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Making the diagnosis in prosthetic joint infection: a European view

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- Prosthetic joint infections (PJI) can be difficult to diagnose.
- Studies have shown that we are missing many infections, possibly due to poor diagnostic workup and the presence of culture-negative infection.
- PJI diagnosis requires a methodical approach and a standardised set of criteria.
- Multiple PJI definitions have been published with improved accuracy in recent years.
- The new European Bone and Joint Infection Society definition offers some advantages in clinical practice. It identifies more clinically important infections and accurately defines those with the highest risk of treatment failure. It reduces the number of patients with uncertain diagnoses.
- Classification of PJIs may offer a better understanding of treatment outcomes and risk factors for failure.

Keywords

- prosthetic joint infection
- diagnosis
- EBJIS
- definition
- classification
- biomarkers
- histology
- microbiology

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Introduction

Prosthetic joint infection (PJI) has been identified as the second most common cause of revision after knee arthroplasty and the fourth commonest cause in hips, in the United Kingdom (1). This may be a major underestimation as new data, from joint registries, has shown that we are missing many infected cases (2, 3). Over 3200 papers were published on PJI between 1998 and 2018, with over 12,000 citations in 2018, alone (4). From this research, there has been a realisation that we do not have a single diagnostic test which can reliably diagnose PJI or exclude it. PJI can present with a wide range of clinical features at all time points after prosthesis implantation. Although PJI is an inflammatory condition, patients vary in the degree of their inflammatory response, making the use of serum biomarkers more challenging for diagnosis (5, 6).

The difficulty in diagnosis is further complicated by the presence of culture-negative infection which may be present in 20–30% of some series particularly in late-presenting cases (7, 8). The culture-negative rate may be reduced with careful sampling protocols (8, 9) but will always be a problem. This means that the diagnosis must often be established using non-microbiological criteria.

How do we define a prosthetic joint infection?

Prior to 2011, there was no agreed PJI definition. To address this, the Musculoskeletal Infection Society (MSIS) in the USA proposed a 'gold standard' definition based on the presence of one of two major criteria (sinus tract or positive microbiology) or the presence of at least four out of six minor criteria (10) (Fig. 1). In 2012, The Infectious Diseases Society of America (IDSA) proposed a simpler definition based on the presence of one out of five diagnostic criteria (11). Both definitions were the result of consensus views from expert groups. The 2011 MSIS definition was further modified in 2013 at the First International Conference on Musculoskeletal Infection (ICM 2013) (12). This remains the most widely used definition set. These definitions were highly successful in focusing attention on diagnosis providing a structure for investigation research. However, it was quickly realised that they may be missing 'low-grade' infections.

In 2018, a new definition was published (13), which stratified cases according to major criteria or a weighted score of minor criteria. This was discussed at the Second ICM Consensus Conference later that year but was not

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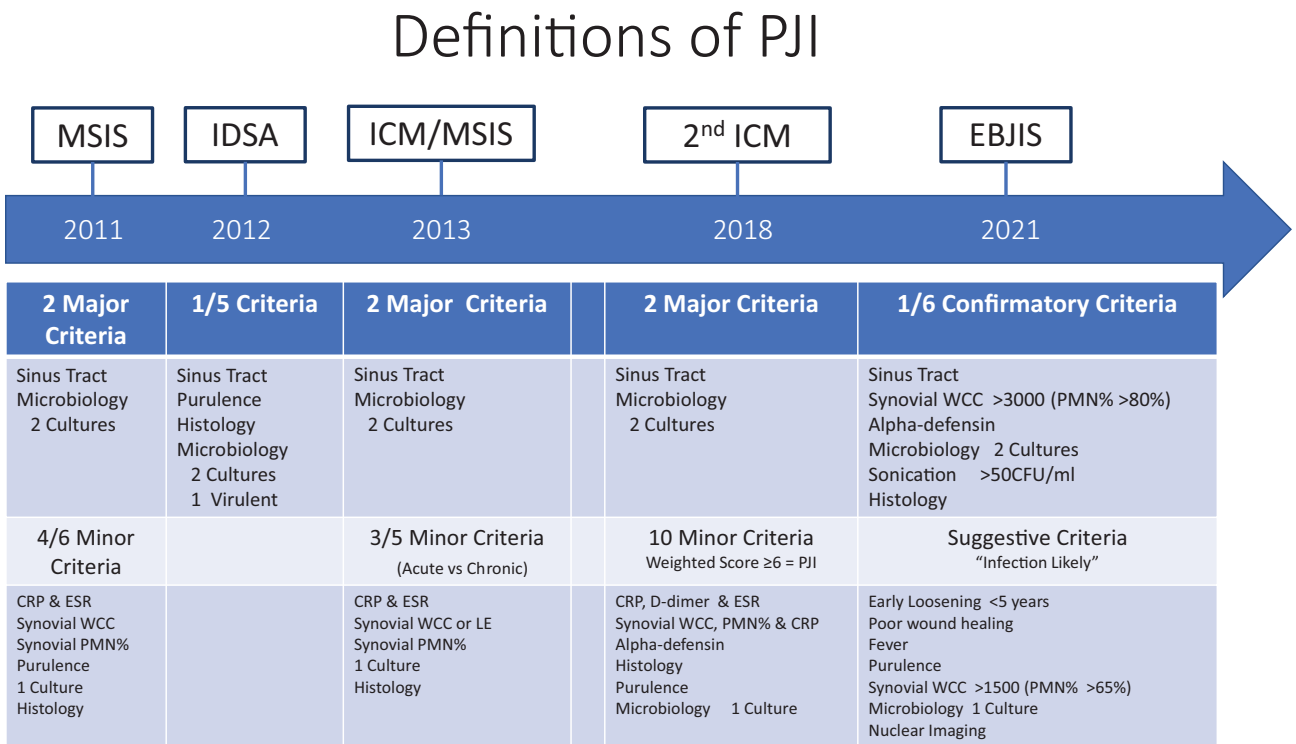

Figure 1
The timeline of PJI definitions.

universally accepted and was not endorsed by MSIS or the European Bone Joint Infection Society (EBJIS).

One major concern about the early definitions was that they presented a bimodal clinical decision (infected or not) based on tests which are neither 100% sensitive nor 100% specific. This was partly addressed in the 2018 definition which allowed an 'inconclusive' group who had some minor criteria present but did not reach the score required for a definitive PJI diagnosis. This 2018 definition was validated in a single cohort, as a complete entity. This study did not validate the magnitude of individual scores allocated to each minor criterion (decided by expert opinion). This would have been a better validation but would require a very large sample size. Nevertheless, the 2018 definition is more sensitive than previous attempts and has been used in several recent studies.

A European initiative on PJI

In 2018, the EBJIS reviewed the literature on the diagnosis of PJI and developed a new type of definition. This recognised that some diagnostic tests were sensitive for infection (C-reactive protein, nuclear imaging) but were also positive in many other conditions. They might suggest infection but could not confirm it even when combining such tests. Other tests were less sensitive but had a very high specificity for infection (sinus tract to the prosthesis positive microbiology positive histology). This principle guided the publication of the EBJIS definition of PJI in 2021 (5) (Fig. 2).

The EBJIS PJI definition defines three distinct groups (infection unlikely, infection likely and infection confirmed). This new concept of the definition includes a middle group where the presence of at least two positive tests suggests that the joint is more likely to be infected than not. This outcome should encourage a treating surgeon to investigate further to establish if confirmatory tests are positive. The presence of any of the confirmatory tests will diagnose a PJI, based on the high specificity of that test.

The elements of the EBJIS PJI definition

The EBJIS working group evaluated many diagnostic tests. All tests were included, or excluded, based only on the published evidence of their diagnostic sensitivity and specificity. Expert opinion alone was not used in deciding the place of any test.

Clinical features

A sinus tract communicating with the prosthesis or joint is pathognomonic of PJI and has been included in all PJI definitions. Other clinical features (fever, erythema,

	Infection Unlikely (all findings negative)	Infection Likely (two positive findings)[a]	Infection Confirmed (any positive finding)
Clinical and Blood Workup			
Clinical Features	Clear alternative reason for implant dysfunction (e.g. fracture, implant breakage, malposition, tumour)	1) Radiological signs of loosening within the first 5 years after implantation 2) Previous wound healing problems 3) History of recent fever or bacteraemia 4) Purulence around the prosthesis[b]	Sinus tract with evidence of communication to the joint or visualization of the prosthesis
C-Reactive Protein		> 10 mg/L (1 mg/dL)[c]	
Synovial Fluid Cytological Analysis [d]			
Leukocyte count [c] (cells/µL)	≤ 1,500	> 1,500	>3,000
PMN (%) [c]	≤ 65%	> 65%	>80%
Synovial fluid Biomarkers			
Alpha-defensin[e]			Positive Immunoassay or lateral-flow assay[e]
Microbiology[f]			
Aspiration Fluid		Positive culture	
Intraoperative (fluid and tissue)	All cultures negative	Single positive culture [g]	≥ 2 positive samples with the same microorganism
Sonication[h] (CFU/mL)	No growth	>1 CFU/mL of any organism[g]	>50 CFU/mL of any organism
Histology[c]			
High-power field (400x magnification)	Negative	Presence of ≥5 neutrophils in a single HPF	Presence of ≥5 neutrophils in ≥5 HPF
			Presence of visible microorganisms
Others			
Nuclear Imaging	Negative 3-phase Isotope Bone Scan[c]	Positive WBC scintigraphy[i]	

Summary Key

[a]Infection is only likely if there is a positive clinical feature or raised serum CRP together with another positive test (synovial fluid, microbiology, histology or nuclear imaging).

[b]Except in adverse local tissue reaction (ALTR) and crystal arthropathy cases.

[c]should be interpreted with caution when other possible causes of inflammation are present: gout or other crystal arthropathy, metallosis, active inflammatory joint disease (e.g. rheumatoid arthritis), periprosthetic fracture or the early postoperative period.

[d]These values are valid for hips and knee PJI. Parameters are only valid when clear fluid is obtained and no lavage has been performed. Volume for the analysis should be >250 µL, ideally 1 mL, collected in an EDTA containing tube and analyzed in <1h, preferentially using automated techniques. For viscous samples, pre-treatment with hyaluronidase improves the accuracy of optical or automated techniques. In case of bloody samples, the adjusted synovial WBC= synovial WBC $_{observed}$ − [WBC $_{blood}$ / RBC $_{blood}$ x RBC $_{synovial\ fluid}$] should be used.

[e]Not valid in cases of adverse local tissue reaction (ALTR), hematomas or acute inflammatory arthritis or gout.

[f]If antibiotic treatment has been given (not simple prophylaxis), the results of microbiological analysis may be compromised. In these cases, molecular techniques may have a place.

[g]Interpretation of single positive culture (or <50 UFC/mL in sonication fluid) must be cautious and taken together with other evidence. If a preoperative aspiration identified the same microorganism they should be considered as two positive confirmatory samples. Uncommon contaminants or virulent organisms (e.g. *S. aureus* or Gram negative rods) are more likely to represent infection than common contaminants (such as coagulase-negative staphylococci, micrococci or *Cutibacterium acnes*).

[h]If centrifugation is applied, then the suggested cutoff is 200 CFU/mL to confirm infection. If other variations to the protocol are used, the published cut-offs for each protocol must be applied.

[i]WBC Scintigraphy is regarded as positive if the uptake is increased at the 20 hour scan, compared to the earlier scans (especially when combined with complementary bone marrow scan).

Figure 2

EBJIS criteria for the diagnosis of clinically suspected prosthetic joint infection is presented. This figure places each diagnostic test in one of three groups, depending on the sensitivity and specificity of that test. The summary key provides caveats and guidance on using the definition clinically. (Reproduced from McNally *et al*. (5))

pain, reduced range of motion) are not specific to PJI but are quite sensitive and so may suggest the presence of infection (infection likely) (14). Similarly, early loosening, previous wound healing problems or recent bacteraemia, all suggest infection but do not confirm it (15, 16, 17).

Serum biomarkers

Serum inflammatory biomarkers are easily accessible worldwide, cheap, quick, and routinely performed preoperatively. When clinical signs are absent, they can be the first indication of PJI. In a review of the most commonly used serum markers (C-reactive protein, erythrocyte sedimentation rate, white blood cell count, percentage of neutrophils, neutrophils to lymphocytes ratio, platelet count to mean platelet volume ratio, fibrinogen, D-dimer, interleukin 6 and procalcitonin), serum C-reactive protein (CRP) and fibrinogen showed the best diagnostic accuracies (18).

However, these parameters show suboptimal performance in confirming PJI, especially in low-grade infections (6, 18, 19, 20). Sensitivities and specificities of serum CRP ranged between 68 and 81% and 66 and 87%, respectively (6, 21, 22, 23). The low specificity may be explained by the increased false positive rate in patients with systemic inflammatory conditions such as extra-articular infections (pneumonia, urinary tract infection, etc.), autoimmune disorders (rheumatoid arthritis, psoriasis, systemic lupus erythematosus, etc.) and active cancer. Serum parameters are systemic markers and are therefore unspecific. On the other hand, low sensitivity may be a result of an inadequate immune response in patients with an infection caused by a low virulent microorganism encapsuled in biofilm formation, with a freely draining sinus, an impaired immune system or under the influence of immunomodulatory or antimicrobial therapy (19, 20). The EBJIS definition includes caveats in the summary key to address these issues. Therefore, serum inflammatory markers can only be recommended as suggestive criteria rather than confirmatory criteria. An elevated CRP (cut off $\geq$ 10 mg/L) (6, 13, 21, 24), without any other cause, should prompt the clinician to investigate further for PJI. Normal CRP levels cannot exclude infection (6, 18, 19).

Synovial markers

Joint aspiration, under sterile conditions, with cytological and microbiological synovial fluid analysis is firmly embedded in the diagnostic work-up of suspected PJI.

Preoperatively, the most accurate diagnostic tests are the synovial fluid white blood cell count (SF-WBC) and the synovial fluid percentage of polymorphonuclear neutrophils (SF-%PMN). SF-WBC shows sensitivities from 78 to 94% and specificities from 81 to 96% (25, 26, 27, 28), and SF-%PMN shows sensitivities from 90 to 97% and specificities from 84 to 90% (25, 26, 28). However, the thresholds for diagnosing PJI vary throughout the literature (1500–4200 cells/mL for SF-WBC and 65–80% for SF-%PMN) (26, 28, 29, 30). This variation is a property of having a bimodal definition applied to a limited cohort. The EBJIS definition places these levels depending on the confidence level for each. The lowest reported thresholds of $\leq$1500 WBCs/mL and $\leq$65% polymorphonuclear neutrophil (PMN) can be used to exclude PJI (infection unlikely). Due to the high specificity in the literature, thresholds of >3000 WBCs/mL and >80% PMN can confirm PJI (13, 25, 31). The significance of levels of 1500–3000 WBCs/mL and 65–80% PMNs remains unclear and are therefore categorised as 'infection likely'. EBJIS highlighted that these parameters can be falsely elevated in the early postoperative period (6 weeks) and in patients with a periprosthetic fracture, dislocation, crystal arthropathy or rheumatoid arthritis (5).

In recent decades, new synovial biomarkers have been investigated to optimise the diagnosis of PJI. Promising results were reported for alpha defensin, an antimicrobial peptide released by neutrophils in response to pathogens. The quantitative alpha-defensin test (ELISA) showed sensitivities ranging from 75 to 100% and specificities from 82 to 100%, and the qualitative alpha-defensin lateral flow test sensitivities from 67 to 97% and specificities from 82 to 100%. Due to the high specificity of both test modalities, it can confirm an infection. However, due to its lower sensitivity, a negative test cannot exclude PJI (32, 33, 34). It should be noted that the level of alpha defensin can be influenced by metallosis, gout or inflammatory diseases (35, 36, 37).

In the EBJIS review of the literature, other synovial markers were evaluated, but at that time, none were sufficiently investigated or widely available. Since 2021, synovial calprotectin has shown encouraging results and may be included in future updates of the EBJIS definition, possibly to exclude PJI (38).

Microbiology

Preoperative synovial fluid culture cannot be used as a screening test for PJI. A negative synovial culture must not reassure the surgeon that the joint is sterile (5). A positive preoperative culture suggests infection (infection likely) (39, 40).

PJI can be confirmed by the presence of phenotypically identical organisms being cultured from two separate intraoperative specimens (41). However, sampling must be performed using a standardised protocol with at least five specimens harvested, each with separate instruments (9, 42). Specimens of bone–implant interface, periarticular membranes and synovium, are recommended. Infection is not uniformly distributed in the joint and multiple representative sites should be sampled (43). Implant-

related infections may require long culture times (12–14 days), but this can be reduced with the use of blood culture bottles and automated culture techniques (44).

The EBJIS definition included culture from the sonication of implants as a diagnostic criterion for the first time. Any positive culture from sonicate fluid should be regarded as suggestive of infection, but >50 colony-forming units/mL will confirm a PJI (42, 43, 45).

Histology

There is a strong correlation between the presence of PMNs in periprosthetic tissues and PJI (33, 46, 47), with good sensitivity (67–100%) and high specificity (93–100%) (46, 47, 48, 49). Due to this high diagnostic accuracy, histopathological analysis can confirm PJI. It is essential to collect at least three, but not more than six, deep tissue samples from the periprosthetic membrane (bone–implant interface membrane) and the pseudocapsule (neo-synovium) for optimal diagnosis (50).

Samples should be processed and interpreted by a pathologist experienced in musculoskeletal infections. Under high power field (HPF) (×400 magnification; conventional light microscope, diameter 0.625 mm, visual field 0.307 mm^2), the sections are investigated for highly inflamed areas. In these areas, only neutrophils within the tissue are counted. Neutrophils within haemorrhagic areas, entrapped in superficial fibrin, migrating from capillaries in granulation tissue or in blood vessels are ignored. In each tissue sample section, 10 HPFs should be investigated. The mean neutrophil count of these 10 HPFs is then calculated. A mean threshold of ≥5 PMNs in 10 HPFs is recommended to distinguish between septic and aseptic failure (47). This threshold is valid for both frozen and paraffin-fixed sections.

Visible microorganisms seen in histological sections can also confirm the diagnosis of PJI (5). Pathogens such as fungi, filamentous bacteria and mycobacteria can be diagnosed in special stains but may be missed in routine microbial cultures. Gram stain has a poor sensitivity but very high specificity for PJI (51).

Nuclear imaging

EBJIS introduced nuclear imaging, mainly as a rule-out test (5). Negative three-phase bone scintigraphy (2 years after total hip arthroplasty (THA) or 5 years after total knee arthroplasty (TKA)) has a high negative predictive value, making PJI unlikely (52). Also, increasing accumulation of isotope in white-blood cell scintigraphy, over a 20-h period, is suggestive of PJI and so has been added to the 'infection likely' category (53).

Table 1 **The percentage rates of PJI diagnosis with each definition, depending on pathogen detection** (adapted from Boelch *et al*. 2021) (7).

	2011 MSIS	2018 ICM	IDSA	EBJIS
PJI rate	20.7	25.4	28.1	32.0
Rate of repeated pathogen detection	98.1	75.4	68.1	57.0
Rate of single pathogen detection	1.9	13.9	13.9	19.8
Rate of PJI without pathogen detection	0.0	10.8	18.1	19.5

Is the EBJIS PJI definition accurate in clinical practice?

True validation of a set of criteria for diagnosis is almost impossible as it requires a reference standard against which the new definition can be assessed. It is possible to compare existing definitions and to look at the outcome of patients categorised into the three groups. It is not correct to talk about sensitivity or specificity because we cannot be sure of when the disease truly exists, without a reference 'gold standard'. In this situation, it is more acceptable to regard the 'sensitivity' of a definition as its ability to identify more cases as infected. It has been shown that different definitions perform differently in this ability, in any given cohort. The 2011 MSIS and its modified 2013 version have consistently been shown to identify less cases as infected (7, 13, 54, 55, 56). The ICM 2018 and the IDSA definitions are more sensitive, but the EBJIS definition identifies the largest proportion of cases as infected (7, 55, 56, 57). This trend may reflect our increasing awareness of so-called 'low-grade infections' or culture-negative infections, with the negative impact of unrecognised PJI on the outcome of revision arthroplasty.

In a study of 349 cases of revision hip arthroplasty (7), the EBJIS definition diagnosed 82 patients with PJI, compared to 53 with 2013 MSIS, 65 with 2018 ICM and 72 with IDSA (Table 1). The increased sensitivity (for both IDSA and EBJIS) was predominantly due to diagnosing PJI in culture-negative cases. This clearly demonstrated that the 2013 MSIS and 2018 ICM definitions were less sensitive for the detection of PJI due to culture-negative or difficult to culture organisms.

In a multicentre study of 697 revisions (56), the failure rate at 2 years after surgery was identical in cases with ≥2 positive cultures (17.9%), a single positive culture (17.0%) or culture-negative microbiology (17.2%), providing that the PJI was confirmed with the non-microbiological criteria in the EBJIS definition. This shows that EBJIS 'confirmed' culture-negative infections behave like EBJIS 'confirmed' culture-positive infections. As our use of newer molecular diagnostic techniques increases, we are discovering many more culture-negative infections which are clinically significant (58, 59).

Is the EBJIS definition over-sensitive?

It is possible that the EBJIS definition is over-sensitive and may over-diagnose PJI. In a study of 206 revisions for suspected infection (55), the EBJIS definition confirmed all

the infections diagnosed by either the IDSA or the 2018 ICM definitions but did not identify any further PJIs alone. It appeared to operate as a unifying definition and was not over-diagnosing infection (Fig. 3).

This question can also be addressed by using the clinical outcome as a 'gold standard' and correlating this with the diagnosis determined by each definition. In the multicentre study (56), it was shown that PJI diagnosis correlated closely with the outcome at 2 years, for all definitions (i.e. infected cases had a higher failure rate than non-infected cases). However, cases identified as 'confirmed' or 'infection likely' by the EBJIS definition that were classified as non-infected (i.e. missed) by 2013 MSIS, 2018 ICM or IDSA definitions had the same high failure rate as those with confirmed infection by any definition. This was true, regardless of the microbiological status (56). The authors concluded that the EBJIS PJI definition more accurately defined patients at high risk of failure due to infection.

How do the definitions perform in the preoperative assessment period?

In all PJI definitions, there are tests which can be performed before surgery and those which require operation (tissue sampling). Sigmund *et al.* (55) showed that the EBJIS preoperative criteria diagnosed 69% of finally 'confirmed' PJIs, with 50% from IDSA and 46% for 2018 ICM. Reciver-operative charateristic (ROC) analysis demonstrated the

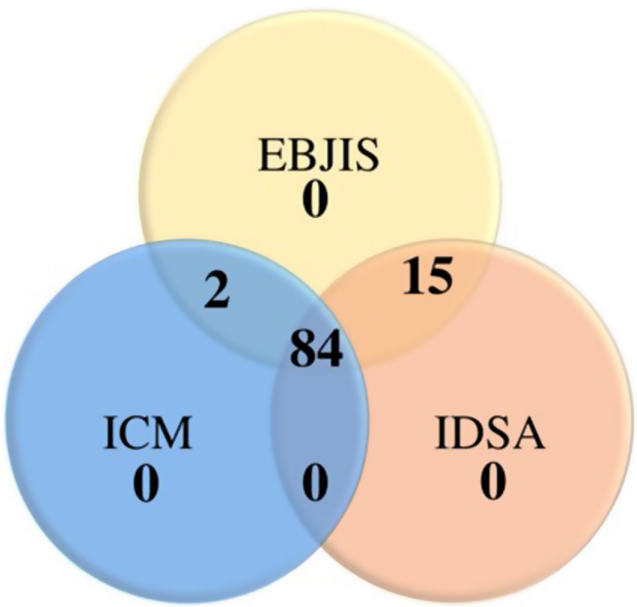

Figure 3
The EBJIS PJI definition identified all cases diagnosed by the 2018 ICM and IDSA definitions. Numbers refer to the actual number of cases with confirmed infection by each criteria (adapted from Sigmund *et al. Bone J Res* 2022) (55).

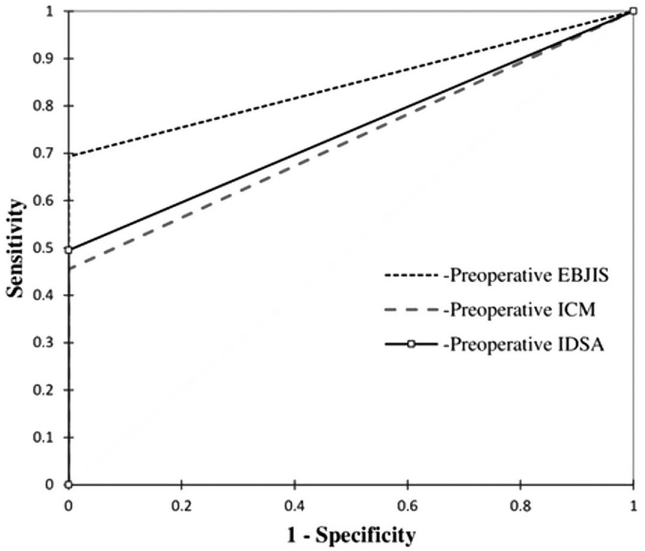

Figure 4
Receiver–operator curve plots for the three definitions (IDSA, 2018 ICM and EBJIS) showing the better preoperative predictive ability of the EBJIS definition (adapted from Sigmund *et al.* 2022) (55).

improved performance of the EBJIS definition (Fig. 4). This finding was also reported by Sousa *et al.* (56), showing that EBJIS had the highest kappa value, comparing preoperative and definitive diagnosis (EBJIS: k=0.9; 2018 ICM: 0.8, IDSA: 0.6, 2013 MSIS: 0.4). Boelch *et al.* (7) showed that the EBJIS definition had the highest specificity and positive predictive value when comparing preoperative joint aspiration results (culture and white cell count) with a definitive diagnosis. These results suggest that the EBJIS definition may be more useful clinically in the preoperative period to select patients for further investigation or treatment.

Does the EBJIS definition address the 'grey zone' of uncertain diagnoses?

Both the 2018 ICM and the EBJIS definition include a category where the infection is not 'confirmed', but there are some criteria present which suggest infection (ICM, 'inconclusive'; EBJIS, 'infection likely'). Two studies have evaluated this question (55, 56). Both showed a significant reduction in the number of uncertain diagnoses when comparing EBJIS to 2018 ICM (Table 2).

Table 2 The number of uncertain diagnoses was reduced by almost half, using the EBJIS PJI definition.

	n	2018 ICM 'inconclusive'	EBJIS 'infection likely'	*P* value*
Sousa *et al.* (57)	472	42 (8.9%)	22 (4.7%)	0.01
Sigmund *et al.* (56)	206	30 (14.6%)	16 (7.8%)	0.029
Total	678	72 (10.6%)	38 (5.6%)	0.0007

*Chi-square test; significance at $P < 0.05$.

How do we use the EBJIS PJI definition in clinical practice?

One criticism of all published PJI definitions is that they require numerous diagnostic tests. While some PJIs may be diagnosed with minimal investigations, more correct diagnoses will be established with more diagnostic tests. For the EBJIS definition, there is a minimum diagnostic set which could be recommended to maximise the accuracy of diagnosis.

At presentation, we recommend taking a full medical history, examination of the limb, a plain x-ray of the joint and a serum CRP for all patients. If a sinus is present, no other preoperative tests are required for diagnosis. Further microbiological tests will be needed to guide antimicrobial therapy. If there is no sinus, the joint should be aspirated for culture, leukocyte count and percentage PMNs. Synovial alpha-defensin assay or white blood cell scintigraphy can be considered.

If these preoperative tests suggest that an infection is likely and surgery is planned, intraoperative sampling with ≥5 microbiological specimens and 3–6 histological specimens should be performed in all operated cases. Implants may be sent for sonication.

If no surgery is planned, nuclear imaging may be considered as a rule-out test.

Are all PJIs the same?

In most PJI studies, patients are grouped together as a single cohort with no attempt to stratify the condition by severity or any other parameter. Occasionally, the duration of the infection is used (acute, early, delayed, late, chronic), but these terms are difficult to define (60, 61). This is surprising as the outcome may be critically dependent on factors which are identifiable before treatment. It would be inconceivable to report open and closed tibial fractures in a single group and combine the outcomes, but we regularly do this with PJI, with and without a draining sinus. Therefore, we need to consider stratifying PJIs after they have been diagnosed.

Classification systems can help describe clinical problems in a standardised and systematic manner, aiding communication and decision-making. A PJI classification should be simple and could guide management or allow a prognosis to be discussed with patients prior to surgery. Three classifications are described: the McPherson classification (62), the PJI-TMN classification (63) and the

	For PJI: Joint (prosthetic)	For Osteomyelitis: Bone involvement	Antimicrobial options	Coverage of ST	Host status
Uncomplicated	J1 Prosthetic joint infection with all of the following: • Primary type implant *in situ* • Minimal or no bone loss* • No evidence of loosening • No history of periprosthetic fracture	B1 Cavitary infection without joint involvement (including cortical, medullary and non-segmental cortico-medullary)	Ax Unknown / culture negative A1 All isolates sensitive to ≥80% of susceptibility tests and resistant to <3 susceptibility tests	C1 Direct closure possible – plastic surgery expertise not required	H1 Well-controlled disease or patient fit and well
Complex	J2 Prosthetic joint infection with either: • associated periprosthetic fracture • Moderate bone loss** • Prosthetic loosening • Non-primary type implant *in situ*	B2 Segmental infection without joint involvement Or Any bone infection with associated joint involvement	A2 Any isolate either: • Sensitive to <80% of all susceptibility tests performed • Resistant to ≥4 susceptibility tests • Resistant to anti-biofilm antibiotics in the presence of an implant	C2 Direct closure not possible – plastic surgery expertise required	H2 Patient with poorly controlled co-morbidity or severe co-morbidity (evidence of end organ damage) Or Recurrent bone infection after previous debridement
Limited options	J3 Prosthetic joint infection with either: • Custom or tumour type implant *in situ* • Custom or total bone replacement required for reconstruction • Major bone loss***	B3 Whole bone involvement	A3 Any isolate sensitive to 0 or 1 susceptibility test		H3 Unfit for definitive surgery despite specialist intervention Or Patient declines surgery

Figure 5

The JS-BACH classification of bone and joint infection. The JS variable is used for PJI and the B variable for osteomyelitis. Both PJI and osteomyelitis use the antimicrobial options, coverage of the soft tissue and the host status variables to determine the complexity of the infection.

JS-BACH classification (64). Each defines different variables deemed to be important in management. A common variable used in each classification is the patient's health, which highlights the importance of systemic and local disease status. Additional variables include the timing of the infection, the infecting organism, loosening of the prosthesis, periprosthetic fracture, soft tissue status and bone loss.

McPherson *et al.* (62) first classified PJI using the duration of infection, medical status of the patient and condition of the local infection site. This classification builds on the Cierny and Mader classification of long bone osteomyelitis (65). Patients with less severe hip PJI (early post-operative infection with no local or systemic compromise) had superior outcomes following single-stage revision compared to two-stage revision (66). Healthy patients also demonstrated improved outcomes after debridement and implant retention (DAIR) (67). These findings demonstrate the importance of including host-comorbidity when predicting surgical outcomes in PJI (62, 68).

The tumour, node and metastasis (TNM) classification of malignancy has been adapted to the context of PJI (63). Three variables were used, T: Tissue and implant conditions, N: Non-human cells (bacteria and fungi) and M: Morbidity of the patient. The PJI-TNM classification incorporates over 200 possible permutations although it has now been simplified in a condensed version, the pTMNr (69). The stated clinical application is to guide management into four possible treatment categories: DAIR (T0N0), implant removal (T1, T2, N1, N2), a 'less aggressive' operation (M3b) or non-operative management (M3a, M3c) (63). An important development of this classification was the inclusion of microbiology, where multi-drug resistant isolates have been shown to be correlated with increased risk of failure (70, 71).

The BACH classification originally included four variables for use in osteomyelitis. These were the Bone involvement (B), available Antimicrobial options (A), Coverage of the soft tissues (C) and Host status (H), each representing one of the key treatment teams in the multi-disciplinary management of bone and joint infections (72). BACH was designed to stratify patients by complexity and guide the triage of cases. It was shown that BACH correlated well with outcome, providing prognostic information to patients (73). BACH was adapted for PJI in 2021 with the addition of a 'joint-specific' (JS) variable (The JS-BACH Classification) (64). The JS variable included information on implant type, loosening, bone loss and history of periprosthetic fracture. This simpler classification offers three groups: 'uncomplicated PJI', 'complex PJI' or 'PJI with limited treatment options' based on the four variables (Fig. 5).

In a study of 220 patients with PJI confirmed by the EBJIS definition, JS-BACH was evaluated to determine its ability to predict clinical outcomes and patient-reported quality of life (64). At a mean of 4.7 years after revision, increasing severity in JS-BACH correlated with a higher rate of treatment failure (Cox proportional hazard ratio for failure for 'uncomplicated PJI' vs 'complex PJI' was 23.7; 95% CI: 3.32–174.0, $P=0.002$). Specifically, the 'JS', 'A' and 'H' variables were all independent predictors of failure after surgery. At 1 year after revision, EuroQol EQ-5D-3L scores were significantly higher for 'uncomplicated PJI' vs 'complex PJI' ($P=0.012$) and vs 'PJI with limited treatment options' ($P=0.005$). There were also significant differences in Oxford hip and knee scores (64).

These results suggest that once the diagnosis of PJI has been established, it is valuable to classify cases to give insight into the efficacy of treatments and the contribution of risk factors for failure.

Conclusion

This review has highlighted the challenges in designing and validating criteria for the diagnosis of an infected prosthesis and stratifying the severity of that infection. Great progress has been made in the diagnostic definitions since the MSIS in 2011. The new EBJIS definition (5) appears to offer some advantages over the previous criteria. It recognises the paramount importance of using only specific tests to confirm infection but allowing other sensitive tests to suggest that infection may be likely. It has been endorsed by the MSIS, the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) study group on implant-related infections (ESGIAI), the British Infection Association (BIA) and the EBJIS. It requires further investigation in larger patient groups and several prospective trials are underway. As new diagnostic tests become available, they can be added to the platform in the most appropriate place, increasing the accuracy of each category.

It should be noted that making the diagnosis of PJI, with any definition, does not dictate any particular treatment. This can only be decided by combining information from the definition and classification together with a full discussion of the patient's needs and wishes. The diagnostic pathway is just the start of the clinician's role in the management of PJI.

ICMJE conflict of interest statement
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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