Diagnosing periprosthetic joint infections

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

I. K. Sigmund, M. Luger, R. Windhager, M. A. McNally
From Medical University of Vienna, Vienna, Austria

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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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.
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. The first infection definition was developed in 2011 by the Musculoskeletal Infection Society (MSIS) at its 21st Annual Meeting. 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. 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. 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 and validated on a selected cohort of patients. This was presented at the 2018 ICM but was only supported by 68% of delegates, 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. This definition recognized the difficulty with a simple ‘septic’ or ‘aseptic’ decision, 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.

**Infection definitions.** A PJI was diagnosed using the ICM 2018, IDSA 2013, and EBJIS 2021 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. 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.

Qualitative alpha-defensin testing was done by using the lateral flow test (Synovasure; Zimmer Biomet,
Intraoperatively, at least three tissue specimens were sent for 14-day culture. 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). Explanted components were sent for culture, after sonication.

For preoperative diagnosis, the following parameters were assessed based on the used infection definition and their specific cut-offs: communicating sinus tract (IDSA, ICM, EB|IS), synovial fluid WBC and %PMN (ICM, EB|IS), positive alpha-defensin lateral flow test (ICM, EB|IS), 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 (EB|IS) 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 EB|IS definition diagnosed PJI in 101 patients (101/206; 49%) (Figure 1).
Enterococcus faecalis > 100 CFU/ml (n = 1), Escherichia coli > 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.

Of the 101 confirmed PJs, 59 patients (59/101; 58.4%) were culture-positive with at least two positive samples with the same microorganism. In three PJ 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 PJ. 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.
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).

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**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)                 | 73 (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.

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**Detected Infections (Included Patients [n=206])**

![Fig. 1](image-url)

Detected infections when using 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
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

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**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) |
|------------------|-----------------------------|---------------------------|-------------------------------|
|                  |                             |                           | Infection confirmed (n = 86)  |
|                  |                             |                           | Diagnosis inconclusive (n = 30) |
|                  |                             |                           | Not infected (n = 90)         |
|                  |                             |                           | ICM 2018 Definition           |
| Major Criterion  | 0                           | 0                         | 86                            |
| Score ≥ 6        | 11                          | 4                         | 15                            |
| Score 2-5        | 78                          | 12                        | 0                             |

EBJIS, European Bone and Joint Infection Society; ICM, International Consensus Meeting.
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), 83.0% (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).
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,\(^3\) 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 EBJS definition could falsely diagnose some aseptic failures as PJIs. However, all EBJS 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 EBJS definition. The EBJS definition was designed to diagnose PJI based on high-sensitivity tests, 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 EBJS 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, and many studies report high sensitivities (84% to 100%) and specificities (94% to 100%).

Two PJI cases, which were only diagnosed with the EBJS 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 with consistently high specificities (WBC: 88% to 93%; %PMN: 80% to 95%).

In addition, alpha-defensin showed good specificities (86% to 98%) 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, haematoma, or acute inflammatory arthritis or gout as mentioned in the practical guidelines of the EBJS for the diagnosis of PJI.

Overall, more patients had an inconclusive diagnosis with the ICM definition (30/206; 15%) in comparison with the EBJS 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 EBJS 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 EBJS 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 EBJS 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. 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 EBJS 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 EBJS definition, suggesting that the EBJS definition can be used alone in diagnosis. This would also allow better comparison of studies in the future. The EBJS 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.

References
1. Osmun DR, Berbari EF, Berendt AR, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013;56(1):e1–e25.
2. McNally M, Sousa R, Wouthuyzen-Bakker M, et al. The EBJS definition of periprosthetic joint infection. Bone Joint J. 2016;98-B(1):18–25.
3. Parvizi J, Zmistowski B, Berbari EF, et al. New definition for periprosthetic joint infection: from the Workgroup of the Musculoskeletal Infection Society. Clin Orthop Relat Res. 2011;469(1):292–299.
4. Parvizi J, Gehrke T, International Consensus Group on Periprosthetic Joint Infection. Definition of periprosthetic joint infection. J Arthroplasty. 2014;29(7):1331.
5. Parvizi J, Tan TL, Goswami K, et al. The 2018 definition of periprosthetic hip and knee infection: an evidence-based and validated criteria. J Arthroplasty. 2018;33(5):1309–1314.
6. Shohat N, Bauer T, Buttaro M, et al. Hip and Knee Section. What is the definition of a periprosthetic joint infection (PJI) of the knee and the hip? Can the same criteria be used for both joints?: Proceedings of International Consensus on Orthopedic Infections. J Arthroplasty. 2018;33(5):S325–S327.
7. Osses JT, Gauld K, Stockley I, Haddad FS. Defining peri-prosthetic infection: do we have a workable gold standard? J Bone Joint Surg Br. 2012;94-B(11):1455–1456.
8. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191–2194.
9. Sigmund IK, Holinka J, Staats K, et al. Inferior performance of established and novel serum inflammatory markers in diagnosing periprosthetic joint infections. Int Orthop. 2021;45(4):837–846.
10. Sigmund IK, Windhager R, Sevelda F, et al. Multiplex PCR Unyvero i60 ITI application improves detection of low-virulent microorganisms in periprosthetic joint infections. Int Orthop. 2019;43(8):1891–1898.

11. Sigmund IK, McNally MA, Luger M, Böhler C, Windhager R, Sulzbacher I. Diagnostic accuracy of neutrophil counts in histopathological tissue analysis in periprosthetic joint infection using the INNO-PAK, LBP, and EBJIS criteria. Bone Joint J. 2021;103(9):526–547.

12. Sigmund IK, Holinka J, Gampier J, et al. Qualitative α-defensin test (Synovasure) for the diagnosis of periprosthetic infection in revision total joint arthroplasty. Bone Joint J. 2017;99-B(6):66–72.

13. Dudareva M, Barrett L, Caffrey M, et al. Sonication versus tissue sampling for diagnosis of prosthetic joint and other orthopedic device-related infections. J Clin Microbiol. 2018;56(12):e00688-18.

14. Wouthuizen-Bakker M, Benito N, Soriano A. The effect of preoperative antimicrobial prophylaxis on intraoperative culture results in patients with a suspected or confirmed prosthetic joint infection: a systematic review. J Clin Microbiol. 2017;55(9):2765–2774.

15. Tan TL, Kheir MM, Shohat N, et al. Culture-negative periprosthetic joint infection: an update on what to expect. JBJS Open Access. 2018;3(3):e0060.

16. Buttaro MA, Martorell G, Quintero T, Comba F, Zanotti G, Piccaluga F. Intraoperative synovial C-reactive protein is as useful as frozen section to detect periprosthetic hip infection. Clin Orthop Relat Res. 2015;473(12):3876–3881.

17. Fink B, Makowiak C, Fuerst M, Berger I, Schäfer P, Frommelt L. The value of synovial biopsy, joint aspiration and C-reactive protein in the diagnosis of late periprosthetic infection of total knee replacements. J Bone Joint Surg Br. 2008;90-B(7):674–678.

18. Pons M, Anglés F, Sánchez C, et al. Infected total hip arthroplasty—the value of intraoperative histology. Int Orthop. 1999;23(1):34–38.

19. Lønner JH, Desai P, Dicesare PE, Steiner G, Zuckerman JD. The reliability of analysis of intraoperative frozen sections for identifying active infection during revision hip or knee arthroplasty. J Bone Joint Surg Am. 1996;78-A(10):1553–1558.

20. Tohtz SW, Müller M, Morawietz L, Winkler T, Perka C. Validity of frozen sections for analysis of periprosthetic loosening membranes. Clin Orthop Relat Res. 2010;468(3):763–769.

21. Levent A, Neufeld ME, Piakong P, Lausmann C, Gehrke T, Citak M. Which International Consensus Meeting preoperative minor criteria is the most accurate marker for the diagnosis of periprosthetic joint infection in hip and knee arthroplasty? J Arthroplasty. 2021;36(11):3728–3733.

22. Schinsky MF, Della Valle CJ, Sporer SM, Paprosky WG. Perioperative testing for joint infection in patients undergoing revision total hip arthroplasty. J Bone Joint Surg Am. 2008;90-A(9):1869–1875.

23. Balato G, Franceschini V, Ascione T, Lamberti A, Balboni F, Baldini A. Diagnostic accuracy of synovial fluid, blood markers, and microbiological testing in chronic knee prosthetic infections. Arch Orthop Trauma Surg. 2018;138(2):165–171.

24. Trampuz A, Hanssen AD, Osmon DR, Mandrekar J, Steckelberg JM, Patel R. Synovial fluid leukocyte count and differential for the diagnosis of prosthetic knee infection. Am J Med. 2004;117(5):556–562.

25. Ghanem E, Parvizi J, Burnett RSJ, et al. Cell count and differential of aspirated fluid in the diagnosis of infection at the site of total knee arthroplasty. J Bone Joint Surg Am. 2008;90-A(8):1637–1643.

26. Renz N, Yermak K, Perka C, Trampuz A. Alpha defensin lateral flow test for diagnosis of periprosthetic joint infection: not a screening but a confirmatory test. J Bone Joint Surg Am. 2018;100-A(9):742–750.

27. Sigmund IK, Yermak K, Perka C, Trampuz A, Renz N. Is the enzyme-linked immunosorbent assay more accurate than the lateral flow alpha defensin test for diagnosing periprosthetic joint infection? Clin Orthop Relat Res. 2018;476(8):1645–1654.

28. Sigmund IK, Holinka J, Lang S, et al. A comparative study of intraoperative frozen section and alpha defensin lateral flow test in the diagnosis of periprosthetic joint infection. Acta Orthop. 2019;90(2):105–110.

29. Balato G, Franceschini V, Ascione T, et al. High performance of α-defensin lateral flow assay (Synovasure) in the diagnosis of chronic knee prosthetic infections. Knee Surg Sports Traumatol Arthrosc. 2018;26(6):1717–1722.

30. Berger P, Van Cauter M, Driesen R, Neyt J, Cornu D, Bellemans J. Diagnosis of prostatic joint infection with alpha-defensin using a lateral flow device: a multicentre study. Bone Joint J. 2017;99-B(II):1176–1182.

31. Yu BZ, Li R, Fu J, Chai W, Hao LB, Chen JY. Leukocyte esterase test and alpha-defensin test have similar accuracy for the diagnosis of periprosthetic joint infection. Int Orthop. 2021;45(7):1677–1682.

32. Bonanzainga T, Zahar A, Dutsch M, Lausmann C, Kendoff D, Gehrke T. How reliable is the alpha-defensin immunoassay test for diagnosing periprosthetic joint infection? A prospective study. Clin Orthop Relat Res. 2017;475(2):408–415.

Author information:
- I. K. Sigmund, MD, Orthopaedic Surgeon
- M. Luger, cand.med., Medical Student
- R. Windhager, MD, Head of the Department, Lead Surgeon
- Department of Orthopaedics and Trauma Surgery, Medical University of Vienna, Vienna, Austria.
- M. A. McNally, MBCh, MD, FRCS(Orth), King James IV Professor, Senior Lecturer, Lead Surgeon, The Bone Infection Unit, Nuffield Orthopaedic Centre, Oxford University Hospitals, Oxford, UK.

Author contributions:
- I. K. Sigmund: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing.
- M. Luger: Data curation, Writing – review & editing.
- M. A. McNally: Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing.
- M. A. McNally is a past president of the European Bone and Joint Infection Society (EBJIS), and I. K. Sigmund is currently an ordinary member of the EBJIS executive committee.

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