Update on the diagnosis and management of prosthetic joint infection in hip and knee arthroplasty

INTRODUCTION

Prosthetic joint infection (PJI) is a major complication following hip or knee arthroplasty, and presents significant challenges in regard to both diagnosis and treatment. Estimates of the risk of PJI after primary total knee arthroplasty (TKA) and total hip arthroplasty (THA) are low, ranging from 0.4% to 2.4%.[1-3] The risk of PJI following revision arthroplasty is greater, at 8% to 10%. However, as an indication for revision, PJI contributes to approximately 20% to 25% of TKA revisions and 10% to 15% of THA revisions.[4-7] Both TKA and THA are surgical procedures that are undertaken very frequently, and the demand for these procedures is predicted to increase globally over the next decade.[8-11] Analyses of temporal trends of PJI have not shown any signs of a decrease in this complication, and so it is not surprising that revision surgery for PJI continues to increase.[12,13]

The burden of PJI to both patients and healthcare systems is significant. Patients with PJI typically suffer pain, reduced function, prolonged antimicrobial therapy, and multiple surgical interventions. PJI has been shown to negatively influence patient quality of life, and to increase the risk of mortality.[14,15] The economic cost of managing PJI is also significant. Estimates from the United States for treating hip and knee PJI demonstrated hospital costs of $566 million in 2009, and a predicted increase to $1.6 billion by 2020.[2] On a per-patient basis, analyses from the United Kingdom have reported costs per revision for infection at approximately £20 000 and £30 000 for hip and knee PJI cases, respectively.[16,17]

Due to the complex nature of managing PJI, it is recommended that treatment should take place in centres with specialist multidisciplinary teams (MDT) to optimize outcomes. Such MDTs should include orthopaedic surgeons, infectious diseases physicians, plastic surgeons, specialist nurses, musculoskeletal radiologists, and a specialist musculoskeletal pathologist. In the United Kingdom, there are a number of formal and informal 'revision' networks centred on specialist centres. These networks represent best practice; surgeons managing PJI should

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consider discussion with a centre of excellence when at all possible. This review aims to provide an overview and update of the diagnostic and treatment options available in managing hip or knee PJI.

PATHOPHYSIOLOGY

Compared to managing soft-tissue infections, PJI presents additional challenges due to the presence of the foreign prosthetic material. The prosthesis provides a material on which microorganisms can adhere, and reduces the bacterial inoculum required to establish infection.[18] The increased difficulty in clearance of infection in PJI is related to the formation of a bacterial biofilm on the implant. Biofilms are formed when bacteria adhere and aggregate on a surface, and embed themselves in a self-secreted extracellular matrix of exopolysaccharides, deoxyribonucleic acids, and proteins. The development of a biofilm is a critical feature in PJI; once established, bacterial populations exhibit increased resistance to antibiotics, improved evasion of host immune mechanisms, and increased horizontal gene transfer (including those for antibiotic resistance).[19,20] The speed at which a mature biofilm forms *in vivo* is unclear, and is affected by both organism and host. *In vivo* studies using mice have demonstrated that with large inoculums, biofilm formation occurs within hours, even though maturation may take up to six weeks.[21] An appreciation of biofilm biology is important, as once the biofilm is mature, eradication of infection is unlikely without exchange surgery.

PJI has traditionally been classified according to the time interval since implantation as acute (within four to six weeks of primary implantation), acute haematogenous (any time after primary implantation, with a short clinical course), or chronic (all others). Acute PJI is widely considered to be a result of perioperative contamination, while acute haematogenous PJI is considered to be a result of microorganism seeding of implants from a distant site (such as from a urinary or respiratory infection). Chronic PJI is considered to be a result of all other PJIs (and represents existence of a mature biofilm). However, there have been recent calls to move away from a time-based approach and towards managing PJI as a spectrum of disease.[21] Nevertheless, the use of a traditional time-based classification system affords some clarity for managing most cases.

A large number of PJI causative organisms have been reported. The majority are Gram-positive cocci (*Staphylococcus aureus, Staphylococcus epidermidis*, and coagulase-negative *Staphylococci* spp.). Less common are streptococci, enterococci, and aerobic Gram-negative bacilli.[22,23] Fungal PJI is rare (predominantly due to *Candida* spp.), is typically seen in immunocompromised hosts, and requires two-stage exchange with prolonged antifungal therapy. There are also concerning reports that the prevalence of infections caused by resistant organisms such as methicillin-resistant *Staph. aureus* (MRSA) and methicillin-resistant *Staph. epidermidis* (MSSA) is increasing.[24] Prevalence of causative PJI organisms differ by region, and readers are encouraged to review their local infection patterns and to ensure their local prophylaxis policy is both up to date and appropriate for the local prevalent organisms.

Finally, there is increased recognition of 'culture-negative' PJIs, in which all evidence suggests the presence of PJI, but no organisms have been cultured. Reports of culture-negative PJI vary widely from 5% to 41%, with 10% a reasonable estimate.[22,23,25] Reasons for negative culture can include fastidious organisms with demanding culture requirements, rare organisms not previously associated with PJI, or failure to obtain a sample including the causative organism. However, the most important cause of culture-negative PJI is antibiotic administration prior to sampling.[26,27]

DIAGNOSIS

The acutely infected prosthetic joint typically presents with a painful, erythematous, and swollen joint, in a potentially septic patient. Pain on weightbearing is a strong clinical indicator of an infected joint and should not be dismissed. Chronic PJI is more indolent and may present with vague symptoms of discomfort and radiological loosening rather than a very painful, hot, or red joint (more obvious findings, such as a draining sinus, may exist in established cases), with additional investigations leading to a diagnosis of PJI. In addition to appropriate history and examination of the patient presenting with a painful joint suspicious for PJI, there exist a number of investigations that can be employed to inform the diagnosis.

Several criteria-based definitions of PJI have been published, with the Musculoskeletal Infection Society (MSIS) arguably the most widely accepted and established system. The original MSIS criteria were developed by working group consensus, and published in 2011.[28] The original criteria have been modified and updated twice following the 2013 and 2018 International Consensus Meetings (ICM) on PJI, to take account of new diagnostic tools and validation studies.[29-30] The 2018 MSIS system takes account of clinical findings and a number of investigations, which are discussed below.

Serum biomarkers

The use of biomarkers for the detection of disease are widespread in medicine, with a biomarker defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention".[31] Both serum and synovial fluid biomarkers are of value in the diagnosis of PJI, with sensitivities and specificities of common markers presented in Table I. Serum markers are advantageous in that samples can be obtained without violating a potentially aseptic joint, and serial measurements can be more easily obtained than articular aspiration. However, the specificity of serum biomarkers is typically less than that of synovial biomarkers. There has been renewed interest in both in recent years.

Traditionally, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) have been used as markers for PJI. CRP is produced by the liver, is released as an acute phase reactant in

Table I. Diagnostic performance of common biomarkers; sensitivities and specificities of selected tests for the diagnosis of chronic prosthetic joint infection, modified from a meta-analysis by Carli et al[41] and results from a study by Shahi et al[34]

Biomarker	Serum biomarkers		Synovial biomarkers	
	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %
C-reactive protein	*84.5*	*81.3*	*88.8*	*93.3*
Erythrocyte sedimentation rate	*81.6*	*79.0*	N/R	N/R
D-dimer	*89.0*	*93.0*	N/R	N/R
Leucocyte count	*41.6*	*89.7*	*90.1*	*92.5*
Interleukin-6	*87.5*	*87.0*	*83.8*	*97.1*
α-defensin (Enzyme-linked immunosorbent assay)	N/R	N/R	*96.7*	*96.8*
α-defensin (Lateral flow test)	N/R	N/R	*82.1*	*95.5*
Leucocyte esterase test strip (2+)	N/R	N/R	*93.0*	*97.1*
Culture	N/R	N/R	*68.6*	*96.4*

N/R, not reported

response to rising interleukin (IL)-6 levels, and can bind to the surface of bacteria to assist binding and activation of the complement system. ESR describes how quickly erythrocytes settle in a column, with increased serum proteins present during inflammation resulting in a more rapid fall, and thus an elevated ESR. These tests are rapid, widely available, economical, and feature in criteria-based diagnostic schemes for PJI. However, CRP and ESR rise as part of a general inflammatory response and so, while reasonably sensitive, are not highly specific for PJI.

Similar to CRP and ESR, the measurement of peripheral white blood cell count (WBC) is well recognized as a marker of infection. Typically, the WBC count will be elevated (with a neutrophilia) in an acute PJI, but in the case of chronic, indolent PJI, or after the administration of antibiotics, WBC counts may be normal. As a result, use of peripheral WBC count as a diagnostic tool for PJI has limited value, and is not included in the major diagnostic schemes for PJI.[32]

New to the updated MSIS criteria for PJI diagnosis is the inclusion of serum D-dimer testing. D-dimer is a fibrin degradation product, released following the enzymatic degradation of thrombus. It has been shown in animal models that fibrin is produced by inflamed synovium, and subsequent breakdown leads to elevated synovial D-dimer levels.[33] Shahi et al[34] demonstrated that serum D-dimer potentially outperforms serum CRP and ESR for PJI diagnosis. However, while D-dimer testing is widely available, it also has the drawback of being raised in a variety of other conditions, and a recent study has suggested limited use as a diagnostic tool for PJI.[35] Additional validation studies to confirm the utility of D-dimer as a PJI biomarker are required.

Additional serum markers for PJI have also received attention recently. IL-6 is secreted by activated monocytes and macrophages, and is a mediator of the acute phase response. IL-6 has a complex modulatory effect on the acute phase response and also has local signalling roles. IL-6 is, however, potentially more attractive than CRP as a PJI marker in the early postoperative period, as levels of IL-6 levels rise and fall more rapidly than CRP.[36] Currently, testing for IL-6 is not routine in clinical practice, owing to availability and the need for additional validation. A number of other potential markers have been identified, such as tumour necrosis factor (TNF)-α, IL-4, and procalcitonin. However, as with IL-6, these markers are not used clinically owing to the need for further validation, concerns regarding sensitivity/specificity, or a lack of routine clinical availability. Combinations of serum biomarkers are also being actively investigated in an effort to improve diagnostic performance for PJI.

Synovial fluid

Synovial fluid presents several diagnostic opportunities for reaching or excluding a PJI diagnosis, with sensitivities and specificities of tests discussed below and provided in Table I. Culture and microscopy of synovial fluid remains a core investigation for PJI assessment, enabling the identification of organisms and determination of antibiotic resistance profiles. The Infectious Diseases Society of America (IDSA) recommends that samples should be sent via sterile containers and processed within two hours. If possible, blood cultures bottles should also be inoculated to improve yield.[37] The 2018 International Consensus Meeting on PJI recommends that cultures are maintained for five to seven days, or up to 21 days if there is suspicion of low-virulence organisms, or where previous culture results have been negative.[38]

Microscopy of synovial fluid to determine nucleated cell counts and the proportion of neutrophils is included in the MSIS minor criteria. Exact thresholds for each, and their associated sensitivity/specificity, vary by report, joint, and timing after implantation. However, the updated MSIS criteria specify a synovial leucocyte count of $>$ 3000 or a neutrophil population of $>$ 80% as being the threshold for suspecting infection. It is important to appreciate that false-positive results can occur, for example in postoperative patients and in patients with haemarthrosis, a failing metal-on-metal prosthesis, or an underlying inflammatory arthropathy. While potentially sensitive, these kinds of microscopy for cell presence are not terribly specific.

Synovial fluid leucocyte esterase (LE) has emerged as an accurate and cost-effective test for PJI in recent years. LE is produced by activated neutrophils, and can be detected using urine dipsticks as a point-of-care test.[39] Care should be taken in the event of a blood-stained aspirate, as this can cloud the result. To overcome this problem, centrifugation of the sample prior to testing is recommended.[40]

Synovial α-defensin has been identified as a valuable PJI biomarker and has been widely studied and discussed.[41-43]. Activated neutrophils produce α-defensin, which disrupts pathogenic

cell membranes. Detection of α-defensin can be achieved using immunoassay, or with a recently commercialized lateral-flow device (Synovasure, Zimmer Biomet, Warsaw, Indiana). Both techniques are expensive and demonstrate high specificity, but the lateral-flow device can be performed as a point of care test, with results available in minutes. The immunoassay test requires submission of samples for laboratory testing, taking approximately 24 hours, but benefits from an approximately 15% higher sensitivity.[41] Compared with existing biomarkers for PJI, α-defensin has demonstrated additional advantages, in that it can be used to detect PJI in the setting of low-virulence organisms and following prior antibiotic use.[42,43] A variety of additional synovial biomarkers are under investigation (for example human β-defensin, LL-37, TNF-α, and several interleukins); however, none are currently in routine clinical use, and so are not discussed further.

Radiology

Imaging in suspected PJI can provide supporting evidence, but cannot be used in isolation. Plain radiographs of the affected joint may demonstrate evidence of radiolucency or an associated periosteal reaction, but with poor specificity. Ultrasound may be used to locate and aspirate a joint effusion, both to reduce bacterial load and to provide samples for culture. Cross-sectional images such as CT and MRI can provide better bone and soft-tissue imaging, but are limited by metal artefact, and are not routinely required. In patients with metal-on-metal hip prostheses, Metal Artefact Reduction Sequence (MARS) MRI should also be used. However, the diagnosis of PJI in the presence of adverse local tissue reaction (ALTR) is very challenging, as many of the standard tests (including serum and synovial biomarkers) can be falsely positive. The recent ICM guidelines suggest that culture and histology are the most reliable diagnostic tests in this setting.[44]

Nuclear imaging techniques can be applied in the diagnosis of PJI.[45] Bone scintigraphy (most often with Technetium-99m) demonstrates high signal at areas of increased bone metabolism, with a meta-analysis demonstrating 80% sensitivity and 69% specificity (specificity increases with time elapsed since surgery).[46] The inclusion of autologous labelled leucocytes in bone scintigraphy improves the sensitivity of the technique to approximately 95%.[46] These techniques demonstrate excellent negative predictive value, and may be of value in ruling out prosthesis-related problems. Finally, positron emission tomography (PET), using ^{18}F-fluorodeoxyglucose (FDG), was found to have 83% sensitivity and 91% specificity in the diagnosis of hip PJI in a meta-analysis of 725 joints.[46] This technique relies on the differential uptake of FDG by cells of differing metabolic activity and glucose transport expression (as seen in activated leucocytes). Nuclear medicine techniques, however, have additional limitations with regard to availability, significant whole body radiation exposure, and cost, so are not used routinely.[45]

INTRAOPERATIVE OPTIONS

Culture

Intraoperative sampling remains an important step. Results can be used to confirm organisms obtained by aspiration and their antibiotic resistance profile, or in the case of exchange arthroplasty, to detect evidence of residual organisms that will alter subsequent management. It is widely recommended that five paired specimens be obtained at the time of surgery for microbiology as well as histology. Importantly, each sample should be taken with a clean set of instruments.[38] Samples should be obtained systematically from areas of visible inflammation, as well as from the implant/bone interface, and each sample should be clearly labelled with its origin to aid decision making in the postoperative period.

Histology

Histological examination of periprosthetic tissue (paired with specimens for culture) from areas suspicious for infection can demonstrate acute inflammation. Neutrophil infiltration is considered suggestive of infection, with more than five neutrophils in at least five high powered (×400) fields being a minor diagnostic criterion in the MSIS PJI definition. Histological examination may be of additional value in patients who have received preoperative antibiotics, as this is unlikely to affect microscopic findings. A 2012 meta-analysis demonstrated an overall likelihood ratio of a positive test of 12 (95% confidence interval (CI) 8.4 to 17.2) when acute inflammation was identified on frozen-section histology.[47] However, histological examination is operator-dependent and low-virulence organisms may not stimulate a neutrophilic response meeting the above criteria.

Sonication

Sonication involves the application of low-frequency ultrasound to the explanted prosthesis when immersed in Ringer's lactate. This frees sessile bacteria from the implant surface, with the sonication fluid subsequently cultured. This technique has demonstrated good sensitivity and specificity (greater than 80%), including in patients who have received antibiotics within two weeks of surgery.[48,49] Sonication may add value in the diagnosis of culture-negative PJIs. However, sonication does require additional resources in the form of specific containers and an appropriately equipped laboratory, and the additional diagnostic accuracy is not firmly established.

EMERGING MOLECULAR TECHNIQUES

The development of novel molecular techniques for the diagnosis of PJI is ongoing, with the falling costs of sequencing technologies presenting new opportunities. These technologies are now becoming more affordable and are being utilized more routinely in many centres. One such example is next-generation sequencing (NGS), in which the DNA of a given sample can be rapidly sequenced to identify multiple organisms and their antibiotic resistance genes. Tarabichi et al[50] used "16S amplicon targeted" NGS to demonstrate an overall sensitivity of 89.3% and specificity of 73.0%. Other authors have demonstrated that another approach of implementing NGS, namely "shotgun metagenomics" (which sequences the whole genomes of all organisms present in a sample) is also very accurate at detecting causative pathogens involved in PJI, and that it may be particularly useful for culture-negative infections.[51] Increasing appreciation of the proteomes and metabolomes associated with PJI present additional opportunities. Many of these molecular techniques are being rigorously investigated as PJI diagnostic tools, and this exciting field is likely to receive increasing attention in the years to come.

MANAGEMENT

Management of the patient with PJI requires an understanding of the causative organism, chronicity of infection, systemic health of the host, and condition of the affected limb. The McPherson staging system (Table II) is recommended, with evidence supporting correlation between stage and treatment success. As previously discussed, treatment of patients with PJI should be provided by a specialized MDT, and

Table II. McPherson staging system

Category	Grade	Description
Infection type	I	Prosthetic joint infection (PJI) < 4 wks after implantation
	II	Acute haematogenous PJI (< 4 wks duration)
	III	Late and chronic PJI
Host grade (systemic)	A	No compromising factors*
	B	Compromised (⩽ 2 factors)
	C	Significant compromise (> 2 factors) or one of the following:
		Absolute neutrophil count < 1000
		$CD4^+$ T-cell count < 100
		Intravenous drug abuse
		Chronic active infection (distant to joint)
		Dysplasia/neoplasm of immune system
Lower limb grade	1	No compromising factors†
	2	Compromised (⩽ 2 factors)
	3	Significant compromise (> 2 factors)

*Systemic compromising factors include: age more than 80 years; alcoholism; hepatitic insufficiency/cirrhosis; chronic active dermatitis or cellulitis; chronic indwelling catheter; chronic malnutrition (albumin < 3.0g/dl); current nicotine use; diabetes mellitus; immunosuppressive medications; active malignancy (or a history thereof); pulmonary insufficiency (arterial saturation of 60% on room air); renal failure requiring dialysis; systemic inflammatory disease; systemic immune compromise from infection or disease
†Limb compromising factors include: local active infection present for more than three months; multiple previous incisions creating skin bridges; soft-tissue loss from prior trauma; subcutaneous abscess > 8 cm^2; synovial cutaneous fistula; prior periarticular fracture or trauma about joint; prior local irradiation to wound area; vascular insufficiency (absent limb pulses, chronic venous stasis disease, significant calcific arterial disease)

identification of causative organisms should ideally be determined before antibiotic administration or operative intervention. In the stable patient, antibiotics should not be given until intraoperative sampling has taken place, in order to maximize organism yield.

There are several management options for PJI, the choice of which is guided by infection characteristics (organism, antibiotic resistance, and chronicity), the health of the host and affected limb (compromised *vs* not), and treatment objective (eradication of infection *vs* functional outcome *vs* symptom control). Where possible, eradication of infection and maintenance of function is the goal. Techniques to achieve this include debridement, antibiotics, and implant retention (DAIR), as well as one- and two-stage revision arthroplasty. These options aim to clear infection while retaining a functional joint. However, in select cases, such an outcome may not be achievable, and therefore long-term antibiotic suppression, arthrodesis, or amputation may be considered. Associated symptoms in challenging PJI cases should also be addressed, for example the use of wound management bags over draining sinuses.

GENERAL CONSIDERATIONS

Regardless of the specific surgical technique selected, there are steps common across DAIR and revision surgery techniques. As previously discussed, paired samples for culture and histology should be obtained from areas of inflammation and the bone/implant interface. Administration of antibiotics prior to sampling can reduce culture yield or lead to negative cultures, as previously discussed. As such, in the stable patient, antibiotic administration should be withheld until after sampling is complete. Antibiotics can then be given, as advised by an infectious disease physician and local protocol. Typically, these will be broad spectrum agents with good bone penetration, with rationalization of antibiotic choice according to culture results.

Postoperative antibiotic regimens are required for DAIR, one-stage procedures, and the first of two-stage procedures. With the second of two-stage procedures, postoperative antibiotics are typically given until intraoperative cultures are reported as negative. Again, the specific agents, route, and duration of therapy will be dependent on culture findings and guided by the infectious disease team. Of note is the recently published Oral Versus Intravenous Antibiotics for Bone and Joint Infection (OVIVA) randomized controlled trial.[52] This demonstrated noninferiority of six weeks of oral antibiotics *versus* six weeks of intravenous antibiotics in bone and joint infection (with treatment failure at one year the primary end point). This is a valuable report, and provides evidence that prolonged intravenous antibiotics may not be necessary. An additional avenue of antibiotic administration is the use of absorbable antibiotic loaded carriers, which allow high intra-articular antibiotic concentrations, while limiting systemic toxicity. However, evidence of benefit for these agents is currently limited, and so they are not in widespread use outside of specialist units.

Clearance of infected material is a critical step, regardless of technique. Debridement should result in clearance of all devitalized, inflamed, or unhealthy tissue and cement/debris. This is followed by joint irrigation using a large volume of aqueous chlorhexidine or povidone iodine (six to nine litres). At this point, the surgical field is considered clean. The surgical instruments should be exchanged for clean instruments, the surgical team should rescrub and the surgical field reprepped and draped. A further irrigation of the joint with more than three litres of saline is then performed prior to any following steps.

It is important to consider the need for soft-tissue cover with each of the techniques discussed below, as excision of previous wound margins or sinus tracts can present challenges. If there is any concern regarding wound closure or soft-tissue tension, the input of a plastic surgeon should be sought. With regard to management of the infected knee arthroplasty, the rotational medial gastrocnemius muscle flap is a common option.[53,54] Rotational muscle flaps utilizing vastus lateralis or gluteus maximus can be used when managing THA PJI.[55] All patients require prolonged monitoring to identify recurrence of infection, with clinical, laboratory, and radiological assessment.

*Debridement, antibiotics, and implant retention (*DAIR*)*

DAIR allows for the retention of the *in situ* prosthesis, and is a treatment option when the prosthesis is well fixed and the PJI is considered acute (either early postoperative or late haematogenous). The importance of chronicity relates to a window in which to intervene prior to the establishment of a mature biofilm. Potential benefits of DAIR include reduced bone and soft-tissue destruction compared with formal exchange revisions, with functional outcomes demonstrated to be superior to staged revision surgery.[56,57] With respect to eradication of infection, quoted success rates vary widely,

with differences in patient selection, treatment technique, and outcome definitions making direct comparisons difficult. A 2018 meta-analysis, however, provides valuable pooled estimates.[58] This demonstrated infection control in 75.40% (95% CI 68.90 to 81.50) for hip PJI and 52.60% (95% CI 45.10 to 60.10) for knee PJI. This analysis also demonstrated that DAIR for acute postoperative and acute haematogenous PJI was more successful than DAIR for chronic PJI, at 67.7% (95% CI 59.60 to 75.50), 52.70% (95% CI 40.80 to 64.50), and 31.90% (95% CI 8.50 to 60.20), respectively. Currently, there is insufficient evidence to recommend a specific timeframe in which DAIR is indicated, but it is clear that success rates fall with increasing chronicity of PJI.

Beyond the timeframe of the onset of infection, there are some further considerations with DAIR that do not apply to other techniques. The prosthesis and all fixed components should be stable and functioning well previously, and primary wound closure at the time of DAIR should be achievable. Relative contraindications to DAIR are the presence of a draining sinus, difficult to treat organisms (e.g. multidrug-resistant bacteria or fungal), or immunocompromised patients, as these are associated with lower success rates. In such cases, exchange revision should be considered. However, in the absence of other contraindications, DAIR can be performed without a preoperative microbiological diagnosis.

It is important that DAIR is not seen as a simple joint washout. Within our centre, experienced revision surgeons are responsible for performing DAIRs, on a planned list as an urgent case, preceded by rapid medical optimization of the patient. DAIR can never be performed adequately using an arthroscopic approach, and is to be discouraged. In the event of an unstable septic patient, arthroscopic washout can be performed, but this should be considered a temporizing measure until formal DAIR (or exchange revision) can be performed. The DAIR procedure crucially involves as radical a debridement as a traditional exchange revision.

The defining feature of the DAIR technique is retention of the implant, which involves key aspects beyond the common steps described above. First, an intraoperative assessment of implant stability needs to be made. If the implant is loose, conversion to a staged revision technique is necessary. Second, all modular components should be removed (femoral heads, acetabular liners, polyethylene trays). This step serves to improve access to soft-tissue structures for thorough debridement, but also removes microorganisms that may be adherent to these components or in the component interfaces. Once the joint cavity has been determined clean, replacement modular components can be implanted. The joint is then closed according to surgeon preference, typically over a deep drain. Ongoing antibiotic therapy is then guided by culture results and infectious disease team input.

One-stage exchange

One-stage exchange is the most common treatment option for PJI in Europe, and involves removal of all implants, debridement, irrigation, and implantation of a new definitive prosthesis during the same procedure.[59] The benefits of one-stage exchange over two-stage exchange include lower morbidity, lower mortality, and lower healthcare resource usage, yet similar functional outcomes and rates of infection recurrence have been reported (approximately 8% for both hip and knee PJI).[60-64] However, these reports are based on heterogeneous studies with disparities in definitions, techniques, and treatment algorithms for PJI. It is accepted that patient selection is a critical moment in achieving a successful outcome, with the indications recommended by ICM 2018 provided in Table III.[64]

The surgical technique for one-stage exchange is similar to DAIR; however, it may require techniques to improve exposure and implant removal, such as a tibial tubercle osteotomy, quadriceps turndown, or extended trochanteric osteotomy. The common steps regarding antibiotics, sampling, excision of sinus tracts, debridement, irrigation, and redraping are equally important when performing one-stage exchange. The primary difference between DAIR and one-stage exchange, however, is the removal of all prosthetic components (including cement mantles) during the debridement stage. Following rescrubbing, redraping, and the second joint irrigation step, a new prosthesis can be implanted using standard revision techniques. Cemented components allow for the use of antibiotic-loaded cement for delivery of local antibiotics at high concentrations. In cases of significant soft tissue or bone loss, a semi-constrained or hinged prosthesis may be necessary, as well as reconstructive augments. As with DAIR, the postoperative antibiotics regimen should be guided by culture results and infectious diseases team input, and monitoring should be in place to detect recurrence of infection.

Two-stage exchange

Two-stage revision differs from DAIR and one-stage revision in that patients undergo two planned procedures. This is the most commonly performed technique for PJI management in North America. As previously discussed, outcomes for one- and two-stage exchange appear to be similar. However, two-stage exchange mandates a secondary procedure for implantation of a definitive prosthesis, with associated morbidity and cost.[64] Outside North America, two-stage exchange is typically indicated for cases not meeting the indications for one-stage exchange (Table III), or where previous one-stage exchange has failed. However, two-stage revision for PJI may not be possible in frailer patients, owing to the morbidity and mortality associated with repeat, major surgery. For these patients a single-stage revision may be preferable and should be considered on a case-by-case basis.

Technically, a two-stage exchange mirrors that of one-stage exchange until the point of reimplantation of the prosthesis. In two-stage exchange, this does not happen, and instead a cement spacer is implanted, which is typically antibiotic loaded. This serves to generate a high local antibiotic concentration, provide joint stability, and maintain soft-tissue tension. Spacers can be static (that is, they do not allow for any joint motion) or dynamic, with evidence to suggest that dynamic spacers provide superior range of movement and patient-reported outcomes (dynamic spacers should be avoided in cases of severe ligamentous laxity or muscle loss, due to the risk of instability and dislocation).[65] Dynamic spacers can be handmade in theatre or alternatively shaped using commercially available moulds (at significantly greater cost).[66] As discussed above, if soft-tissue procedures are required to ensure coverage, these should be undertaken at the first stage.

Postoperatively, patients receive a course of antibiotics, typically via the intravenous route with broad spectrum agents in the immediate postoperative period. Antibiotic choice and route of administration are rationalized according to culture results and antibiotic resistance profile, under infectious diseases physician guidance. There is currently no specific recommended interval between the first and second stages to

Table III. Indications for single-stage revision in prosthetic joint infection (PJI)

Indications	Contraindications
Preoperatively identified organism	Culture-negative PJI
Susceptibility to available antibiotics	Highly virulent or multiple-resistance organism
Healthy, uncompromised host	Fungal infection
Absence of severe sepsis	Cases where radical debridement not achievable (e.g. involvement of major neurovascular bundles)
Minimal bone or soft tissue loss	Inability to achieve primary wound closure
	Insufficient bone stock for new prosthesis

optimize treatment success, due in part to heterogeneity of studies investigating this variable. As such, the recommendation is to perform the second stage when the treating team consider the infection to be controlled, based on clinical judgement, laboratory, and radiological markers.[67] With regard to preoperative joint aspiration prior to the second stage reimplantation, the exact role of this traditional practice remains undefined. Culture of synovial fluid from a joint with an antibiotic-loaded cement spacer *in situ* has been shown to have low sensitivity for demonstrating persistence of infection, and so the general consensus from the most recent ICM guidelines is that they are not necessary.[68] However, it is very important to carry out repeat sampling intraoperatively at the time of reimplantation and these results should be relied upon. Patients with positive microbiology at this point should receive further antibiotic therapy, as the presence of organisms during the second stage has been shown to correlate with higher rates of failure and early reinfection.[69,70]

In a subset of patients whose inflammatory markers do not improve, or who experience poor/delayed wound healing, then a repeat first stage should be undertaken, with an exchange of cement spacer, and definitive components implanted in a 'third' stage.

During the second stage, sampling, debridement, and irrigation are repeated, prior to implantation of definitive components (which may require increased levels of constraint, as well as augments to manage associated bone and ligament insufficiency). This is similar to the implantation stage of a one-stage procedure. Postoperatively, patients should be placed on broad spectrum antibiotics until intraoperative cultures are reported negative.

Antibiotic suppression

Long-term antibiotic suppression of PJI as a definitive treatment is reserved for patients who will not benefit from surgery. Examples include patients who are unfit for surgery, who no longer wish to undergo further surgery, or in whom repeated exchange revisions have failed to eradicate PJI. However, for antibiotic suppression to be a viable option, the PJI must be the result of a low-virulence organism, with a tolerable oral antibiotic option and with well-fixed implants. This treatment is not a curative option, with the objective instead being to suppress bacterial activity and minimize symptoms. Compliance with a lifelong antibiotic regimen can be difficult for patients to manage, with intolerance and side effects being common problems.

Salvage procedures

Finally, in cases where eradication of PJI, has been unsuccessful, despite all efforts, salvage procedures represent an option for infection clearance, but with a loss of function. The point at which salvage procedures are considered is made on a case-by-case basis, and with input from both the specialist clinical team, the patient, and their carers. Typically, these procedures are reserved for patients who have failed multiple previous attempts at infection eradication or have an unreconstructable joint (as a result of soft-tissue or bone loss).

Arthrodesis

Knee fusion is a salvage technique to provide the patient with a stable, pain-free joint with which they can mobilize. Evidence of outcomes of knee arthrodesis for PJI are limited to small series, with generally good rates of infection clearance, but at the cost of a reduced quality of life.[71] Knee arthrodesis can be achieved using intramedullary nail, external fixator, or internal plate fixation.[72]

Amputation

Amputation for persistent PJI of the hip or knee is a last resort, typically after multiple two-stage revisions with extensive soft-tissue and bone loss as a consequence. Rarely, amputation may be necessary for critical sepsis as a life saving measure or in the event of irreparable neurovascular injury. Both hip and knee amputation result in a significant functional deficit, and significantly higher metabolic requirements to mobilize.[73,74] As a consequence, the significant loss of independence should be explained to the patient during counselling.

Permanent resection arthroplasty

Permanent resection arthroplasty constitutes removal of the prosthesis and extensive debridement of soft tissue and bone. While high success rates have been reported for resection arthroplasty, the procedure typically results in an unstable limb, with associated disability, pain, and reduced quality of life.[75] As such, this procedure is reserved for patients who would not be able to ambulate following alternative salvage procedures.

CONCLUSION

PJI is a significant challenge facing the orthopaedic community. With increasing numbers of patients living with a major joint arthroplasty, and with demand for such procedures rising, this challenge is expected to grow. While this review has discussed options for diagnosis and management, a critical component of care is the prevention of PJI. Infection prevention is a topic worthy of its own discussion, with patient optimization, surgical technique, implant factors, antibiotic usage, and service factors all key components. However, when PJI is considered the possible cause of a failing hip or knee arthroplasty, accurate diagnosis and appropriate management is key. Diagnostic markers for PJI are an area of active investigation, and, as such, it is likely that new tools (such as NGS) will become available to orthopaedic surgeons. However, validation and evidence of superiority and cost-effectiveness over existing methods need to be published. We recommend that patients diagnosed with PJI should be managed within specialist centres using an MDT approach in order to optimize outcomes. Such centres have a responsibility to drive forward knowledge in the field, as there remain uncertainties in the diagnosis and management PJI.

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