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INFECTION

Diagnosing periprosthetic joint infections

A COMPARISON OF INFECTION DEFINITIONS: EBJIS 2021, ICM 2018, AND IDSA 2013

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Aims

This study evaluated the definitions developed by the European Bone and Joint Infection Society (EBJIS) 2021, the International Consensus Meeting (ICM) 2018, and the Infectious Diseases Society of America (IDSA) 2013, for the diagnosis of periprosthetic joint infection (PJI).

Methods

In this single-centre, retrospective analysis of prospectively collected data, patients with an indicated revision surgery after a total hip or knee arthroplasty were included between 2015 and 2020. A standardized diagnostic workup was performed, identifying the components of the EBJIS, ICM, and IDSA criteria in each patient.

Results

Of 206 included patients, 101 (49%) were diagnosed with PJI with the EBJIS definition. IDSA and ICM diagnosed 99 (48%) and 86 (42%) as infected, respectively. A total of 84 cases (41%) had an infection based on all three criteria. In 15 cases (n = 15/206; 7%), PJI was present when applying only the IDSA and EBJIS criteria. No infection was detected by one definition alone. Inconclusive diagnoses occurred more frequently with the ICM criteria (n = 30/206; 15%) compared to EBJIS (likely infections: n = 16/206; 8%) (p = 0.029). A better preoperative performance of the EBJIS definition was seen compared with the ICM and IDSA definitions (p < 0.001).

Conclusion

The novel EBJIS definition identified all PJIs diagnosed by any other criteria. Use of the EBJIS definition significantly reduced the number of uncertain diagnoses, allowing easier clinical decision-making.

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Keywords: Periprosthetic joint infection, Infection definition, Diagnosis, revision arthroplasty, revision total hip arthroplasty, revision total knee arthroplasty

Article focus

- In this study, three infection definitions (European Bone and Joint Infection Society (EBJIS) 2021, International Consensus Meeting (ICM) 2018, Infectious Diseases Society of America (IDSA) 2013) were assessed in a consecutive series of patients having revision surgery after a total hip or knee arthroplasty. The aim was to find the most clinically useful definition, with high sensitivity and fewest inconclusive diagnoses.

Key messages

- The EBJIS definition identified all periprosthetic joint infections (PJIs) diagnosed by any definition with no further infections, suggesting that EBJIS is more sensitive in comparison to the other two definitions.

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- The EBJIS preoperative criteria demonstrated improved accuracy in predicting definitive diagnosis.
- Significantly fewer patients had an inconclusive diagnosis, which is important in guiding clinical decision-making.

Strengths and limitations

- This is the first comparison of these three infection definitions.
- This analysis addresses a valid clinical problem and provides important information for clinical routine.
- Due to the lack of a gold standard, it is difficult to evaluate the 'real' performance of the PJI definitions.

Introduction

Effective treatment of periprosthetic joint infection (PJI) begins with an accurate diagnosis. Although many diagnostic tests are available, no single test has absolute accuracy. Hence, different groups have developed PJI definitions combining clinical findings, laboratory parameters (blood and synovial fluid), microbiological and histological analyses, and intraoperative findings.[1-6] The first infection definition was developed in 2011 by the Musculoskeletal Infection Society (MSIS) at its 21st Annual Meeting.[3] Due to concern around reduced sensitivity to detect low-grade PJI, this was modified by a consensus group (400 experts from 52 countries) at the International Consensus Meeting (ICM) in Philadelphia, Pennsylvania (USA) in 2013.[4] In the same year, the Infectious Diseases Society of America (IDSA) published an evidence- and opinion-based guideline for diagnosing PJI including only major criteria.[1] The IDSA emphasized that even if none of the criteria were met, an infection may still be present. In 2018, a weight-adjusted scoring system was designed by Parvizi et al[5] and validated on a selected cohort of patients. This was presented at the 2018 ICM but was only supported by 68% of delegates,[6] and was not endorsed by the European Bone and Joint Infection Society (EBJIS) or the MSIS.

In 2021, the EBJIS published a new concept of a three-level 'traffic light' definition including an 'infection likely' group.[2] This definition recognized the difficulty with a simple 'septic' or 'aseptic' decision,[7] and placed diagnostic tests as confirmatory (infection present) or suggestive of infection (infection likely), based on the specificity or sensitivity of published and validated tests. However, no 'gold standard' infection definition exists, making comparison between different infection definitions difficult. Nevertheless, a standardized and uniform infection definition is needed, not only to diagnose and treat PJI accurately but also to provide a basis for comparison between studies. An infection definition providing higher sensitivity and fewer inconclusive cases would be highly desirable for clinical use. With a higher number of true positive infections and a lower number of inconclusive cases, the surgeon's decision-making for the optimal treatment (aseptic vs septic revision) would be easier and the reinfection rate might be reduced.

Hence, we assessed three infection definitions (EBJIS 2021, ICM 2018, IDSA 2013) in a consecutive series of patients having revision surgery after a total hip arthroplasty (THA) or total knee arthroplasty (TKA). We aimed to find the most clinically useful definition, with high sensitivity and fewest inconclusive diagnoses.

Methods

Study design and population. This retrospective analysis of prospectively collected data was performed in a tertiary orthopaedic hospital specializing in the treatment of PJI (Department of Orthopaedics and Trauma Surgery, Medical University of Vienna, Vienna, Austria). Between January 2015 and June 2020, patients having revision surgery of hip or knee, due to septic or aseptic failure, were included. Patients with surgery within the last six weeks, an antibiotic-loaded bone cement spacer in place, the second stage of two-stage revision, and periprosthetic fractures were excluded from this study. The study was approved by the institutional ethical review board of Medical University of Vienna and performed in accordance with the Declaration of Helsinki.[8]

Infection definitions. A PJI was diagnosed using the ICM 2018,[5] IDSA 2013,[1] and EBJIS 2021[2] criteria (Tables I to III).

Data collection. A standardized diagnostic workup was performed in each patient. Patient characteristics, radiographs, results of blood and synovial fluid samples, intraoperative findings (purulence), histology, and microbiology were recorded, to identify the components of the three definitions.

Demographic details. A total of 206 patients (60% female; median age 74 years (interquartile range (IQR) 65 to 80)), having revision surgery after a THA (n = 104, 50%) or TKA (n = 102, 50%) were included (Table IV). Overall, 16 patients (8%) had inflammatory joint disease, with no difference between the septic and aseptic groups (aseptic: n = 7/105, 7%; septic: n = 9/101, 9%; p = 0.609, Fisher's exact test).

Diagnostic test methods. Preoperatively, the presence of a sinus tract was noted, and blood samples were taken for serum CRP.[9] A cut-off of > 10 mg/l was used based on the ICM and EBJIS criteria. Implant loosening was defined on radiographs, or CT.

Joint aspiration was performed under sterile condition. Then, 1 ml of the aspirate (in ethylenediaminetetraacetic acid (EDTA)) was used for automated quantification of the white blood cell count (WBC) and the percentage of polymorphonuclear neutrophils (%PMN). Established thresholds of ≥ 3,000 cells/µl and ≥ 80% were used according to the EBJIS and ICM criteria. Thresholds of ≥ 1,500 cells/µl and ≥ 65% PMN were allocated to the "Likely Infection" group when using the EBJIS definition. Remaining synovial fluid was sent for 14-day culture and processed per standard laboratory protocol.[10]

Qualitative alpha-defensin testing was done by using the lateral flow test (Synovasure; Zimmer Biomet,

Table I. 2013 Infectious Diseases Society of America (IDSA) definition for the diagnosis of periprosthetic joint infection.

2013 Infectious Diseases Society of America (IDSA) definition
PJI: at least one criterion needs to be fulfilled
1. Communicating sinus tract
2. Visible purulence surrounding the prosthesis
3. Positive histological analysis of periprosthetic tissue
4. ≥ 2 positive tissue cultures or a combination of positive synovial fluid culture and tissue culture with phenotypically identical microorganisms
5. ≥ 1 virulent microorganism (e.g. *Staphylococcus aureus*) of tissue culture or synovial fluid culture

PJI, periprosthetic joint infection.

Table II. Second version of the International Consensus Meeting (ICM) definition (2018) for the diagnosis of periprosthetic joint infection.

2018 International Consensus Meeting (ICM) definition			
Major criteria (PJI: at least one criterion needs to be fulfilled)			
1. Two positive cultures of the same organism			
2. Sinus tract with evidence of communication to the joint or visualization of the prosthesis			
Minor criteria			
Preoperative diagnosis		**Score**	**Decision**
Serum			
	1. Elevated CRP (> 10 mg/l) or D-dimer (> 860 ng/ml)	2	
	2. Elevated ESR (> 30 mm/h)	1	≥ 6: infected
Synovial			2 to 5: possibly infected*
	3. Elevated synovial WBC (> 3,000 cells/µl) or LE (++)	3	0 to 1: not infected
	4. Positive alpha-defensin (signal-to-cut-off ratio > 1)	3	
	5. Elevated synovial PMN% (> 80%)	2	
	6. Elevated synovial CRP (> 6.9 mg/l)	1	
Intraoperative diagnosis			
	1. Preoperative score	-	≥ 6: infected
	2. Positive histology	3	2 to 5: possibly infected†
	3. Positive purulence	3	0 to 1: not infected
	4. Single positive culture	2	

*For patients with inconclusive minor criteria, intraoperative criteria can also be used to diagnose periprosthetic joint infection.
†Consider molecular diagnostics (e.g. next generation sequencing).
PJI, periprosthetic joint infection; PMN%, percentage of polymorphonuclear neutrophils; WBC, white blood cell count.

Switzerland),[11] during a second aspiration before arthrotomy.

Intraoperatively, at least three tissue specimens were sent for 14-day culture.[10]

At least two tissue samples of the pseudocapsule and periprosthetic membrane were collected for histopathological analysis. Tissue neutrophils were counted with a cut-off of ≥ 5 polymorphonuclear neutrophils/high power field (HPF).[11] Explanted components were sent for culture, after sonication.[12]

For preoperative diagnosis, the following parameters were assessed based on the used infection definition and their specific cut-offs: communicating sinus tract (IDSA, ICM, EBJIS), synovial fluid WBC and %PMN (ICM, EBJIS), positive alpha-defensin lateral flow test (ICM, EBJIS), positive microbiology in the synovial fluid (IDSA: ≥ 1 virulent microorganism), elevated serum CRP (ICM), and visible purulence surrounding the prosthesis (IDSA).

Statistical analysis. For descriptive analysis, continuous variables are summarized as median and IQR, and categorical variables as absolute and relative frequencies. To compare metric variables, the independent-samples *t*-test was used. For the comparison of binary variables, the Fisher's exact test or chi-squared test was used. The preoperative performances of the three infection definitions were evaluated by calculating sensitivity, specificity, accuracy, positive (PPV) and negative predictive value (NPV), and area under the curves (AUC), using all definitive postoperative diagnoses as reference. Likely infections (EBJIS) or inconclusive diagnoses (ICM) were grouped with the uninfected group for analysis. Their 95% confidence intervals (CIs) were calculated, and individual receiver operating characteristic (ROC) curves were drawn. The AUCs of the preoperative results of the three criteria were compared using the z-test. A significance level of 5% was used. Statistical analyses were undertaken using XLSTAT statistical and data analysis solution (version 2021.4.1; Addinsoft, USA).

Results

Confirmation of infection. The EBJIS definition diagnosed PJI in 101 patients (101/206; 49%) (Figure 1).

Table III. 2021 European Bone and Joint Infection Society (EBJIS) definition for the diagnosis of periprosthetic joint infection.

EBJIS criteria for the diagnosis of clinically suspected periprosthetic joint infection			
	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 yrs 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
CRP		> 10 mg/l (1 mg/dl)[c]	
Synovial fluid cytological analysis[d]			
Leukocyte count (cells/µl)[c]	≤ 1,500	> 1,500	> 3,000
PMN%[c]	≤ 65%	> 65%	> 80%
Synovial fluid biomarkers			
Alpha-defensin[e]			Positive immunoassay or lateral-flow assay
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,i]			
HPF (400× 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[j]	

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 hip and knee periprosthetic joint infection. 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 < 1 h, preferentially using automated techniques. For viscous samples, pretreatment with hyaluronidase improves the accuracy of optical or automated techniques. In case of bloody samples, the adjusted synovial WBC = synovial $WBC_{observed} - (WBC_{blood}/RBC_{blood} \times RBC_{synovial\ fluid})$ should be used.
e. Not valid in cases of ALTR, haematomas, 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. Results of culture may be obtained from preoperative synovial aspiration, preoperative synovial biopsies, or (preferred) from intraoperative tissue samples.
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. *Staphylococcus 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 cut-off 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. Histological analysis may be from preoperative biopsy, intraoperative tissue samples with either paraffin or frozen section preparation.
j. 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).
CFU, colony-forming units; EBJIS, European Bone and Joint Infection Society; EDTA, ethylenediaminetetraacetic acid; HPF, high power field; PMN%, percentage of polymorphonuclear neutrophils; RBC, red blood cell; WBC, white blood cell count.

Overall, 84/101 patients (83%) fulfilled two or more confirmatory criteria (Figure 2).

Of the 101 confirmed PJIs, 59 patients (59/101; 58.4%) were culture-positive with at least two positive samples with the same microorganism. In three PJI cases, which were also confirmed by the IDSA and ICM criteria, sonication showed microbial growth (*Escherichia coli* > 100 CFU/ml (n = 1), *Enterococcus faecalis* > 100 CFU/ml (n = 1), *Staphylococcus aureus* > 100 CFU/ml (n = 1)). In total, 62/101 patients (61.4%) showed microbial growth and 39/101 patients (38.6%) showed no microbial growth at all.

The IDSA definition diagnosed 99 patients (99/206; 48%) with PJI. Of these, 64/99 (65%) fulfilled two or more criteria (Figure 2) and 59 patients (59/99; 59.6%) were culture-positive with at least two positive samples

Table IV. Demographics when using all definitive postoperative diagnosed infections.

Characteristic	Aseptic group (n = 105)	PJI group (n = 101)	p-value	Total (n = 206)
Median age, yrs (IQR)	74 (66 to 81)	74 (63 to 80)	0.534*	74 (65 to 80)
Female sex, n (%)	70 (67)	53 (52)	**0.047**†	123 (60)
Median BMI (IQR)	27 (24 to 31)	28 (24 to 32)	0.384*	28 (24 to 31)
ASA grade, n (%)				
Type 1	10 (10)	3 (3)	0.083†	13 (6)
Type 2	46 (44)	42 (42)	0.779†	88 (43)
Type 3	48 (46)	54 (53)	0.329†	102 (50)
Type 4	1 (1)	2 (2)	0.616†	3 (1)
Localization, n (%)				
Hip	55 (52)	49 (49)	0.676†	104 (50)
Knee	50 (48)	52 (51)	0.676†	102 (50)
Rheumatic disease, n (%)	7 (7)	9 (9)	0.609†	16 (8)

Statistical significance was set at $p < 0.05$.
*Independent-samples *t*-test.
†Fisher's exact test.
ASA, American Society of Anesthesiologists; IQR, interquartile range; PJI, periprosthetic joint infection.

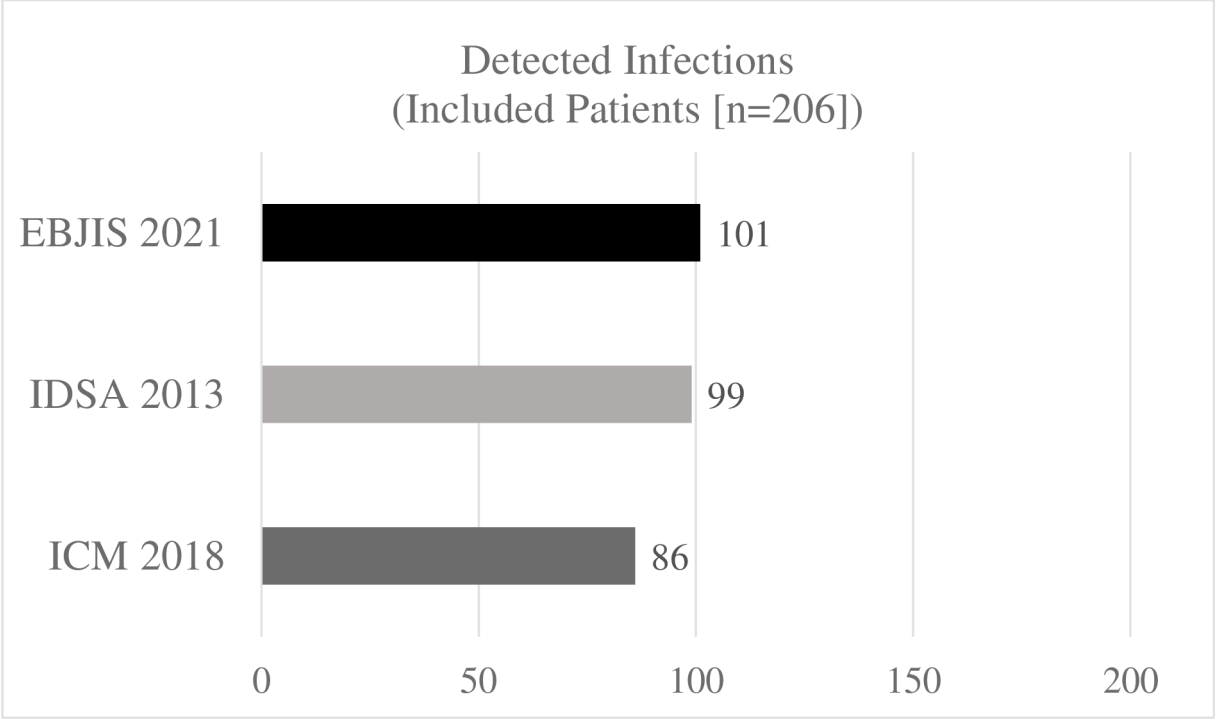

Fig. 1

Detected infections when using the European Bone and Joint Infection Society (EBJIS), Infectious Diseases Society of America (IDSA), and International Consensus Meeting (ICM) definitions.

with the same microorganism. If sonication is excluded (it is not included in the IDSA criteria), 40/99 patients (40.4%) were culture-negative infections.

The ICM definition classified 86 cases (86/206; 42%) as infected. Of these, 61/86 (71%) were diagnosed on major criteria and 25 on minor criteria alone (score ≥ 6 points; median 10 (IQR 8 to 11)). In total, 59 patients (59/86; 59.6%) were culture-positive with at least two positive samples with the same microorganism, three patients (3/86; 3.5%) had one positive culture, and 24 patients (24/86; 27.9%) showed no microbial growth.

There was no significant difference between the three definitions for confirmed infections (EBJIS (n = 101) vs IDSA (n = 99), p = 0.844; EBJIS vs ICM (n = 86), p = 0.138; IDSA vs ICM, p = 0.198, all chi-squared test).

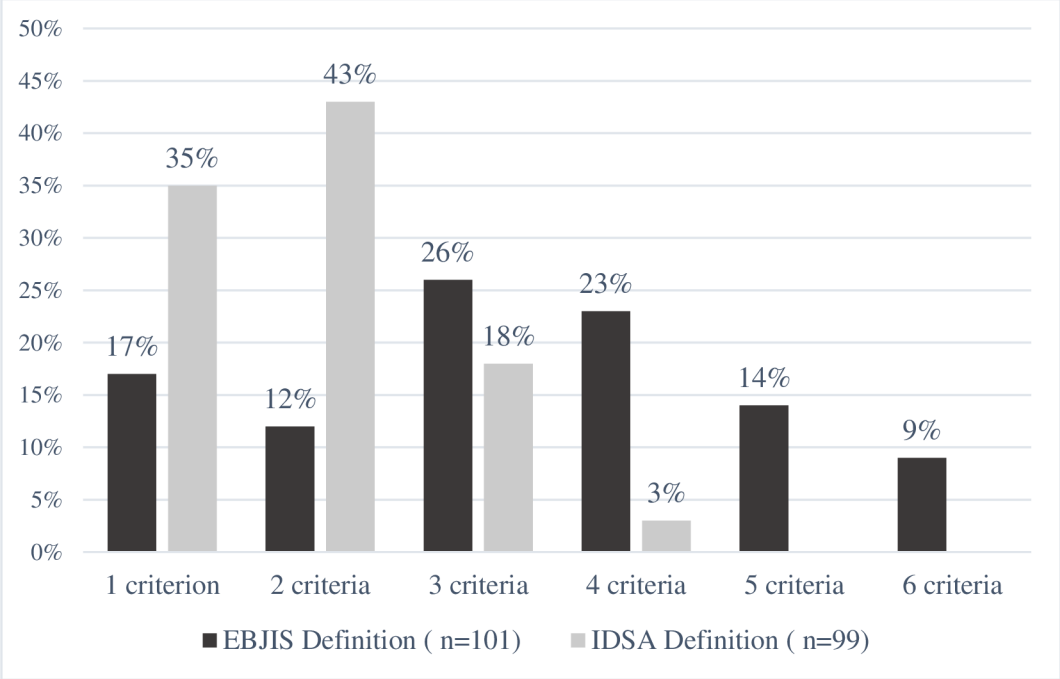

Fig. 2

The percentage of patients who fulfilled one, two, three, four, five, or six confirmatory criteria when using the European Bone and Joint Infection Society (EBJIS) definition or Infectious Diseases Society of America (IDSA) definition.

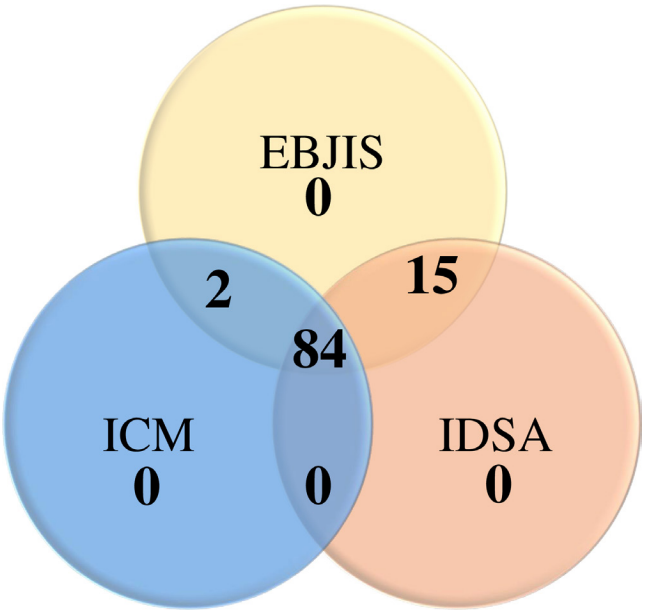

Fig. 3

Venn diagram of the detected infections based on the European Bone and Joint Infection Society (EBJIS), Infectious Diseases Society of America (IDSA), and International Consensus Meeting (ICM) definitions.

A total of 84 cases (84/206; 41%) were diagnosed with PJI by all three definitions (Figure 3). In 99 cases (99/206; 48%), a PJI was diagnosed with both the IDSA and EBJIS definitions. ICM classed 15 of these as inconclusive. Three (3/15; 20%) cases reached a score of five points, with preoperative elevated CRP levels and positive histopathology. In the remaining 12 patients (n = 12/15; 80%), only histology was positive. Seven patients showed signs of early loosening, two with previous wound healing problems, one with a positive WBC scintigraphy, and one with a recent bacteraemia (EBJIS 'infection likely' criteria).

In 86 patients (n = 86/206, 42%), an infection was present according to the ICM and EBJIS definitions. Two of these (n = 2/86; 2%) were missed by IDSA. The first patient had elevated serum CRP (92.8 mg/l), WBC (44,730 cells/µl), %PMN (81%), and a positive alpha-defensin lateral flow test. In the second patient, increased serum CRP levels (59.5 mg/dl), WBC (31,590 cells/µl), and %PMN (84%) were observed. Neither patient had inflammatory joint disease.

All infections confirmed by any definition were identified by the EBJIS criteria, and no infections were confirmed by EBJIS alone.

Inconclusive cases based on the ICM 2018 definition. The ICM criteria categorized 30 cases (n = 30/206; 15%) as inconclusive (Figure 4). Overall 15 of these (15/30; 50%) were categorized as infected by the IDSA or EBJIS criteria showing positive histology in 12 cases (ICM score 3), or a raised CRP and positive histology in three cases (ICM score 5). Four of the remaining 15 cases were classed as 'infection likely' by EBJIS (Table V). One of these (n = 1/4) had additional radiological signs of loosening, a positive WBC scintigraphy, and underwent two-stage revision due to infection (reinfection) three years later. Another case showed microbial growth in the sonication

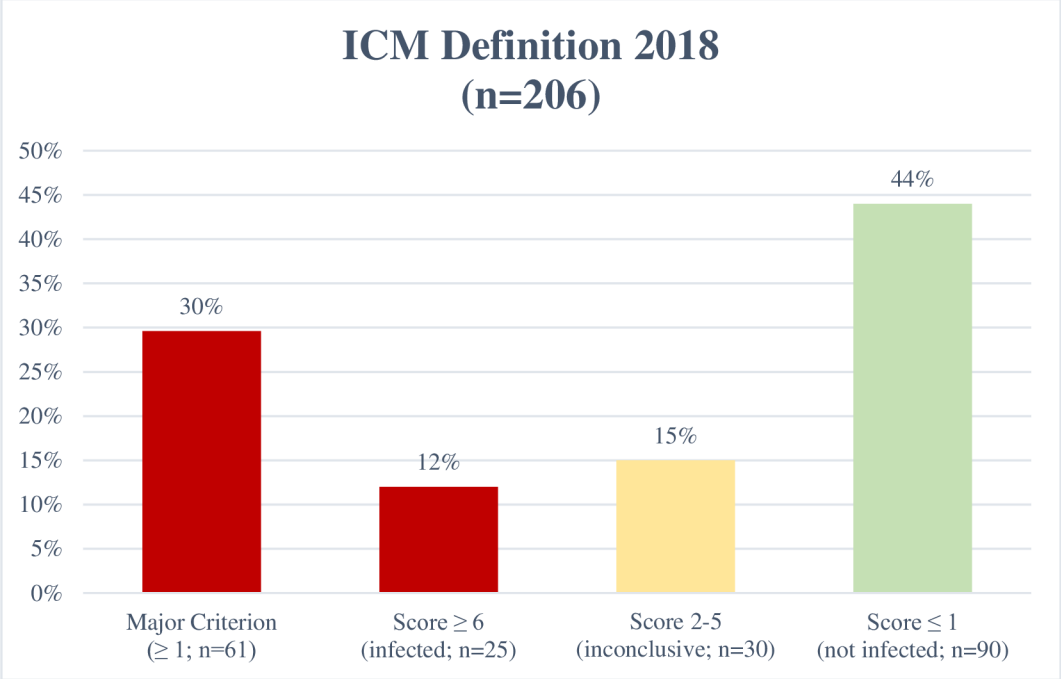

Fig. 4

Distribution of the whole study cohort when using the International Consensus Meeting (ICM) definition.

Table V. Distribution of the whole study cohort when comparing the European Bone and Joint Infection Society definition and the International Consensus Meeting 2018 definition.

EBJIS Definition				
Infection unlikely (n = 89)	**Infection likely (n = 16)**	**Infection confirmed (n = 101)**		
0	0	86	**Infection confirmed (n = 86)**	**ICM 2018 Definition**
11	4	15	**Diagnosis inconclusive (n = 30)**	
78	12	0	**Not infected (n = 90)**	

EBJIS, European Bone and Joint Infection Society; ICM, International Consensus Meeting.

fluid of > 1 CFU/ml (*Staphylococcus epidermidis* (4 CFU/ml), *Corynebacterium accolens* (9 CFU/ml)) and radiological signs of loosening. No (re-)infection occurred after a follow-up of 23 months. The third patient had a positive WBC scintigraphy and elevated serum CRP (36.7 mg/dl) with no (re-)infection until the last follow-up after 66 months. In the last patient with a history of previous wound healing problems, radiological signs of loosening and elevated serum CRP levels (11.5 mg/dl) were observed. No (re-)infection occurred after a follow-up of 33 months. The remaining 11 cases showed only elevated CRP levels (median 21.7 mg/l (IQR 16.3 to 34.5)). No (re-)infection was seen after a median follow-up of 27 months (IQR 17 to 37).

'Likely infections' based on the EBJIS definition. A total of 16 patients (n = 16/206; 8%) were classified as 'infection likely' by the EBJIS criteria (Figure 5). Four cases were already discussed in the 'inconclusive cases based on the ICM-criteria' section. All remaining 12 patients (n = 12/16; 75%) showed radiological signs of loosening within the first five years after implantation. Of these, six patients additionally showed microbial growth in the sonication fluid of > 1 CFU/ml (coagulase-negative staphylococci (n = 3), *Bacillus spp* (n = 1), *Corynebacterium spp* (n = 1), *Cutibacterium spp* (n = 1)). One patient also had previous wound healing problems and a positive sonication fluid culture of > 1 CFU/ml (*S. aureus*). Two patients additionally had a positive WBC scintigraphy, and another two had elevated WBC of > 1,500 cells/µl (1,758 cells/µl, 1,556 cells/µl) including one with > 65% PMN (77%). One patient with signs of loosening, a positive WBC scintigraphy, and previous wound healing problems presented with a (re-)infection three months after the one-stage revision. In addition, one other patient showed a reinfection as described in the 'inconclusive cases based on

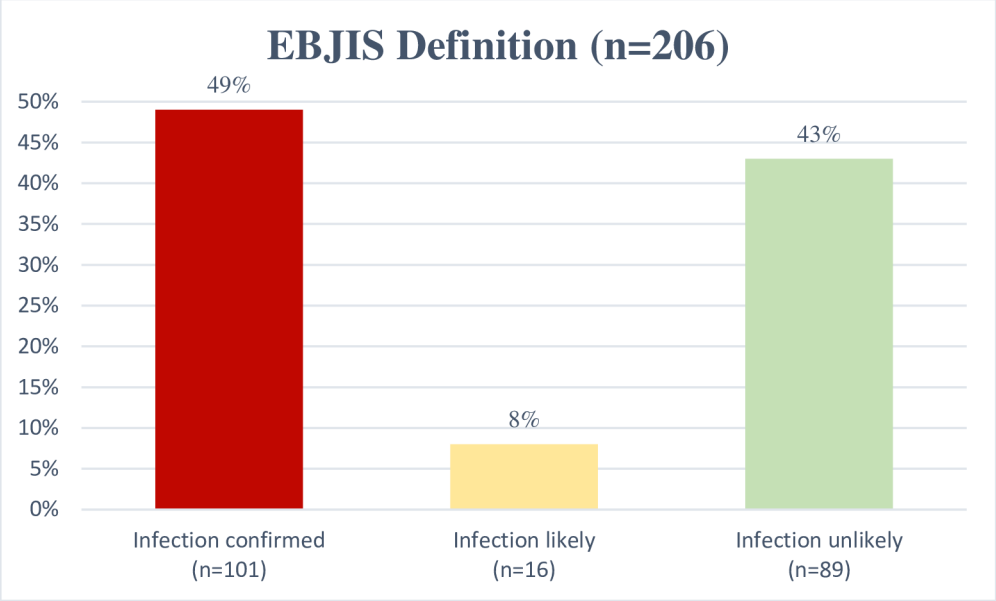

Fig. 5

Distribution of the whole study cohort when using the European Bone and Joint Infection Society (EBJIS) definition.

the ICM-criteria' section. Overall, two patients (n = 2/16; 13%) showed a (re-)infection in this likely infection group. The remaining 14 patients showed no (re-) infection at a median follow-up of 41 months (IQR 30 to 51).

Significantly more inconclusive diagnoses were observed when the ICM criteria (n = 30/206; 15%) were used in comparison to the EBJIS criteria (n = 16/206; 8%) (p = 0.029, chi-squared test).

Accuracy of preoperative diagnosis compared to definitive diagnosis. All three definitions contain tests which can be performed preoperatively. The ability of these preoperative tests to rule in or rule out infection was assessed. For this analysis, all cases classed as infected by either EBJIS, ICM, or IDSA (n = 101) were regarded as having a confirmed infection.

Using the EBJIS infection definition, 70 of the postoperative 101 confirmed infected patients were diagnosed with a confirmed infection (70/101; 69%) preoperatively and 17 with a likely infection (17/101; 17%). Overall, 25 patients were classed as having a likely infection preoperatively (25/206; 12%), and 17 of these (n = 17/25; 68%) were confirmed as infected after surgery. Before surgery, 111 patients were classed as infection unlikely, and 14 were subsequently confirmed as infected (n = 14/111; 13%) and nine (9/111; 8%) as likely infection postoperatively. In the first performance analysis, likely infections were grouped with the uninfected group, as 'infection not confirmed'. Using all confirmed infections as reference, sensitivity, specificity, accuracy, PPV, NPV, and AUC of the preoperative diagnosis were 69.3% (95% CI 59.7 to 77.5), 100% (95% CI 95.6 to 100), 85.0% (95% CI 80.1 to 89.8), 100% (95% CI 100), 77.2% (95% CI 70.2 to 84.3), and 0.847 (95% CI 0.801 to 0.892), respectively. In our second performance analysis, likely infections were grouped with the infected group as 'infection confirmed', to estimate the NPV of a negative preoperative result. Sensitivity, specificity, accuracy, PPV, NPV, and AUC of the preoperative diagnosis were 81.2% (95% CI 73.1 to 87.3), 100% (95% CI 94.9 to 100), 89.3% (95% CI 85.1 to 93.5), 100% (95% CI 100), 80.2 (95% CI 72.8 to 87.6), and 0.906 (95% CI 0.870 to 0.942).

The ICM definition classed 46 patients (46/101; 46%) as infected preoperatively and 38 (38/101; 38%) had an inconclusive diagnosis. Overall, 53 patients (53/206; 26%) had an inconclusive diagnosis preoperatively. Of these, 38 patients (38/53; 72%) were confirmed as infected after surgery and 18 (18/53; 34%) remained with an inconclusive diagnosis. ICM defined 107 patients as not infected before surgery, and 17 patients (17/107; 16%) were classed as infected after intraoperative tests. In the first performance analysis, inconclusive cases were included in the uninfected group. Sensitivity, specificity, accuracy, PPV, NPV, and AUC of the preoperative diagnosis were 45.5% (95% CI 36.2 to 55.2), 100% (95% CI 95.6 to 100), 73.3% (95% CI 67.3 to 79.3), 100% (95% CI 100), 65.6% (95% CI 58.3 to 73.0), and 0.728 (95% CI 0.679 to 0.777), respectively. In our second performance analysis, inconclusive cases were grouped with the infected group as 'infection confirmed'. Sensitivity, specificity, accuracy, PPV, NPV, and AUC of the preoperative diagnosis were 85.3% (95% CI 77.6 to 90.7), 100% (95% CI 95.0 to 100), 91.7% (95% CI 88.0 to 95.5), 100% (95% CI 100), 84.1% (95% CI 77.2 to 91.0), and 0.927 (95% CI 0.894 to 0.959).

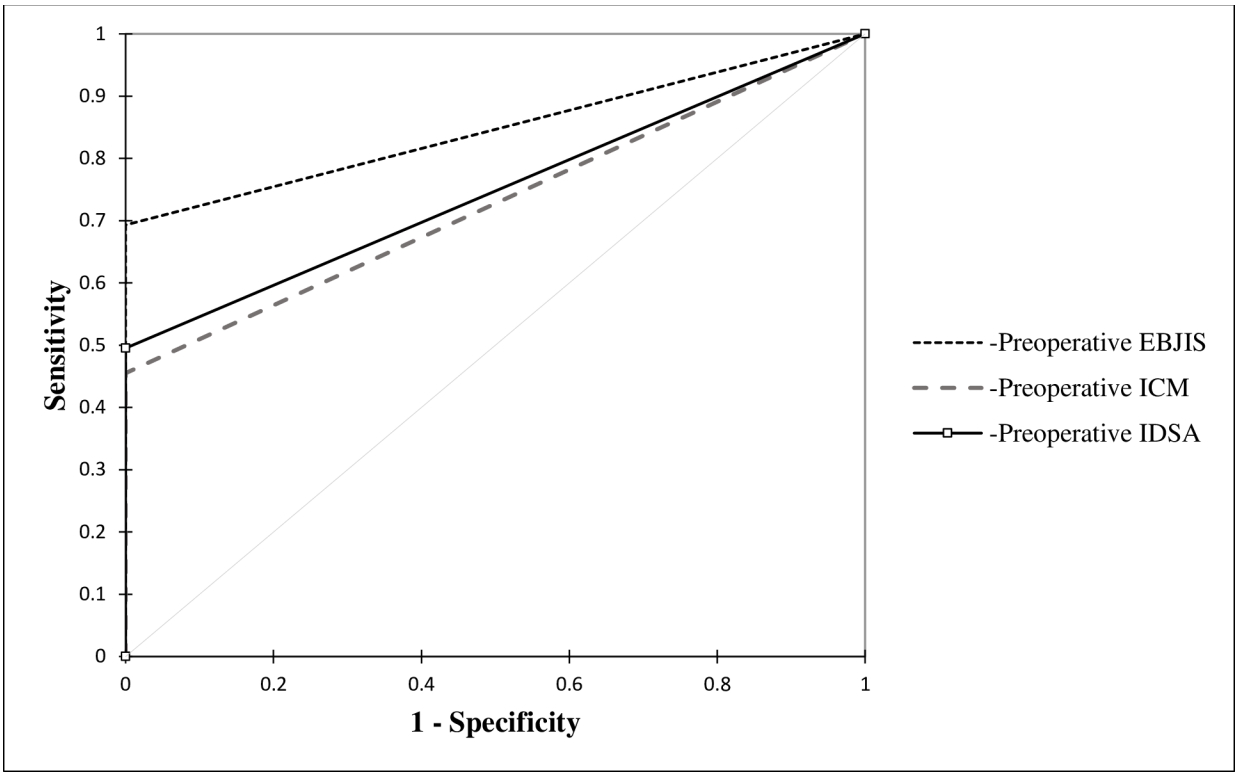

Fig. 6

Receiver operating characteristic curves for accuracy of preoperative diagnosis of the three infection definitions (European Bone and Joint Infection Society (EBJIS), International Consensus Meeting (ICM), and Infectious Diseases Society of America (IDSA)) compared to definitive diagnosis.

Using the IDSA criteria, 50 PJIs (n = 50/101; 50%) were diagnosed with an infection preoperatively, with 156 (156/206; 76%) classed as not infected. Of these, 49 (49/156; 31%) were classified as infected after surgery. Sensitivity, specificity, accuracy, PPV, NPV, and AUC of the preoperative diagnosis were 49.5% (95% CI 40.0 to 59.1), 100% (95% CI 95.6 to 100), 75.2% (95% CI 69.3 to 81.1), 100% (95% CI 100), 67.3% (95% CI 59.9 to 74.7), and 0.748 (95% CI 0.699 to 0.797), respectively.

Comparing AUCs of the three different infection definitions, a better preoperative performance of the EBJIS definition was seen compared with the ICM and IDSA definitions ($p < 0.001$, z-test). Comparing ICM with IDSA definitions, no statistically significant difference was found ($p = 0.204$, z-test) (Figure 6).

Discussion

The absence of a perfect diagnostic test for PJI makes the use of standardized criteria essential for clinical diagnosis and research.[2] The introduction of definitions by the MSIS in 2011 and IDSA in 2013 allowed greater clarity between studies investigating diagnostic tests and treatments.[1,3] In recent years, novel tests have been introduced and infection definitions have evolved. To the best of our knowledge, the recent definitions have not been compared in the literature. Therefore, this study was conducted to find the most sensitive definition and to evaluate the clinical utility of each.

In our study, the novel 2021 EBJIS definition detected more infections (n = 101) than the 2018 ICM definition (n = 86) and the 2013 IDSA definition (n = 99). The EBJIS definition identified all PJIs diagnosed by any definition with no further infections, suggesting that EBJIS is more sensitive in comparison to the other two definitions, but not at the expense of reduced specificity. However, since there is no 'gold standard' for the diagnosis of PJI, we were not able to analyze independent diagnostic performance of each infection definition.

Parvizi et al[5] defined their surrogate "gold standard" (definitive Infections) as "patients who were treated as PJI cases with two-stage revision and failed with a reinfection within one year", and aseptic cases as "cases undergoing single-stage revision for a diagnosis other than infection who did not fail with infection within one year, nor had any further reoperation on the same joint". In addition, patients were only classified as infected if they met one of the major diagnostic criteria of MSIS (sinus tract or two positive cultures) in their developmental model. Sinus tracts are an infrequent finding, particularly in PJI of the hip, and positive cultures are often absent.[2,13–15] Both criteria therefore have low sensitivity to select patients for inclusion. This may have contributed to the lower identification rate for low-virulence infections and culture-negative PJIs,[5] which may be detected by EBJIS and IDSA.

Low-grade infection is usually associated with a reduced inflammatory response and may require a lower score (< 6 points) in the 2018 ICM definition, but this could adversely affect specificity. In this study, only 70% of PJIs were diagnosed by ICM 2018 using major criteria, so the validity of minor criteria scores is critical. A true validation trial, independently evaluating the scores for each minor criterion, would require a very large sample size. Due to these limitations, we did not use their or any surrogate standards to compare the three criteria in our analyses.

The EBJIS definition could falsely diagnose some aseptic failures as PJIs. However, all EBJIS confirmed PJIs were also diagnosed either by the ICM or IDSA definitions (Figure 3). Hence, it seems that all infections (classified by the ICM or IDSA) can be diagnosed by the EBJIS definition. The EBJIS definition was designed to diagnose PJI based on high-specificity tests,[2] which was supported by the fact that PJI diagnosis was confirmed in over 83% of cases with multiple confirmatory criteria.

Regarding PJI cases, diagnosed only with the EBJIS and IDSA criteria due to a positive histopathological analysis, most had additional suggestive features of infection (early loosening, previous wound healing problems, positive WBC scintigraphy, history of recent bacteraemia). These cases were categorized as inconclusive when using the ICM definition, with scores ranging from three to five. However, it has been demonstrated that histology showed high accuracies regardless of the infection definition,[11] and many studies report high sensitivities (84% to 100%) and specificities (94% to 100%).[16–20]

Two PJI cases, which were only diagnosed with the EBJIS and ICM criteria, showed elevated serum CRP and synovial WBC and %PMN (one patient: additional positive alpha-defensin lateral flow test). The IDSA criteria were not able to identify these two patients as these inflammatory markers are not included in this older definition. Synovial fluid WBC and %PMN are perhaps the best preoperative diagnostic test methods[21] with consistently high specificities (WBC: 88% to 93%; %PMN: 80% to 95%).[21–25] In addition, alpha-defensin showed good specificities (86% to 98%)[26–31] in the literature and may, therefore, confirm infection. It is important to note that the results of these parameters are not valid in patients with adverse local tissue reactions, haematomas, or acute inflammatory arthritis or gout as mentioned in the practical guidelines of the EBJIS for the diagnosis of PJI.[2]

Overall, more patients had an inconclusive diagnosis with the ICM definition (30/206; 15%) in comparison with the EBJIS criteria (Infection likely: 16/206; 8%) ($p = 0.029$, chi-squared test). Half of the ICM inconclusive patients (15/30) were categorized as infected when using the IDSA or EBJIS criteria. The remaining 15 cases showed only non-specific increased CRP levels.

Patients who cannot be classified as either septic or aseptic are challenging to manage. It is difficult to decide the optimal surgical and antimicrobial treatment. Hence, it is of the utmost importance to define more infections in this so-called 'grey zone'. We believe that the EBJIS definition is able to reduce the number of inconclusive cases and can identify more of these 'hidden' infections in this challenging group of patients. The EBJIS definition was also user-friendly, and cases can be categorized easily with the three-level 'traffic light' concept.

This study is limited by its retrospective nature. Some parameters included in the three infection definitions were not available in all patients, which is a reflection of everyday practice.[9,32] Another limitation is the fact that patients with a rheumatic disease (n = 16/206; 8%) were included in our study, which can influence the results of different test methods (e.g. synovial fluid leucocyte count, histology). We were not able to calculate the definitive performance of the three infection definitions by comparing their diagnostic values against a 'gold standard' test for PJI. However, if we did have such a test, we would not need any other criteria for diagnosing PJIs. Due to this lack of a gold standard, it is currently impossible to evaluate the 'real' performance (sensitivity, specificity, PPV, NPV) of the PJI definitions.

In conclusion, in this cohort the novel EBJIS definition seems to be more sensitive for the diagnosis of PJIs in comparison to the IDSA and ICM definitions. All infections classified by either the IDSA or ICM criteria were identified by the EBJIS definition, suggesting that the EBJIS definition can be used alone in diagnosis. This would also allow better comparison of studies in the future. The EBJIS preoperative criteria also demonstrated improved accuracy in predicting definitive diagnosis after surgery. In addition, significantly fewer patients had an inconclusive diagnosis, which is important in guiding clinical decision-making.

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