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Approach to patients with a potential prosthetic joint infection

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What you need to know

- Prosthetic joint infections (PJIs) can occur at any time following surgery, with variable symptoms and signs
- A high index of suspicion for PJI is necessary for patients presenting with unexplained pain in their joint
- Serum biochemistry tests cannot be used in isolation to confirm or exclude a PJI
- Empirical antibiotics should not be started in the community or emergency department unless red flags for sepsis are evident

Hip and knee arthroplasty are safe, cost effective, and reliable surgical procedures that significantly improve patient quality of life by alleviating pain and restoring mobility.[1] Every year, more than 2 million people in countries of the Organisation for Economic Co-operation and Development undergo hip or knee replacement, mostly for osteoarthritis.[2] This number will rise with increasing life expectancy, bringing with it more patients at risk of developing a prosthetic joint infection (PJI).[3 4]

Hip and knee PJIs occur in approximately 1% of primary total hip replacements (THR) and approximately 2% of primary total knee replacements (TKR).[1] PJI is a serious complication, with high morbidity and mortality (>10% mortality for patients aged over 80[4]) and requires prolonged and complex treatment with substantial healthcare costs.[5] Recent studies estimate the cost at around £36 000 to treat an infected arthroplasty.[6] For revision arthroplasty, the risk of PJI is increased, occurring in approximately 4% of cases.[7] Worldwide, the incidence of PJIs is similar,[1] but with a considerable economic burden in developing countries, where treatment costs on average 4.5 times that of the original arthroplasty.[8]

How do patients with a prosthetic joint infection present?

The clinical presentations of PJIs vary considerably, contributing to the diagnostic challenge. Factors affecting the presentation include the joint involved, route and timing of infection, causative organism, and the patient's systemic response (table 1).[1] In native joint infections, the patient usually has a grossly reduced range of movement and an inability to weight bear, which may be absent in PJI because of the lack of native articular surface and denervation of the joint during surgery. In PJI, symptoms may also be acute, with overt signs of infection, or insidious in onset with vague signs and symptoms.[1 5 10]

Table 1 | Classification according to onset of symptoms after implantation, route of infection, and common causative organisms[1 5 7 9]

Time after implantation	0-3 months	3-24 months	>24 months
Type of infection	Early	Delayed	Late
Proportion	~30%	~40%	~30%
Route	Perioperative	Perioperative	Haematogenous
Signs	Acute	Chronic	Acute or subacute
Common pathogens	Virulent* organisms - *Staphylococcus aureus* - Streptococci	Indolent* organisms - Coagulase negative staphylococci - *Cutibacterium* sp	Virulent organisms - *S aureus* - *Escherichia coli* - *Klebsiella* - *Enterobacter*

* Virulence can be defined as a pathogen's ability to cause damage to a host. With virulent organisms being much more capable of causing infection as opposed to slow growing (indolent) organisms.

Early infections (0-3 months postoperative)

Early infections typically present with local signs of a joint infection: pain, erythema, warmth, effusion, and discharge from the wound site. Very early infections pose a diagnostic challenge as the normal postoperative joint can be painful, swollen, and warm to touch, which mimics some infective signs.[1 11] Systemic symptoms, particularly fever, severe pain, spreading cellulitis, purulent discharge, and a decline from initial postoperative function, are clues in differentiating an early infection from the body's normal response to surgery.

Delayed infections (3-24 months postoperative)

Delayed infections can present acutely, as described above; however a typical presentation is more insidious, with vague signs and symptoms and often unremarkable clinical examinations.[11] Patients may describe persistent pain and/or deterioration in joint function over weeks to months, often without overt signs of infection.[11] Patients with delayed infection may report that the joint has "never been right" or that their preoperative pain did not improve.

Late infections (>24 months postoperative)

Late infections have a range of presentations, therefore a high index of suspicion is necessary in all patients. Patients may present acutely with a hot, erythematous, and/or swollen joint as described above, however presentation can also be insidious, with general malaise or sepsis of unknown origin. Late PJIs are often secondary to a different focus of infection, most commonly gastrointestinal or genitourinary, that results in haematogenous seeding to the prosthesis.[5 9 12]

What risk factors increase the risk of developing a prosthetic joint infection?

Risk factors can be subdivided into patient related factors and surgical factors. A systematic review and meta-analysis of 66 observational studies found patient related factors associated with increased PJI to be male sex, body mass index (BMI) of >30 kg/m^2, concurrent diabetes mellitus, rheumatoid arthritis, steroid use, and a history of malignancy.[3] These findings were echoed in a more recent study which investigated more than 3600 TKRs revised for infection over a 10 year period.[13] The authors found that a BMI of 30 kg/m^2 or higher was associated with an increased risk of revision for infection compared with BMI lower than 25 kg/m^2. The study also reported an increased risk of infection in patients with a score of 2 or higher (mild systemic disease) on the American Society of Anesthesiologists (ASA) scale, as compared with those with ASA score of 1 (an otherwise healthy individual). The same study reported increased rates of PJI in patients with chronic pulmonary disease, diabetes, liver disease, connective tissue or rheumatic disease, or peripheral vascular disease, compared with those without.[13] These risk factors were mirrored in a 2021 meta-analysis that included prospective cohort and retrospective case-control trials looking at PJI in THRs.[14] Surgical factors increasing the risk of PJI in both hip and knee arthroplasty include previous surgery to the joint, history of infection within the joint, and indication for the primary arthroplasty being an inflammatory arthropathy or trauma.[13 14] History of postoperative wound infection is also a risk factor for PJI.[3]

How should you approach a patient with a potential prosthetic joint infection?

Take a thorough history and examination. The most commonly reported symptoms of PJIs are pain, joint swelling, erythema, warmth, discharge, and fever,[1 5] although, as mentioned, some infections present insidiously with no obvious signs. Patients without specific symptoms may disclose a general discomfort with the prosthesis or a feeling that "something isn't right." Have an especially strong suspicion of infection in patients with risk factors who develop unexplained persistent pain in the joint.

Examine the range of movement in the affected joint, testing for effusions, ability to weight bear, and distal neurovascular status, with a view to narrowing the differential diagnosis and excluding other potential sources of symptoms. In the hip this may be greater trochanteric pain syndrome or femoroacetabular impingement. Pain in the knee or leg may commonly be due to bursitis, deep vein thrombosis or a ruptured Baker's cyst.

The presence of a sinus tract within the boundaries of the original incision is pathognomonic[9 15] for a prosthetic joint infection and needs urgent referral to secondary care; however, well defined sinus tracts are uncommon and absence does not exclude a PJI.

Additionally, seek out specific information relating to the prosthesis, including the date of the arthroplasty, any risk factors for PJI, any postoperative complications such as superficial wound infections, and whether the patient received antibiotics at that time.

What tests support a diagnosis of a prosthetic joint infection?

Diagnosis of a PJI is challenging as no single investigation has adequate sensitivity and specificity to diagnose or exclude the presence of a PJI in isolation.[1] Diagnosis is based on a combination of clinical findings, inflammatory markers, synovial fluid analysis and culture, histological analysis of tissue surrounding the prosthesis, and intraoperative findings.[1 10 12] The European Bone and Joint Infection Society lists specific diagnostic criteria for diagnosing PJIs that incorporate many of these factors.[16]

Investigation of a suspected PJI (including if the only symptom is pain) includes a full blood count and inflammatory markers; C reactive protein (CRP), D-dimer, and erythrocyte sedimentation rate (ESR). If the patient has no signs of sepsis or shows no overt signs of infection, investigative tests can be done in a community setting. CRP is elevated during the first few weeks postoperatively, usually reaching a peak at day 3 and with a gradual and variable return to normal within 28 days. For this reason, a single elevated CRP is not diagnostic of infection, and a rising trend would be more concerning.[9 17 18] Additional serum biomarkers, eg procalcitonin and IL-6, are more costly, provide similar diagnostic information as CRP, and are of limited value.[19]

Updated diagnostic criteria from the Musculoskeletal Infection Society give a very high reported sensitivity (97.7%) and specificity (99.5%) for the diagnosis of PJI (table 2). A retrospective, multicentre study looking at possible PJIs more than three months after surgery showed that patients with a raised CRP (cut off values 10 mg/L for infections presenting >90 days from surgery and 100 mg/L for infections presenting <90 days from surgery), D-dimer (cut off value 860 ng/mL), and/or ESR (cut off value 30 mm/h) should raise suspicion of a PJI and the patient should undergo aspiration by the orthopaedic team.[20]

Table 2 | Musculoskeletal Infection Society 2018 major and minor preoperative diagnostic criteria for PJI. Modified[20]

Major criteria (at least one of the following)				Decision
Two positive cultures of the same organism				Infected
Sinus tract with evidence of communication to the joint or visualisation of prosthesis				
Pre-operative diagnosis	Minor criteria		Score	Decision
	Serum	Elevated CRP* or D-dimer (>860 ng/mL)	2	≥6 Infected 2-5 Possibly infected 0-1 Not infected
		Elevated ESR (>30 mm in first hour)	1	
	Synovial	Elevated synovial white blood cells† or leucocyte esterase (++)	3	
		Positive α-defensin (signal to cut off >1)	3	
		Elevated synovial polymorphonuclear neutrophils‡	2	
		Elevated synovial CRP (>6.9 mg/L)	1	

* CRP>100 mg/L if <90 days post op or CRP>10 mg/L if >90 days post op.

† Elevated synovial white blood cells >10×109/L if <90 days post op or >3×109/L >90 days post op.

‡ Elevated synovial polymorphonuclear neutrophils >90% if <90 days post op or >80% if >90 days post op.

In all cases, obtain plain radiographs of the affected joint, but note that radiography has 14% sensitivity and 70% specificity in detecting implant associated infections,[21] and is more useful to exclude confounding diagnoses such as dislocation, fractures surrounding the implants, loosening of the prosthesis, and rare causes such as concurrent bone malignancy.[22] Although periprosthetic lucency, prosthetic loosening, new periosteal bone formation, and effusions can occur with PJI, these findings are neither sensitive nor specific and are also often found in association with aseptic loosening of the prosthesis.[21] Radiographs can be requested by the GP if the referral to orthopaedics is done semi-urgently, or can be done in the emergency department if the patient is being referred as an emergency (further discussed below).

Aspiration of a suspected PJI is an essential investigation that should be performed only in a sterile environment by the receiving orthopaedic team. Synovial fluid analysis includes differential cell counts, Gram staining, culture, and antimicrobial susceptibilities[9] to identify the causative pathogen(s) and establish the sensitivity of microorganisms to antimicrobial agents.[1] Note that culture negative PJI (clinically infected without microbiological evidence) can occur in around 25% of cases,[23] and extended cultures can be used, especially to detect less virulent organisms.[24]

Synovial biomarkers, eg α-defensin, are modern markers used to aid in the diagnosis of PJI, with α-defensin (signal to cut off ratio >1) reported as showing a sensitivity and specificity of up to 100%.[25] These tests can be useful in patients with initial negative aspirates or where the diagnosis is uncertain; however, because of the high costs, they are not first line investigations.

Care of patients with prosthetic joint infection and when to refer

Management of a confirmed PJI includes eradicating infection and restoring joint function to prevent associated morbidity and mortality.[1] A patient with infection requires orthopaedic referral, although when they need to be seen is variable, as outlined below.

Systemically unwell (septic) patients

Initial clinical assessment determines if the patient has overt signs of infection and systemic symptoms. Transfer unstable patients immediately to a local emergency department for urgent management following local sepsis guidelines. In this situation, obtaining a joint aspirate in a sterile environment may not be feasible before intravenous antibiotics, and blood cultures taken before antibiotic therapy may be relied upon to detect the responsible organism.

Patients without sepsis red flags

If the patient shows signs of infection but has no red flag symptoms[26] (box 1), refer directly to the local on-call orthopaedic team for same day assessment and investigation.[10 27]

Box 1: Sepsis red flags from the Sepsis Manual[26]

- Patient responds only to voice or pain/ is unresponsive
- Acutely confused state
- Systolic blood pressure ≤90 mmHg (or drop >40 from normal)
- Heart rate >130 beats/min
- Respiratory rate ≥ 25 breaths/min
- Needs oxygen to keep SpO2 ≥92%
- Non-blanching rash, mottled/ashen/cyanotic
- Not passed urine in last 18 hours/output <0.5 mL/kg/hour
- Lactate ≥ 2 mmol/L
- Recent chemotherapy

Patients without overt infection

For patients with an insidious onset of symptoms such as pain and/or deterioration in joint function over time with no overt signs of infection, a semi-urgent (within four weeks) outpatient orthopaedic referral is acceptable,[27] changing to an urgent referral if the patient's clinical condition deteriorates in the interim. In the meantime, patients can also be sent for routine blood tests, including CRP and ESR, which are beneficial to the orthopaedic surgeon when reviewing in clinic. Ensure that the patient has adequate analgesia.

Unless clinically unstable, patients should not receive empirical antibiotics before formal diagnosis. Initiating empirical antibiotics risks delaying diagnosis and treatment, reduces diagnostic culture, and may confer antibiotic resistance.[10 28] Antibiotics should be

avoided for at least two weeks before aspiration or biopsy for patients with suspected PJI unless they show signs of sepsis (box 1).[27]

A full medical and social history is useful to understand baseline functioning, patient independence, and to help establish the aim of treatment. Revision surgery is high risk and may not be suitable for medically unfit patients where suppressive antibiotic therapy may be the only alternative, providing the causative organism has been isolated.[28]

Management of a PJI requires a specialist multidisciplinary team comprising orthopaedic surgeons and microbiologists. Empirical antibiotic therapy after diagnosis needs to be based on local policies due to different trends of antibiotic resistance. Patients require a long course of antibiotics which is given intravenously initially, however this can often be done as an outpatient in parenteral antibiotic therapy clinics. Patients often switch to oral antibiotics once their inflammatory markers are within the normal limits, and usually receive a minimum of six weeks of antibiotics.[1 9 15]

In most cases, surgical management is required, including debridement, antibiotics, and implant retention or revision arthroplasty (one or two stage),[1 5] with recent systematic reviews and meta-analyses putting the success rates (95% confidence intervals) at 61.4% (57.3 to 65.4), 92.4% (86.9 to 96.6), and 91.2% (89.4 to 92.8), respectively.[29 30] Deciding which surgical option to use is guided by the duration of symptoms, time since implantation, stability of the implant, condition of surrounding soft tissues, and (if a suitable antibiotic is available) based on the susceptibility profiles of cultured organisms.[5 9]

Education into practice

- How do you care for patients in your practice who have painful joint replacements without overt signs of infection?
- In what instances have you diagnosed superficial wound infections in joint replacement patients, and prescribed antibiotics?
- After reading this article, how might you change your practice?

How this article was made

We conducted a systematic search for literature in four biomedical databases: PubMed, EMBASE, MEDLINE, and Cochrane Central Library in May 2019 and updated in June 2021. Search terms selected were "hip," "knee," "arthroplasty," "prosthetic joint infection," "periprosthetic joint infection," "revision surgery," "debridement, antibiotics and implant retention," "post-operative." All terms were searched in a combination of title, abstract, and medical subject headings to retrieve the best results. We applied a filter for the English language, and included all publication types and publication years.

How patients were involved in the creation of this article

We interviewed three patients who had undergone replacement joint surgery for a prosthetic joint infection. Their input guided our writing, particularly regarding the impact of treatment on a patient's quality of life. The patients emphasised the importance of being kept informed throughout the uncertainty of investigation and treatment.

Contributorship and the guarantor: RB conceptualised the article and was the overall supervisor and guarantor. BA did the literature review and wrote the first draft. LD, PC, and KZ reviewed, edited, and amended the manuscript and tables. All authors approved the final version.

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