Prosthetic joint infection diagnosis in an age of changing clinical patterns of infection and new technologies

Joint replacement surgery is one of the most successful interventions in modern medicine, restoring joint function, mobility and quality of life in those with severe osteoarthritis. In 2022, 126 000 knee and hip replacements were performed in Australia,[1] adding to the pool of about 1 million Australians currently living with one or more joint replacements in situ.[2] Unfortunately, around 4000 Australians are diagnosed with a prosthetic joint infection (PJI) annually.[3] This devastating complication leads to high health care costs, prolonged hospital stays, and mortality.[4,5] Unlike most infections, PJI involves the interaction of microorganisms with both host tissues and synthetic implants. Hence curative treatment involves surgery to debride or replace the infected components as well as prolonged courses of antibiotics. Early and accurate diagnosis of PJI is vital to enable timely management and improved patient outcomes.

In this article, we summarise the current approaches to the diagnosis of PJI and their challenges, and discuss innovation in PJI diagnosis.

Definition and classification

PJI refers to infection involving the bone–prosthesis interface, the joint space, and the surrounding tissues. Wound infections may precede or co-exist with PJIs but are not themselves PJIs. PJIs can be classified as early (within 30–90 days following joint replacement, usually due to peri-operative acquisition of pathogenic bacteria), chronic (months to years post-operatively with low grade symptoms), and late acute (months to years post-operatively with an acute onset of symptoms in a previously well functioning joint, usually caused by bacterial seeding during blood stream infections). This classification is important because of differences in underlying bacterial aetiology,[6] diagnostic criteria, empirical antibiotic choices,[7] surgical strategy, and outcome.[8]

Because there is no definitive gold standard, diagnostic criteria with multiple components have been developed for PJI (Box 1). Traditionally, these require a clinically suspected infection plus a combination of clinical, imaging and laboratory findings. Of the criteria, those of the European Bone and Joint Infection Society[11] and the International Consensus Meeting[12] are the most up to date, widely used, and accurate.[13] These criteria are primarily intended for research and should be used to supplement rather than replace clinical judgement. In both diagnosis and management of PJI, it is important to have input from a multidisciplinary team, including orthopaedic surgeons, infectious diseases physicians, and clinical microbiologists.

Uncertainties in diagnosis

Culture-negative prosthetic joint infection and culture contaminants

Not all patients with PJI have a causative organism identified, and conversely, not all patients with positive deep cultures have a PJI. Culture-negative PJI occurs when diagnostic criteria are met but no organism is cultured (Box 1). This occurs in 5–10% of all PJIs[13] and may be explained by organisms not growing due to recent antibiotic use or fastidious growth requirements. It is therefore important to delay empirical antibiotic therapy until after diagnostic sampling unless the patient has sepsis. Contaminants are also common, particularly with normal skin flora such as coagulase-negative staphylococci. For this reason, at least five deep periprosthetic fluid or tissue specimens should be collected for culture and histopathology, using separate sterile instruments and collection pots for each specimen.[14] If a low virulence organism (such as a coagulase-negative *Staphylococcus*) is grown from only a single specimen, it is generally not considered clinically significant, and is regarded as a contaminant.

Delayed post-operative wound healing: how long is too long?

After an elective joint replacement, it is common to have bleeding, inflammation of the surgical wound, and raised serum C-reactive protein levels for several days post-operatively, as part of the normal host response to the tissue trauma of surgery. A common conundrum is a patient presenting with a red or weeping surgical wound in the post-operative period. In a recent prospective study, 1019 patients recorded their wound status daily for 30 days after elective joint replacement. Sixteen of them developed a proven PJI, and the strongest predictors were persistent wound drainage in the third post-operative week, and newly developed wound drainage following a week of no wound drainage.[15] A discharging wound on or after the third post-operative week should therefore be considered evidence of a PJI until proven otherwise.

If a patient presents to primary care or the emergency department with wound concerns in the first month after elective joint replacement, a common response is to start them on oral antibiotics. Since PJI requires surgery and prolonged high dose antibiotics for cure, a course of oral antibiotics at this stage will mask the problem and delay proper treatment. Rather, the patient's orthopaedic surgeon or their team should be contacted so urgent assessment can be arranged, with consideration of open debridement and tissue sampling.

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1 Diagnostic criteria for prosthetic joint infection (PJI)

Diagnostic criteria	IDSA (2013)[9]	MSIS/ICM (2013)[10]	EBJIS (2018)[11]	ICM (2018)[12]
Definition	Any 1 criterion	≥ 1 major or 3 minor criteria	≥ 1 confirmed or two likely criteria	≥ 1 definitive criterion, or total score ≥ 6
Clinical findings				
Presence of sinus tract	Definitive	Major criterion	Confirmed	Definitive
Pre-operative tests				
Serum C-reactive protein > 10 mg/L		Minor criterion	Likely	2 points
Serum D-dimer				1 point
Blood erythrocyte sedimentation rate				1 point
Abnormal labelled WBC scan			Likely	
Synovial fluid tests				
Raised synovial WBC count (cells/μL)*		Minor criterion (> 1700)	Confirmed (> 3000) Likely (> 1500)	3 points
Neutrophil proportion*		Minor criterion	Confirmed (> 80%) Likely (> 65–79%)	2 points
Positive α-defensin			Confirmed	3 points
Intra-operative or deep specimen tests				
Visible purulence at operation	Definitive		Likely	3 points
≥5 neutrophils per high powered field on histological examination of tissue	Highly suggestive	Minor criterion	Confirmed (> 5 HPF) Likely (> 1 HPF)	3 points
Growth of the same microorganism from ≥ 2 separate deep specimens	Definitive	Major criterion	Confirmed	Definitive
Growth of a microorganism from 1 deep specimen	Highly suggestive	Minor criterion	Likely	2 points
Growth from sonication fluid			Confirmed (> 50 CFU/mL) Likely (> 1 CFU/mL)	

CFU = colony-forming units; HPF = high powered field; ICM = International Consensus Meeting; IDSA = Infectious Diseases Society of America; MSIS = Musculoskeletal Infection Society; EBJIS = European Bone and Joint Infection Society; WBC = white blood cell. * Synovial fluid WBC counts and neutrophil proportions are higher in early and late acute PJI than in chronic PJI. Cut-offs are mainly derived from chronic PJI studies and are not well validated for early and late acute infections. ◆

Low grade chronic joint pain and dysfunction

Another common conundrum is the patient who had a joint replacement years ago and has developed low grade chronic pain and stiffness of the joint. This could represent either chronic infection, aseptic loosening of the prosthesis, or metallosis where there is an inflammatory host response to particles of metal shed from the prosthesis. These conditions can be challenging to distinguish, since bacteria may be hidden in biofilm on the surface of the implant in a dormant state, making them difficult to culture and protecting them from the host immune response and systemic antibiotic treatment. Clues suggestive of infection rather than aseptic loosening include pain at rest or in bed rather than only during or after activity; a history of pain and dysfunction ever since the original joint replacement surgery; raised serum C-reactive protein levels; redness, swelling or warmth of the affected joint; and peri-articular inflammation seen on nuclear medicine imaging. However, all these features can be absent in a chronic infection, and some can be present in aseptic loosening. Discharge from the wound suggests infection and may represent a sinus communicating with the joint space, which is diagnostic of a chronic PJI. In the absence of a sinus, diagnosis requires either aspiration or surgical biopsy and hence the patient should be referred to an orthopaedic surgeon.

Recent developments in diagnosis

Established and emerging methods for diagnosis of PJI are summarised in Box 2.

Synovial fluid biomarkers

Raised synovial fluid white blood cell count is a key component of all diagnostic criteria for PJI. Since this represents an inflammatory host response, multiple other synovial fluid biomarkers have been evaluated. These include pro-inflammatory cytokines such as interleukin (IL)-1, IL-6 and C-reactive protein, leucocyte esterase (detected by a urine dipstick test) and α-defensin, an antimicrobial peptide secreted by human neutrophils in response to pathogens. Of these, α-defensin has been most extensively evaluated. It can be measured in a laboratory using enzyme-linked immunosorbent assay, or at the bedside using a lateral flow assay. α-Defensin has both sensitivity and

2 Established and emerging methods for diagnosis of prosthetic joint infection (PJI) and their strengths and weaknesses

Approach	Strengths	Weaknesses
Joint aspiration and culture	• Directly samples joint fluid for microbiological analysis • Gold standard for diagnosis • Allows for antibiotic sensitivity testing	• Invasive procedure with associated risks • False negatives due to prior antibiotic use • Limited sensitivity in chronic infections • Contamination during sample collection may lead to false positives
Nuclear medicine imaging (bone, gallium and positron emission tomography scans)	• Whole-body imaging for systemic evaluation • Can detect early signs of infection • Useful for identifying multifocal infections	• Limited specificity as uptake may be seen in non-infectious conditions • Radiation exposure • Not suitable for early post-operative infections
Synovial fluid α-defensin	• Potential for increased sensitivity and specificity compared with traditional white blood cell count • Can be done at the bedside as well as in a laboratory	• α-Defensin assays are more expensive than and likely not superior to traditional synovial fluid white cell count and differential • α-Defensin lateral flow assay (bedside test) has lower sensitivity than laboratory test
Sonication of explanted components	• Disrupts biofilm from the surface of explanted prosthetic components • Potential to detect dormant bacteria and those embedded in biofilm	• Requires special equipment and more laboratory time • Increased sensitivity may lead to higher contamination (false positive) rates • Value of routine sonication in addition to traditional approaches remains to be proven
Polymerase chain reaction (PCR)	• Amplifies nucleic acid, detecting pathogens not growing under traditional culture conditions • Targeted PCR only detects specified bacteria, but 16S PCR can detect any bacterium • Not affected by recent use of antibiotics by the patient • Potential for faster turnaround times than culture-based methods	• High sensitivity can lead to diagnostic dilemmas and unclear clinical significance • Challenges in interpretation of PCR for PJI diagnosis • Commercial assays are expensive
Metagenomics (shotgun sequencing)	• Broad approach detecting any DNA or RNA in a clinical specimen • Redefines understanding of PJI, suggesting polymicrobial infection is more common	• Not widely available; role in diagnosis yet to be defined • Potential for detecting unexpected pathogens of unclear significance • Role and practical application not yet established

specificity of about 90%[16] when evaluated against PJI diagnostic criteria (Box 1). Lateral flow assay is quicker and more convenient but has lower sensitivity.[17] However, α-defensin is a product of neutrophils, and hence is an indirect way of measuring neutrophil number and activation. Compared with the traditional, cheap and widely available synovial fluid white cell count and differential, α-defensin assays are not clearly superior[18] and should not be routinely used.

Sonication of explanted components

High energy sound waves applied through a water bath have been traditionally used to polish jewellery. This same approach can be used to disrupt biofilm from the surface of explanted components of joint prostheses, and may therefore theoretically increase the sensitivity of bacterial culture.[19] However, this increased sensitivity also makes it more likely for contaminants to be cultured, and the value of routine sonication in addition to traditional approaches remains to be proven.

Polymerase chain reaction

Polymerase chain reaction (PCR) is used to amplify nucleic acid such as bacterial DNA. This has the potential to detect pathogens which will not grow under traditional culture conditions, such as anaerobic or fastidious organisms, and unlike culture, is not affected by recent use of antibiotics. PCR assays can be targeted to a specific pathogen (eg, *Kingella kingae*), multiplex assays to detect multiple known pathogens (eg, BioFire [bioMérieux] synovial fluid assay, which detects 39 target organisms), or broad range assays across an entire kingdom. The most commonly used broad range PCR test is 16S pan-bacterial PCR, which amplifies and sequences gene coding for bacterial ribosomal RNA and is highly conserved across all bacteria. This gene sequence is then compared against a reference database to identify one or more bacteria. Pan-fungal and pan-mycobacterial PCRs are also available in reference laboratories.

PCR assays can detect very small numbers of organisms or their components in a sample, whereas culture requires a higher number of organisms which must viable. While PCR approaches hold promise, their high sensitivity can be a double-edged sword. The clinical significance of a low copy number of *S. epidermidis* (for example) in a single tissue specimen is unclear and challenges remain in the interpretation of PCR for PJI diagnosis. Discordance between culture results and PCR not infrequently creates diagnostic dilemmas for the treating team.

Metagenomics

An even broader approach to molecular diagnostics is metagenomics using shotgun sequencing, which

can detect and identify any DNA or RNA in a clinical specimen.[20] This is redefining our understanding of PJI, suggesting that polymicrobial infection is more common than traditionally thought, that unexpected pathogens may have a role in PJI, and that aseptic loosening is often not actually aseptic.[21] Metagenomics is not yet widely available, and its role is yet to be defined.

Conclusion

Timely and accurate diagnosis of PJI can be challenging but is important to allow appropriate management. Over the past decade, diagnostic criteria have been progressively improved, but still rely largely on traditional clinical and laboratory approaches. Novel diagnostics including synovial fluid biomarkers, sonication of explanted prosthetic components, and molecular microbiology assays have the potential to transform the field but are not yet ready for prime time.

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