing infection in TJA although the reported sensitivity ranges from 45% to 100%. This sensitivity can be improved by repeated aspiration and by deferring aspiration for 2 weeks in patients taking systemic antibiotics. The fluid cell count obtained at aspiration can be helpful, with a white blood cell count of more than 2500 cells/mm^3 and 60% polymorphonuclear cells indicative of probable infection. Leucocyte count in synovial fluid is highly sensitive and specific for infection, but glucose, lactate or CRP in synovial fluid are not particularly useful.

White cell count and neutrophil differential:

Preoperative aspiration for determination of white cell counts and percentage of polymorphs has high sensitivity and specificity for PJI. The threshold for a positive test differs based on study populations and joint types. An important caveat is that patients with inflammatory causes of joint disease, such as rheumatoid arthritis may have a higher baseline level. Also, false elevation of synovial fluid cell count is encountered while using automated counters in specimens from metal-on-metal hips. This problem can be overcome if the cell count is done manually.

Synovial Fluid Leukocyte Esterase

Leukocyte esterase is an enzyme present in neutrophils. A colorimetric strip measuring leukocyte esterase is widely available for pyuria. This strip is being used to test synovial fluid from either preoperative or operative aspirates. It may be a useful adjunctive test to confirm the diagnosis of PJI intraoperatively when PJI is suspected but has not been confirmed during preoperative evaluation. The role of this test for screening at the time of routine revision for presumed aseptic failure or for reimplantation arthroplasty as part of a two-stage arthroplasty exchange for infection is still unclear. It may not be an ideal test for this situation as it is low on sensitivity, and also because more reliable tests like frozen section are available.

Other synovial fluid markers: Several other inflammation markers, some used in serum, have shown promise for the diagnosis of PJI, including synovial fluid *CRP* and *IL-6* levels (sensitivity of 69 to 100% and specificity of 93 to 100%). Determination of synovial fluid *IL-1*β levels demonstrated slightly lower sensitivity and specificity. One study found both IL-6 and IL-1β tests to be superior to synovial fluid cell counts. Synovial fluid procalcitonin has also been evaluated, but there are still no definitive reports on its usefulness.

α- and β-defensins

Antimicrobial peptides produced as part of the innate immune response and found in bone and synovial tissue, are being looked into as potential markers, including for intra-operative quick diagnosis. The Synovasure test which looks for α-defensin achieved a sensitivity of 69% and a specificity of 94% in a recent study. It is easy to use, and provides results in ten minutes. α-defensin assay is now being used more commonly during revisions as an adjunct in the diagnosis of PJI.

Synovial Fluid Culture

In addition to confirming the diagnosis of PJI, preoperative synovial fluid culture is invaluable for early identification of the infecting pathogens and determination of antimicrobial susceptibility. This information will affect the choice of systemic antibiotics and also the construction of antibiotic-loaded cement during surgery. Ideally, antibiotics should be withheld at least 2 weeks prior to aspiration, if this is clinically possible and patient is not systemically unwell, and local soft tissue conditions permit. The aspirate should be inoculated directly into blood culture bottles as this increases the yield.

Imaging

Plain Radiographs

These rarely have any definitive role in diagnosis, but may help identify other causes for symptoms like periprosthetic fractures, fractures of the arthroplasty material, or dislocation. Detection of periprosthetic lucency/cyst, loosening of the prosthesis components, effusion, adjacent soft tissue gas or fluid collection, or periosteal new bone formation may suggest infection but is neither sensitive nor specific. Periosteal new bone formation alone was 100% specific but occurred in only 16% of patients with PJI. Serial radiographs with progressively expanding lucency over several months may also suggest PJI. Plain radiographs also assist the surgeon with preoperative planning.

Nuclear Medicine Scans

can be helpful in the evaluation of a painful TKA. Comparing the differential periprosthetic uptake on a technetium scan with the uptake on an indium-labeled white blood cell scan is a technique for differentiating infection from aseptic loosening, with reported sensitivities of 64% to 77% and specificities ranging from 78% to 86%. Although these scans cannot be advocated for routine use, they may be indicated when clinical examination, radiograph, and laboratory information are equivocal in diagnosing infection.

Advanced Imaging Studies

CT and MRI scans provide a 3-dimensional picture of the periprosthetic tissues but whether this aids in diagnosis, or even in pre-op planning is unclear. They are also greatly limited by imaging artifacts due to the metal prosthesis.

Three-Phase Bone Scan

is among the most commonly used imaging modalities for diagnosing PJI. Increased uptake at the prosthesis interfaces in the blood pool and delayed phases suggests PJI. However, this lacks specificity. Asymptomatic patients frequently show increased uptake

in the delayed-phase for 1–2 years post-implantation. Three-phase bone scintigraphy may be more useful for PJI occurring late (beyond 1–2 years) after arthroplasty.

Radioactive ^{111}In labeled autologous leukocytes increase the diagnostic capability when used as delayed 24hour images. An increased uptake on the labeled leukocyte image, with absent or decreased uptake at this site on the late-phase bone scan is considered positive. [^{18}F]Fluoro-2-deoxyglucose positron emission tomography (FDG-PET) is emerging as a diagnostic modality for PJI.

Most patients with suspected PJI do not need an advanced imaging modality for diagnosis. Select patients may benefit from certain imaging. But before these are ordered, it is best to liaise with a radiologist specialised in this area. It is also important to consider cost factor, usefulness of likely information gained towards treatment, and the likely time to be taken for the results.

Periprosthetic Tissue

Preoperative periprosthetic tissue biopsy:

not routinely recommended as it adds to expense and complications without any extra benefit gained.

Intraoperative periprosthetic tissue Gram staining:

theoretically useful, but in practice, has a very low sensitivity. Given the availability of frozen sections and numerous other available preoperative tests, tissue Gram staining is not routinely recommended.

Intraoperative periprosthetic tissue culture: Periprosthetic tissue culture is a valuable diagnostic tool for PJI. Multiple tissue specimens must be retrieved, ideally 5 or 6, with 3 or more specimens yielding an indistinguishable microorganism being the ideal cutoff. A single positive culture considered as a contaminant, especially if its a low-virulence organism. However, a single positive culture may be important when a virulent organism (such as S. aureus, beta-hemolytic streptococci, or aerobic Gram-negative bacilli) is isolated; or when the same organism is found in a different specimen type, such as synovial or sonicate fluid. Nevertheless, submission of single tissue specimens for culture is not recommended.

Both aerobic and anaerobic cultures should always be done. Traditionally, incubation was for upto 4 days for aerobic, and for 7 days for anaerobic cultures. Longer incubation is believed to increase the number of contaminants. However, several studies have recently challenged this, suggesting that both aerobic and anaerobic cultures should be incubated for 14 days. The optimal duration of culture is yet unclear but may depend on the culture medium used.

Cultures obtained by using swabs:

These have a limited role in the microbiological detection of PJI. Even though the presence of a sinus tract is considered definitive evidence of PJI, swabs taken from its drainage are neither sensitive nor specific. Sinus tract culture cannot be recommended for PJI diagnosis or the definition of its microbiology.

Intraoperative cultures obtained via swabs are less accurate than tissue cultures.

Histological analysis of periprosthetic tissue:

Tissue sampling of periprosthetic tissues which appear infected on gross inspection is recommended. Neutrophilic infiltrate in these samples is suggestive of PJI. This is unaffected by preoperative antibiotics, and with the use of frozen-section, results will be available to the surgeon in the theatre. The disadvantages include the need for a trained pathologist and variability in the definition of inflammation, depending on the pathologist interpreting the specimen. Also, some pathogens like P. acnes and coagulase-negative staphylococci do not always elicit a decent neutrophilic response. The commonly used criterion of acute inflammation is the presence of at least 5 neutrophils per high-powered field, in at least 5 separate microscopic fields. An alternate system classifies the histological findings of the periprosthetic membrane into four different types. Type I is "wear-particle-induced" macrophages, multinucleate giant cells, and foreign-body. Type II or infectious histology shows a predominantly neutrophilic infiltrate with few foreign-body particles. Presence of both Types I and II changes classifies as Type III, and type IV histology is indeterminate. Even though this system is not used commonly, it highlights the fact that the inflammatory response seen in infection may co-exist with other histological findings. There are some classic anatomical sites from where periprosthetic tissue biopsy is ideally taken. This includes the joint pseudocapsule and the periprosthetic interface membrane between the prosthesis and the adjacent bone. The interface membrane was much more sensitive(83%) than the the pseudocapsule(42%). The specificity was 98% for both specimen types. In contrast, the microbiological yield from the interface membrane does not appear to be superior to that from the pseudocapsule.

Sonication of Removed Prosthetic Components:

Removed prostheses are placed in Ringer's Lactate in solid containers, placed on a vortex device for 30seconds, then treated with low-frequency ultrasonic waves, and then centrifuged. This sonically treated fluid can then be cultured which avoids the cumber-

some problem and practical difficulties of culturing the prosthesis itself. Sonication has been performed on hip, knee, shoulder, elbow, and ankle prostheses, with a range of observed diagnostic accuracies. Most studies in the last ten years have demonstrated that culture of sonication fluid is more sensitive(62 to 94%) than that of periprosthetic tissue(54 to 88%). Additional testing of the sonicate fluid has been evaluated. Similar to periprosthetic tissue, Gram staining of sonicate fluid is insensitive (as low as 45%) but highly specific.

The use of PCR technology in PJI can decrease turnaround time, and is potentially more sensitive than conventional microbiological methods, especially for patients who have been treated with antibiotics. Broad-range PCR assays and multiplex or multiassay PCR is used by different investigators. A rigorous definition of PJI is essential when evaluating molecular diagnostic tests as contamination can occur at any point during the procedure. Some investigators first use other microbiological tests to define infection, and then compare molecular diagnostics with these. PCR studies maybe done on synovial fluid, periprosthetic tissue and sonicate fluid. PCR electrospray ionization mass spectrometry (ESI-MS) has recently been evaluated for use with sonicate fluid and synovial fluid for the detection of PJI. PCR ESI-MS may be useful where conventional methods have failed to establish a microbiological diagnosis. Further improvements in this technology with greater specificity can be expected in the future.

Treatment

General Principles

Successful management of PJI requires surgical intervention and medical therapy in the majority of cases. Close collaboration is needed between orthopedic surgeons, infectious disease specialists, trained nursing staff, outpatient physicians and antimicrobial therapy monitors, and other clinicians involved in the care of the patient.

The goals of PJI treatment are to eradicate infection clinically and microbiologically without relapses, freedom from subsequent surgical intervention, and freedom from mortality related to the PJI. Temporally, this is classified as short-term success (2 years), mid-term success (5–10 years) and long-term success (10 years or more).

PJIs can be treated by a number of different medical and surgical strategies. These include open or arthroscopic debridement with prosthesis retention, removal of the prosthesis without reimplantation, removal of the prosthesis with reimplantation of a new prosthesis either at the time of removal (one-stage or direct arthroplasty exchange) or delayed by weeks to months (two-stage arthroplasty exchange), arthrodesis, amputation, or antimicrobial suppression without surgery. The surgical goal is to remove all infected tissue and hardware or to decrease the burden of biofilm if any prosthesis is retained, so that postoperative antibiotics therapy can then eradicate the remaining infection. Antibiotics should be withheld until multiple intraoperative specimens are sent for microbiological analysis, unless the patient requires antimicrobials to treat a systemic infection.

Debridement with Prosthesis Retention

This is commonly referred to as a DAIR — debridement, antibiotics, and implant retention — and should be performed by using an open arthrotomy. The previous incision is opened and thorough irrigation and debridement is performed, with evacuation of any purulent or suspect tissue around the prosthesis. Stability of the prosthesis is assessed intraoperatively, typically followed by exchange of liners or modular components. The entire joint is then aggressively irrigated and closed over a drain. DAIR has been performed arthroscopically by some surgeons but this tends to be suboptimal. One study found a >4-fold increase in the risk of treatment failure when arthroscopic debridement was performed compared to an open procedure. Open debridement should therefore be performed whenever possible.

Antimicrobial treatment with the DAIR procedure:

Antibiotics are withheld prior to surgery if the microbiology result is undetermined. Broad-spectrum therapy is indicated in the immediate postoperative period till culture results are available. Once the pathogen and sensitivity are known, treatment is accordingly tailored. Current guidelines recommend 4 to 6 weeks of intravenous therapy with PJI due to organisms other than staphylococci or when rifampicin combination therapy cannot be used.

The ideal patient to benefit from a DAIR should have:

i. short duration of symptoms

ii. stable implant

iii. no sinus tract, no frank purulence

iv. known pathogen with known susceptibility (which maybe known only after surgical samples are cultured)

Thus, the ideal candidates are those with early infections (within a month) or with haematogenous infection (of less than 3 weeks). Even if xrays show lucency around the implant, if there is no actual mechanical loosening, results are not necessarily compromised.

The presence of a sinus tract poses an increased risk of treatment failure.

Other notable risk factors for treatment failure are Staphylococcal infection, MRSA, vancomycin-resistant enterococci and fluoroquinolone-resistant Gram-negative bacilli. Multiple comorbidities or a compromised immune status, prior revision and arthroscopic debridement were all predictive of treatment failure.

The success rate of DAIR reported in the literature over the last 15 years ranges from 31 to 82% among infections with a variety of microorganisms. With better control over the appropriate antibiotic for the appropriate pathogen, results appear to improve.

PJI due to staphylococci treated with the DAIR procedure:

A successful outcome with DAIR done for S. aureus is usually less likely than when done for other organisms. *S*taphylococci are one of the commonest causative in early-onset and late hematogenous PJIs. A prolonged rifampi*ci*n-based combination increases the cure rate, but the s*taphylococcus* species being treated as such should be susceptible to it. Rifampicin should not be used as monotherapy, to prevent resistance; close attention must also be paid to drug interactions with this agent. For both S. aureus and coagulase-negative staphylococci, rifampicin is typically given with an intravenous agent, most commonly a β-lactam or glycopeptide, for the initial 2 to 6 weeks. This is followed by continued rifampicin combined with a fluoroquinolone to complete either a 6-month (knee) or a 3-month (hip, shoulder, and elbow) total duration of rifampicin combination therapy. The longer duration of oral combination therapy is predicated on the often larger amount of soft tissue infection in knee arthroplasty infections. Some clinicians use a fluoroquinolone combined with rifampicin even during the initial phase of therapy. When rifampicin cannot be administered, the initial period of intravenous antimicrobials should be at least 4 weeks. Among intravenous agents, cefazolin or antistaphylococcal penicillins are preferred over vancomycin for treatment of infection with methicillin-susceptible S. aureus (MSSA).

The treatment of PJI due to MRSA is challenging, and failure seems to be more common and occurs more often during antimicrobial therapy than for MSSA PJI. Fusidic acid appears to be a suitable companion to rifampicin in place of a fluoroquinolone Other companion drugs that may be given with rifampicin include trimethoprim-sulfamethoxazole and minocycline. Vancomycin remains the preferred intravenous antibiotic for PJI due to MRSA, while daptomycin may be an option. Even though some studies suggest that it may be tolerated long-term, prolonged use of linezolid can cause bone marrow suppression, and so close monitoring of complete blood counts is recommended.

Management after treatment failure:

Patients who fail a DAIR usually undergo a two-stage arthroplasty exchange. Another option after failure of a DAIR procedure is repeated debridement followed by chronic antimicrobial therapy. But the likelihood of success for a repeated DAIR procedure after prior failure is low.

One-Stage Arthroplasty Exchange

A one-stage arthroplasty exchange procedure is also referred to as a direct exchange procedure. Here, open arthrotomy and debridement are performed, followed by complete removal of the prosthesis and any PMMA present. Aggressive and skilful total debridement is critical to the success of this strategy. A new prosthesis is implanted during the same procedure, typically using antibiotic-loaded PMMA.

There are several antimicrobial strategies used for a one-stage arthroplasty exchange. Most commonly, 4 to 6 weeks of iv antibiotics is followed up with 3 to 12 months of oral antibiotics.

This is typically used only for patients with hip arthroplasty infection. An ideal patient should have adequate remaining bone stock, a known pathogen susceptible to available antibiotics (both systemic and for PMMA mix), and good surrounding soft tissue. In general, a one-stage arthroplasty exchange offers results comparable to those of a two-stage arthroplasty exchange and is superior to a DAIR procedure.

Two-Stage Arthroplasty Exchange

A two-stage arthroplasty exchange, considered the most definitive strategy in terms of infection eradication and preservation of joint function, involves at least two surgeries. In the first outing, samples are taken for culture, thorough debridement is performed and all components removed. An antibiotic-laden spacer is implanted which maintains joint space and limb length, and also delivers antibiotics locally. Systemic antibiotics are continued for 4-6 weeks, and then stopped for 2-6 weeks during which time the patient is closely monitored for recurrence using inflammatory markers levels and synovial fluid aspiration. If there is evidence of ongoing infection, a repeat debridement procedure may be performed, followed by a further course of antibiotic before reimplantation. During reimplantation, specimens are retrieved for frozen-section and permanent histopathology as well as culture. Frozen-section can detect ongoing inflammation prior to placement of a new prosthesis. If the result is negative, a new prosthesis is implanted, using antibiotic-loaded PMMA. Intravenous antibiotics

are continued until the reimplantation cultures are confirmed negative. If reimplantation cultures are positive, antibiotics are again given for a variable amount of time.

Antibiotic-loaded PMMA spacers:

These spacers maybe static or articulating. Static, or block or non-articulating spacers are handmade in the theatre and serve to fill the gap left by prosthesis removal. Articulating spacers on the other hand serve to somewhat recreate the joint and provide some function. These may be either readymade ones, or custom-molded spacers. They may be made solely from PMMA or may be a composite of PMMA, polyethylene, and metal. Some studies have mentioned use of resterilized prostheses as temporary spacers during a two-stage arthroplasty exchange, but this is not widely accepted.

Spacers serve two purposes: i. provide mechanical support between stages, maintaining joint position and preventing muscle contractures; and ii. provide local antibiotic concentrations to augment the systemic antibiotic therapy, without major toxic effects. Static spacers can cause bone loss; articulating spacers can lead to extensor mechanism damage and wound dehiscence. Antibiotics used in the spacer must be heat stable to withstand the exothermic reaction, and water soluble to be able to diffuse into tissues. Commonly used agents are 1-3g vancomycin with 1.2-4.8g of an aminoglycoside like gentamicin or tobramycin in 40g of PMMA. Macrolides, antifungals, β-lactams etc have also been used.

Antibiotic treatment with two-stage arthroplasty exchanges: Compared to DAIR or one-stage exchange procedure, there is no new retained prosthesis between stages and so rifampicin is not needed. Sensitivity based antibiotics are given iv for this period.

Risk factors for treatment failure:

Maybe host-related, pathogen-related, or treatment-related. Host factors like poor local skin, sinus tracts, lymphedema, previous multiple surgeries, diabetes, rheumatoid arthritis, compromised cardiac/renal status, malnutrition etc can affect outcomes negatively. Presence of MRSA and absence of any definite pathogen (culture negative) have an increased risk of treatment failure. Treatment factors include duration between stages, antibiotic cover during this time, culture results and appropriate antibiotic changes, and thorough assessment for signs of infection prior to final reimplantation.

Treatment success rates:

Two-stage arthroplasty exchange is generally reported to have success rates of 87-100% in hips, 72-95% in knees, similar rates for shoulders, and a relatively poorer outome for elbows, with rates as low as 72% at best.

Candidal or other fungal infection is more appropriately treated in stages or even with permanent resection rather than implant retention. The prognosis of fungal PJI is guarded, even with two-stage arthroplasty exchange. Culture-negative PJI and MRSA also similarly appear to be treated more successfully with two-stage arthroplasty exchange.

Failure after two-stage arthroplasty exchange:

Infection following prior two-stage arthroplasty exchange may be due to a relapse or infection with a new microorganism. Over two-thirds of these are actually new infections rather than relapses, and are therefore host related susceptibility issues rather than an actual failure of management. The median time to failure across studies has ranged from 9 months to over 3 years. The most common pathogen again are Gram-positive cocci.

Options for management after prior two-stage exchange include antimicrobial suppression without surgical treatment, DAIR followed by antimicrobial suppression, repeat two-stage arthroplasty exchange, resection without reimplantation, arthrodesis, or amputation. A decision has to be made factoring medical comorbidities, soft tissue envelope, available bone stock, and most importantly the patient's need/expectation and ability to go through repeat procedures.Careful patient selection is critical in deciding for a repeat two-stage procedure. The option of amputation should be discussed too.

Arthroplasty Resection without Reimplantation

Resection without reimplantation can be offered as a salvage measure to avoid amputation after prior failed treatment attempts, or in those who do not want to undergo multiple procedures, or in patients with severe comorbidities in whom aggressive surgery is unlikely to offer scope of greatly improving mobility. In some patients, when a first stage surgery has caused great morbidity, the spacer may be allowed to remain insitu indefinitely.

Arthrodesis may be offered to patients following resection of a knee arthroplasty. Even though some patients may ambulate with a knee resection, arthrodesis provides additional stability. The options are long IM nail, and external fixation, with greater success probably with the former. With hips, it is uncommon to attempt arthrodesis because of the Girdlestone procedure, which provides great infection control and

pain relief, and also allows useful mobility, even though with limp and length discrepancy.

Antibiotics should be continued iv for 4-6weeks after resection. Sometimes, a longer course maybe indicated as in when an arthrodesis has been attempted and fails to achieve union.

Amputation

When all treatment options fail, or when there is life-threatening infection, the drastic measure of amputation may have to be resorted to. The incidence is fortunately very low, at 0.1% of primary arthroplasties in large series. The duration of antibiotics depends on whether or not all infected tissue is removed. If the margin is clear, 1-2 days should be enough. This may not always be the case and longer duration of antibiotics will be then required, especially if there is residual osteomyelitis.

Antimicrobial Treatment

Antimicrobial treatment alone:

It should be considered only in those who are unfit for any surgery because of multiple comorbidities; or in those with a well-fixed prosthesis with infection caused by an organism that is susceptible to oral antibiotics. This strategy is likely to be more successful in early rather than delayed or chronic infections.

Usually, patients are given 4 to 6 weeks of antibiotics based on aspirate results. This may be given as combination therapy with rifampicin. Many patients will end up with needing long-term indefinite suppression. This must take into account toxicity, oral bioavailability, cost, frequency, drug interactions, and the need for ongoing therapeutic monitoring. Almost a fifth of patients on antibiotic suppression develop complications. When outpatient intravenous antibiotics are used, lab testing should be done weekly to look for adverse effects. Laboratory monitoring for patients on prolonged oral antibiotics should be done at approximately 2, 4, 8, and 12 weeks, with yearly monitoring thereafter.

Prevention

Identification and optimization of any modifiable risk factors prior to joint arthroplasty are central to the prevention of PJI. High-risk conditions like obesity, diabetes mellitus, inflammatory arthritis or malnutrition should be optimised. Patients should be strictly advised to stop smoking. Other potential sources of infection should be identified and managed prior to surgery, like urogynecological and ENT foci.

Reduction of Skin Flora

Selective identification and decolonization of patients colonized with Staph Aureus has been proposed. Guidelines recommend mupirocin nasal ointment for patients with S. aureus nasal colonization. Chlorhexidine wipes is also a measure sometimes adopted. However, these are not definitely proven to help and so consider the risk of bacterial resistance to mupirocin/chlorhexidine, and the possibility of adverse reactions to either before they are routinely employed.

Perioperative Antimicrobial Prophylaxis

Perioperative antibiotics reduce the risk of surgical site infection by >80%. Cefazolin or cefuroxime can be safely used in most patients. However, if there is allergy to β-lactams, vancomycin or clindamycin should be considered. Cefalosporin is administered within 60 min prior to incision. With vancomycin, this is 60-120 min prior. Unless there is excess bleeding (greater than 500ml) or the surgery is prolonged (greater than 4 hours), single dose should suffice. Else, a repeat second intraoperative dose should be given. A second dose of vancomycin is not necessary. There is no benefit from antibiotics beyond the first 24 hours.

In PJI, perioperative antibiotics are withheld till specimens have been retrieved at surgery, unless of course serious systemic infection makes early start of antibiotics unavoidable. This optimises the yield of cultures to identify the correct infecting agent. Antibiotics prior to revision for presumed aseptic failure may potentially decrease the detection of occult PJI.

Laminar Airflow and Body Exhaust Suits

Ultraclean air within the operating theatre should decrease contamination and thus minimise infection. Using all other measures to minimise contamination, laminar air flow and body suits do not by themselves seem to greatly reduce infection any further. However, most modern theatres are laminar flow, and many arthroplasty surgeons use body suits.

Antibiotic-Loaded PMMA

The purpose of antibiotic loaded PMMA is to provide higher local concentrations of antibiotics. Some surgeons routinely use these, but there is no real evidence to state that it can definitely decrease incidence of infection. At the same time, there is no lowered risk of PJI in the setting of uncemented revisions.

Antibiotic Prophylaxis Prior to Procedures

Antibiotics given prior to dental procedures do not seem to decrease the risk of subsequent PJIs. Antibiotic prophylaxis is also not indicated for prevention of PJI in patients undergoing routine urologic or endoscopic gastrointestinal procedures. Upper endoscopy with biopsy was associated with a 4-fold increase in

subsequent PJI in a recent study. Considering the heterogenous nature of these procedures, individualised decisions should be made.

Conclusions

PJIs are disastrous, but with a systematic approach and multi-disciplinary co-operation, patients can get reasonably acceptable outcomes. High degree of suspicion in a previously fine but now symptomatic arthroplasty, and prompt diagnosis and prudent treatment plans arrived at based on broader guidelines yet individualised to suit the specific patient are essential. Injudicious antibiotic usage should be discouraged and microbiologic inputs alone should dictate their use. Aggressive and skilful surgical debridement, and patient waiting for quiescence is critical. Once quiescent, the patient should be given the best available prosthetic option for return to good quality function. In the unfortunate event of recurrent failures, long-term antibiotic suppression, resection arthroplasties as well as drastic surgeries like arthrodesis or amputation may have to be considered.

Considering that in India there are about 250million people in the 40-60 year age group alone, the numbers of total joint replacements are going to be phenomenal over the next few decades. Even with an infection rate of less than 1%, that would mean huge numbers of PJIs. There is need for further refinement of diagnostic and treatment guidelines in this disastrous subset of arthroplasties. The future lies in identifying patients at high risk for infection, with a view to preventing these. We should also look towards learning from the volumes of currently available systematic registries worldwide, and aim to develop our own registry which alone can help us identify and target issues that need to be improved.

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