Periprosthetic hip infection: current concepts

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Abstract

Periprosthetic joint infection (PJI) following total hip arthroplasty (THA) is a devastating problem for surgeons, but worse for the patients involved. If diagnosed early, prompt intervention and treatment can vastly improve outcomes. Increased risk of PJI relates to decreased ability to fend off disease, along with modifiable and non-modifiable risk factors. PJI occurs due to either surgical site contamination, local spread or spread from a distant infection elsewhere in the body. Gram-positive organisms remain the most common causative microbes. Patients with PJI can present with a range of symptoms, from florid sepsis to decreased performance in a well-functioning joint. Here, the array of diagnostic tests available are used, and these are the focus of this article. The Second International Consensus Meeting on Musculoskeletal Infection 2018 advocated a scoring system for pre- and intraoperative non-microbiological tests. It highlights the importance of using multiple tests in tandem when faced with a failing arthroplasty or prosthesis, but with no organism cultured. Treatment options range from traditional two-stage revision surgery, through to single-stage surgery and antibiotic suppression. Treatment plans must be patient-specific, but all are significant undertakings. Therefore, the role of prevention must continue to be at the forefront of any arthroplasty surgeon's mind.

Keywords diagnosis; infection; periprosthetic; prevention; total hip arthroplasty; treatment

Introduction

As the world's population increases in age, the incidence of 'wear-and-tear' pathology is almost certain to increase alongside. Consequently total hip arthroplasty (THA) is more often required, and in 2017, 105,306 THAs were added to the National Joint Registry, up 3.6% from the previous year.[1] For the majority of patients, these operations are lifestyle-saving, and can provide many years of pain-free function.[2] Unfortunately, no surgical procedure is without risk, and arguably the most feared of all complications is infection. The rate of periprosthetic joint infection (PJI) following THA is cited at around 1–2%,[3–6] and it is one of the main reasons for revision surgery to be performed, costing an estimated £20,000 to the NHS per case.[7]

Despite being a well-documented and frequently encountered problem, diagnosis remains challenging. Significant effort is being put into establishing a gold-standard diagnostic tool. Prompt diagnosis and initiation of appropriate management vastly improves outcomes, and aims to prevent prolonged hospital admission, multiple further surgical interventions, and even permanent deformity or death.[5]

Risk factors

Many of the risk factors for PJI relate to the body's ability to combat infection preoperatively. A high (>35) or low (<20) body mass index, smoking, diabetes mellitus, advanced age, HIV infection, malnutrition, and co-morbidities including rheumatoid/psoriatic arthritis (especially if on disease-modifying antirheumatic drugs (DMARDs)) all fit into this category.

There are some modifiable risk factors from around the time of surgery that can increase the risk of PJI. Prolonged operating times has been shown to vastly increase the risk, potentially because of the longer timeframe available for bacterial colonisation, or alternatively simply because the operation was likely to be more complex if it was longer. Allogeneic blood transfusion increases the risk of PJI, although autologous blood transfusion through means of intraoperative cell salvage does not carry any increased risk. A concurrent urinary or respiratory tract infection at time of surgery increases the risk of PJI, however asymptomatic bacteriuria without the presence of any clear symptoms has no effect on risk. Thorough operative field decontamination decreases the chances of skin flora entering the wound and causing problems later on.

Postoperative complications including wound haematoma, superficial infection or dehiscence all have a role in increasing the risk of infection. Medical complications such as cerebrovascular events or acute coronary syndromes often require treatment by anticoagulation, which can then lead to haematoma formation. Down the line, haematogenous spread from other sources within the body including the urinary, respiratory or gastrointestinal tracts, dental or cutaneous infections can also contribute.[3,5,8]

Pathogenesis[3,5]

There are three main methods by which a THA can become infected: contamination at time of surgery, spread from concurrent infections elsewhere in the body, and haematogenous spread.

Surgical site contamination

The majority of PJIs occurring within the first year after implantation are secondary to microorganisms entering during the initial operation. These organisms may be from the patient's own skin flora, from the operating surgeon, the implants used or from the surroundings in which the operation takes place.

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Infection from a nearby site

As mentioned above with respect to risk factors, there is always a chance that microorganisms causing infections in nearby parts of the body can lead to PJI. This most commonly occurs during the early postoperative phase, where haematomas or wound infections track down to involve the prosthesis.

Haematogenous spread

Although rare, this can occur at any point following insertion of a prosthesis. Patients present clinically unwell, septic, and with signs of prosthetic joint infection. It is even more important to act quickly in these circumstances.

Microbiology

Gram-positive bacteria tend to predominate in PJI, with *Staphylococcus aureus* and coagulase-negative staphylococci as the main classes of organisms involved, resulting in over half of all PJIs.[2,3,6,8–12] *Staphylococcus epidermidis* and other skin flora are also important causative organisms.[4,5] Dental infections can result in haematogenous spread of *Streptococcus viridans* and anaerobic bacteria. Enterobacteria are often of urinary or gastrointestinal tract origin.[4] Chronic infection by indolent organisms such as the skin commensal *Propionibacterium acnes* can prove a real challenge to eradicate.[8] Many PJIs are also either polymicrobial, or the culture yields no result.[3]

When discussing the microbiology of PJIs, it is important to mention the role of biofilm in this disease process. A biofilm can be thought of as a 'city for microbes' — where microorganisms join together by means of an extracellular matrix, often forming on surfaces of foreign bodies. Because of this extracellular matrix, bacteria are relatively protected from the actions of antibiotics, and so the only true way to clear the infection is to remove the foreign body — the joint prosthesis. Biofilms also complicate the diagnosis of PJI, as it means that culture of fluid aspirated from the joint may not yield a diagnosis.[3–5]

Clinical presentation

Patients presenting with PJI can come with varied, subtle symptoms. It is important to differentiate between acute and chronic PJI; acute PJI presents with the classical infective symptoms of erythema, heat, swelling, tenderness, discharge and fever, whereas chronic PJI is more likely to present insidiously without significant systemic upset. In chronic PJI persistent or progressing pain is the salient symptom to watch out for, along with implant failure.[4]

Diagnosis of an acute PJI in an unwell patient follows the path which everyone learns early on in their medical career of history, examination, conventional blood tests and taking cultures both from peripheral veins and any wound discharge. If the patient is relatively stable, there is significant merit in trying to obtain samples from the joint itself prior to starting antibiotics in order to have the best possible chance of obtaining a true positive culture. However, this has to be weighed up against the patient's clinical condition — if they are in septic shock, prompt antibiotic administration should be prioritized.

The vague and non-specific nature of the presenting features of chronic PJI make for a degree of diagnostic challenge, especially differentiating between septic and aseptic implant failure.[4] If the patient is clinically well, albeit in pain, then there is time to thoroughly investigate prior to subjecting them to a difficult and lengthy treatment plan.

Diagnostic investigations

Despite being a feared complication of THA, with potentially disastrous consequences, the diagnosis of PJI lacks a gold standard test. Substantial effort is being put into developing this one-stop test, with a variety of avenues being pursued. In the meantime, the investigating surgeon can start simple and work upwards in an attempt to establish the diagnosis.

Peripheral blood tests

Full blood count:[3] often the first place to start when assessing a patient for any form of infection or inflammation, a full blood count can be of use in this scenario also. Although the sensitivity is reported to be low, it has a high specificity, and so like most tests described here, in isolation it is of limited value.

C-reactive protein and erythrocyte sedimentation rate:[3–5] again, often ordered as a matter of routine, in combination these non-specific markers of inflammation are more useful to rule out PJI than to diagnose it. Suggested thresholds of 30 mm/hour for erythrocyte sedimentation rate and 10 mg/litre for C-reactive protein have shown good sensitivity for excluding PJI. The challenge however comes when one or both are positive, as there is barely a condition in medicine which does not affect the results.

Radiological imaging

Plain radiograph:[3–5] the simplest of all imaging techniques, all patients with a suspected PJI should be referred for a plain radiograph. Although non-specific, these images can add another piece to the puzzle, and also rule out other causes of ongoing pain post-THA, including periprosthetic fracture or subluxation/dislocation. Areas of lucency and endosteal erosion around the implant can raise suspicion of PJI, however issues arise when trying to differentiate between infective and non-infective causes of loosening of an implant.

Ultrasonography:[5] this has a limited role but can be useful for identifying fluid collections around the prosthesis.

Computed tomography:[3,5] not all patients require advanced imaging modalities such as computed tomography (CT) scans and the other techniques described below, but these can be used as adjuncts when there is any uncertainty regarding the diagnosis. CT is helpful to distinguish between infective and non-infective implant loosening, by looking at the surrounding soft tissue structures for any signs of an infective process.

Three-phase bone scintigraphy:[3–5] this nuclear medicine scan is useful in detecting late PJI, though can produce confusing results if performed within two years of the original surgery, as remodelling takes place following insertion of the prosthesis and this is hot on the scan. The principle behind this technique is that technetium^{99}, a radioactive compound, is injected and gathers over time in areas of high cell turnover in and around bones, and

this accumulation can be detected by means of a gamma camera. Again, this technique is excellent at ruling out PJI, however it is very non-specific. The specificity can be improved when three-phase bone scintigraphy is combined with radioactive labelling and injection of autologous leucocytes the day prior to scanning.

Synovial fluid analysis

Although more difficult to obtain from a hip than a knee, and often requiring ultrasound or fluoroscopic guidance, synovial fluid samples can add real weight to the diagnosis of PJI. These can be obtained preoperatively if surgery is not imminently necessary and the patient is stable. Ideally, patients should be off all antibiotic therapy for 2 weeks prior to any fluid sampling.[3] A number of investigations can be performed on the samples.

Fluid cell count:[3–5] a raised fluid white cell count, with a high percentage of these being neutrophils, has been shown to be a good predictor of PJI. However, the reference ranges applied to the hip joint vary, with some studies quoting more than 4200 cells/ml with over 80% neutrophils, and others quoting lower values, for example 1715 cells/ml as a cell count range. Ultimately, if the result is extremely raised, then the diagnostic process becomes easier, however if the result comes back in the middle ranges, then the test cannot (and would not) be used in isolation, but rather as part of the workup.

Fluid culture:[3–5] this is an obvious test to perform, but has a number of limitations, including the time taken to receive a result, the high proportion of false-negatives and false-positives, and the difficulty in distinguishing between 'pathogen and passenger'. To increase the chance of obtaining a valid result, samples should be placed into a blood culture bottle.

Fluid leucocyte esterase testing:[3,4,6] leucocyte esterase testing has been a part of everyday life within healthcare for a number of years, principally in the diagnosis of urinary tract infections as part of the 'urine dip'. It is an enzyme found in neutrophils. The pad of the strip contains a substance to lyse these cells, causing leakage of leucocyte esterase. Upon this happening other chemicals within the pad cause it to change to a purple colour. The more leucocyte esterase present, the darker the purple colour, and therefore the more neutrophils present. This colour change can be analysed either manually or through a machine. This has recently been introduced as an option for testing synovial fluid, and evidence thus far[6] is encouraging, showing good correlation with white cell count and an excellent negative predictive value. These strips are also cheap and readily available within hospitals already. The downsides of this test are to do with inter-observer reliability when interpreting the result on a colorimetric scale, and also the fact that any contamination of the sample with blood or other substances interferes with the result.

Fluid α-defensin testing:[7] α-defensin is a peptide found within neutrophils, that acts on a number of different bacteria classes to disrupt cell wall synthesis. Testing for its presence within synovial fluid has shown great promise in aiding the diagnosis of PJI. This test can be carried out in a laboratory by means of an enzyme-linked immunosorbent assay (ELISA), or alternatively it can be carried out at the bedside or in theatre using point-of-care testing kits (Synovasure® α-defensin lateral flow test kit, Zimmer Biomet, Warsaw, Indiana, USA), which have a similar appearance, and work in a similar way, to a home pregnancy test. It is worth noting that the laboratory assay has a much better sensitivity and specificity than the point-of-care testing kit (laboratory assay sensitivity 0.95 (95% CI 0.91–0.98) and specificity 0.97 (95% CI 0.95–0.98), lateral flow kit (sensitivity 0.85 (95% CI 0.74–0.92) and specificity 0.90 (95% CI 0.91–0.98), although availability is an obvious downside of the laboratory-based test. Again, these tests are not currently recommended for use in isolation, but rather as adjuncts.

Perioperative tissue sampling and culture[3–5]

This has long been considered the strongest test in the arsenal to definitively achieve the diagnosis, however in order to achieve this the surgeon has likely already made the decision to revise the patient's THA. It is recommended that at time of surgery, multiple representative samples (typically at least five, as recommended by the work of the Oxford Bone Infection Unit) are taken and processed individually by the microbiology laboratory, in order to have the best possible chance of achieving a valid result. The duration of incubation required when assessing for PJI is debated. If one sample comes back positive then it may be a contaminant (especially if it is a species of low virulence), or alternatively it may be a significant but lucky culture of a difficult-to-catch species. There is a limited role for swabbing the wound. Histological analysis may also be useful in some circumstances, such as in the presence of a metal-on-metal bearing.

It is also important to not discount the implant itself, which can be a valuable source of organisms, although it is also likely to harbour a number of contaminants. The use of sonication to disrupt the biofilm on the surface of the implant along with the bacteria within it, followed by culture of the sonicate, is an option, but not readily available everywhere.

MSIS 2013 diagnostic criteria

Originally produced in 2011, the Musculoskeletal Infection Society issued guidance on diagnostic criteria for PJI. These were updated in 2013[13] (Table 1), with PJI being defined as present when one major criterion exists, or three minor criteria. Thresholds for the minor diagnostic criteria were also issued (Table 2).

In 2018, as part of the work performed for the Second International Consensus Meeting on Musculoskeletal Infection in Philadelphia, Parvizi et al.[14] proposed an update to these diagnostic criteria, using a scoring-based system (Table 3).

Treatment

It will come as no surprise that PJI is difficult to treat. Management strategies aim to alleviate pain and restore function, whilst eradicating the source of infection so that patients can remain well in the long-term.[3] The lengthy surgical procedures required are a serious undertaking, and a risk-benefit analysis should be performed with each individual patient, so that a personal management plan can be formed.

Musculoskeletal Infection Society diagnostic criteria periprosthetic joint infections

Major criteria (presence of one required)	• Two identical periprosthetic cultures • Sinus tract present which communicates with the joint
Minor criteria (presence of three or more required)	• Elevated serum C-reactive protein and erythrocyte sedimentation rate • Elevated synovial fluid white cell count OR '++' change on leucocyte esterase testing strip • Elevated synovial fluid white count neutrophil percentage • Positive histological analysis of periprosthetic tissue • A single positive culture

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Table 1

Two-stage revision surgery

For many years, this treatment modality has been widely considered the gold standard option for PJI.[3,4,9,11,15] First, all prostheses and infected tissues are removed, and deep microbiological samples are taken. This stage is separated from reimplantation of new metalwork by a prolonged period of antibiotic therapy, often around 6–12 weeks. Alongside this, cement spacers loaded with antibiotics can be used in the interim period to deliver high concentrations of antibiotics directly to the site of infection. PROSTALAC (Vancouver) or CUMARS (Exeter) may also help in keeping the tissues out length, especially in patients who are unlikely to be fit enough to return to a second stage; they are however complicated by higher dislocation rates if they are articulating. With regular review, inflammatory markers should hopefully be seen to fall to normal, and only then will the second stage be performed.

Advantages to the two-stage method include the highest rates of infection eradication, reported at over 90% in most studies.[4] Antibiotic therapy can be guided by microbiology results.

There remain a number of uncertainties on how best to carry out this method. There is limited guidance on how long to continue antibiotics between procedures, and whether these antibiotics should be through intravenous or oral routes. Of course, you are subjecting an often-frail patient cohort to at least two significant surgical procedures, and so this approach is not without its downsides.

Debridement, antibiotics, implant retention (DAIR) procedures

If infection occurs early (within 6 weeks of the primary surgery), or infective symptoms begin to occur acutely in a previously well-functioning THA, then DAIR procedures should be considered.[11] The principle behind this option is that if an infection is caught early, or there are no signs of prosthesis loosening, then it can be argued that there is no need to disturb the prosthesis. DAIR procedures have been shown to have similar complication rates to the two-stage revision approach, albeit with slightly lower infection eradication rates.[8,9]

DAIR is also of value in the frailer patient population who require quicker, less invasive operations.[8,10] Ultimately, with careful patient selection, it is not always necessary to fully replace the prosthesis, and so there is real promise in implant retention strategies. Further research is required to fully evaluate the role of DAIR in PJI.

Single-stage revision surgery

It can be possible to perform revision THA surgery for PJI as a single-stage procedure, however it is important to know the causative organism and its sensitivities.[4] If the organism cultured is fully sensitive to the antibiotics impregnated within the cement used, and the patient is relatively fit and well with good wound healing potential, then a single-stage procedure can be considered. The 'direct arthroplasty exchange' can be followed by a prolonged period of antibiotics.

Single-stage revision is rising in popularity, with recent evidence suggesting re-infection rates are comparable to the two-stage option.[15] There are obvious advantages when it comes to cost, mortality and poorer function postoperatively. It is important that meticulous debridement is performed at the time of surgery, to give the best possible chance of infection-free survival.[3]

Single-stage procedures have been reported as less successful for polymicrobial PJI, PJI with resistant causative organisms, or patients with more co-morbidities[4]. Despite this, there are many ongoing developments to try and improve single-stage surgery, and so this may become more widely adopted in future.

Musculoskeletal Infection Society minor diagnostic criteria for periprosthetic joint infections (PJI) thresholds

Minor criteria	Acute PJI (<90 days)	Chronic PJI (>90 days)
Erythrocyte sedimentation rate (mm/hour)	Not deemed helpful	30
C-reactive protein (mg/litre)	100	10
Synovial white cell count (cells/μl)	10,000	3,000
Synovial neutrophil percentage	90	80
Leucocyte esterase testing strip	+ or ++	+ or ++
Histological analysis of tissue	>5 neutrophils per high-power field in five high-power fields (x400)	>5 neutrophils per high-power field in five high-power fields (x400)

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Table 2

Score-based system for diagnosis of periprosthetic joint infections proposed by Parvizi et al.[14]

Major criteria				**Decision**
Two positive cultures of the same organism				Infected
Sinus tract with evidence of communication to the joint or visualization of the prosthesis				
Minor criteria			**Score**	**Decision**
Preoperative diagnosis	Serum	Elevated C-reactive protein (CRP) or D-dimer	2	≥6 infected
		Elevated erythrocyte sedimentation rate	1	2–5 possibly infected
	Synovial	Elevated synovial white blood cells or leucocyte esterase	3	0–1 not infected
		Positive α-defensin	3	
		Elevated synovial polymorphonuclear cell percentage	2	
		Elevated CRP	1	
Intraoperative diagnosis		Inconclusive preoperative score or dry tap	Score	Decision
		Preoperative score	–	≥6 infected
		Positive histology	3	4–5 inconclusive
		Positive purulence	3	≤3 not infected
		Single positive culture	2	

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Table 3

Suppression therapy

Our population is ageing, and people are living longer with significant comorbidities. If someone who is particularly frail has a THA that becomes infected, this can present a significant challenge. All of the treatment options described thus far are not small undertakings, and sometimes the risks of subjecting someone to such a procedure is so high that an alternative plan must be formed. The use of prolonged courses of suppressive oral antibiotics has been described.[10] This can be an attractive palliative option, assuming that the causative organism is sensitive to oral antibiotics that do not have a significant side effect profile. If there are signs of a sinus tract, or large collection, then this patient cohort may tolerate simple excision/drainage of these, and then can remain on oral antibiotics to control symptoms rather than control the cause.

It is worth mentioning that in some circumstances, either arthroplasty resection or amputation may be required, if all other surgical and medical treatment options have been exhausted.[3]

Prevention

With the significant healthcare burden PJI provides, its prevention has become a matter of routine in most orthopaedic centres, and a number of tactics are employed as second nature. The World Health Organization (WHO) has issued guidance on how to prevent infection postoperatively, based around optimizing any reversible risk factors:[12]

- Both meticillin-sensitive (MSSA) and -resistant *Staph. aureus* contribute to a large number of PJIs. Despite being often seen as a pathogen, they are often seen as a 'passenger' as part of the normal skin flora, especially within the nose. As a result, swabs are often taken prior to admission to detect these organisms, and if present, decolonization regimens in the form of mupirocin ointment are used to clear this prior to admission to an orthopaedic ward,[3,12] and its benefits have been proven.[2]
- Preoperatively, any optimization of the patient's health that is possible should be attempted. This includes weight, glycaemic control and discussion with any relevant specialties regarding pausing the use of immunosuppressive medications.
- Traditionally, the use of body exhaust suits ('space suits') was thought to be useful in the prevention of infection. However, the evidence for these is equivocal.
- Having lower levels of traffic going through theatre has been shown to help with preventing infection. Other small points that are a matter of routine for surgeons such as hair removal, adequate oxygenation and wound irrigation are all encouraged.
- Part of standard operative procedure today is to clean the skin with an iodine or chlorhexidine-based solution prior to any incision being made. Indeed, there is some evidence that washing the area with the same solutions the night prior to surgery may also have benefit.
- Preventative antibiotic use around the time of surgery is widely used in a variety of forms. On induction a broad-spectrum antibiotic is often given, and its use continued for the initial 24-hour postoperative period.
- Interestingly, the WHO does not advocate the use of laminar air flow in theatre, but it depends on the local set-up.

Future directions

To conclude, there are a number of factors that are going to result in PJI becoming even more of a challenge to clinicians. Patients are undergoing THA at a younger age, rates of antibiotic resistance are increasing and patients are living longer with more extensive comorbidities. Combine these issues and there are no

signs that management of PJI is going to become any more straightforward.

There are a number of management strategies available and selecting the right treatment for the right patient at the right time is what is ultimately going to make the difference. If a PJI can be caught early, then rates of eradication are significantly better. However, if a PJI is missed, the morbidity and mortality of the condition remains extremely high – comparable to some of the common cancers.

Further research is required into how to improve our current therapeutic choices, with specific focus on early diagnosis and management, and with a number of different research strategies ongoing. This includes looking at the implants themselves to make them less 'infectible' – this is an exciting area to watch for the future. ◆

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