Diagnosis

2.1. DIAGNOSIS: DEFINITIONS

Authors: Noam Shohat, Thomas Bauer, Martin Buttaro, Nicolaas Budhiparama, James Cashman, Craig J. Della Valle, Lorenzo Drago, Thorsten Gehrke, Luiz S. Marcelino Gomes, Karan Goswami, Nils P. Hailer, Seung Beom Han, Carlos Higuera, Yutaka Inaba, Jean-Yves Jenny, Per Kjaersgaard-Andersen, Mel Lee, Adolfo Llinás, Alex Mclaren, Konstantinos Malizos, Michael A. Mont, Rhidian Morgan Jones, Javad Parvizi, Patricia Peel, Salvador Rivero-Boschert, Carlo Romano, John Segreti, Alex Soriano, Ricardo Sousa, Mark Spanghel, Timothy L. Tan, Rashid Tikilov, Ibrahim Tuncay, Heinz Winkler, Eivind Witso, Marjan Wouthuyzen-Bakker, Simon Young, Xianlong Zhang, Yixin Zhou, Wer Zimmerli

QUESTION 1: 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?

RECOMMENDATION: See Figure 1, Proposed 2018 International Consensus Meeting (ICM) criteria for PJI.

Major Criteria (at least one of the following)	Decision
Two positive growths of the same organism using standard culture methods	Infected
Sinus tract with evidence of communication to the joint or visualization of the prosthesis	

Minor Criteria	Threshold		Score	Decision
	Acute€	Chronic		
Serum CRP (mg/L) *or* D-Dimer (ug/L)	100 Unknown	10 860	2	Combined preoperative and postoperative score: ≥6 Infected 3 to 5 Inconclusive* <3 Not Infected
Elevated Serum ESR (mm/hr)	No role	30	1	
Elevated Synovial WBC (cells/µL) *or* Leukocyte Esterase *or* Positive Alpha-defensin (signal/cutoff)	10,000 ++ 1.0	3,000 ++ 1.0	3	
Elevated Synovial PMN (%)	90	70	2	
Single Positive Culture			2	
Positive Histology			3	
Positive Intraoperative Purulence¥			3	

€This criteria were never validated on acute infections. ¥ No role in suspected adverse local tissue reaction.
*Consider further molecular diagnostics such as next-generation sequencing

FIGURE 1. Proposed 2018 ICM Criteria for PJI.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 68%, Disagree: 28%, Abstain: 4% (Super Majority, Weak Consensus)

RATIONALE

The introduction of the MusculoSkeletal Infection Society (MSIS) criteria for PJIs in 2011, which was later altered by the 2013 ICM, resulted in immense improvements in diagnostic confidence and research collaboration [1]. In recent years, numerous serum and synovial markers have been evaluated and have become widely available [2–14]. Moreover, publications in recent years show different sensitivities and specificities for the various tests used [4,14] and highlight the value of a high pretest probability in the overall diagnosis [9,15,16]. These advancements in the field call for the modification of current diagnostic criteria to an evidence-based one.

In a recent multi-institutional study [17], we proposed a new definition considering the relative and quantitative weight of established, as well as newer, markers [7,9,11]. The new diagnostic criteria also consider chronicity and invasiveness of the diagnostic tests, making the preoperative diagnosis of infection easier compared to previous definitions. By using a stepwise approach in developing the current criteria which was based on the current American Academy of Orthopaedic Surgeons (AAOS) guidelines [18], we were able to provide relative weights for each diagnostic marker/finding. The threshold for infection of the combined score was determined in a way that would keep false positives to a minimum (threshold for infection), but also reduce false negatives (threshold for not infected). By performing this in a stepwise manner, we were able to maximize sensitivity in early stages of the workup (to avoid under-diagnoses), as well as to maximize specificity in later stages (to avoid over-diagnoses).

This proposed definition showed a high level of performance using an independent multi-institutional cohort for validation and a better performance compared to previous MSIS and ICM definitions. The new criteria demonstrated a sensitivity of 97.7% compared to the MSIS (79.3%) and ICM definition (86.9%), with a similar specificity of 99.5%. It also enabled one to reach an earlier diagnosis compared to previous criteria, as more than 80% of the PJI cases using the new definition were diagnosed prior to surgery. This enhanced the importance of a joint aspiration prior to surgery and supported it in becoming the cornerstone of diagnosing PJIs. Another novel finding of the present definition is the introduction of patients in which a diagnosis is inconclusive. These patients are often encountered in clinical practice and represent a real diagnostic challenge. Pointing out this unique group or "gray area" of patients promotes awareness in both clinical practice and the need for further research focused on this cohort.

ICM Discussion and Controversies

The criteria have been reviewed and altered by a group of recognized international experts who were also delegates of the ICM. This question and the proposed criteria have been discussed and debated extensively during the ICM and reached only a weak consensus, with 28% disagreeing with it. Our group wishes to point out some important clarifications and controversies that were raised during the meeting:

1. The proposed definition was developed and validated on a cohort with chronic PJIs. Patients with acute PJIs and acute hematogenous PJIs (with < 6 weeks of symptoms) were excluded from this study since we were not able to define a proper control group for them. A control group for acute infections would be patients following joint arthroplasty undergoing a serum and synovial fluid investigation, but proven to not be infected—isolating and defining the control cohort is challenging and rare. Different thresholds for acute infections have been suggested in the literature and we used the previous ICM thresholds for the parameters used. While we believe these new criteria should apply also for acute and acute hematogenous infections, both the scoring system and the proposed thresholds require further validation on this specific population.
2. The proposed criteria may under-diagnose less overt infections. Defining PJIs based on major criteria for developing the scoring system may have affected the thresholds of different markers and has the potential to under-diagnose more overt infections. That being said, 30% of the cohort used for developing the scoring system had Coagulase-negative Staphylococcus (CoNS), which is not considered to cause a major immune response. Moreover, we validated the scoring system on an external cohort of infected and non-infected patients, independent from any previous criteria. In this group of patients, there were many culture negatives as well as so called "low grade infections," and the new criteria demonstrated a high sensitivity of 97.7%. Future research should be aimed on validating the utility of the new definition in more overt infections.
3. For the current definition, a decision tree index (Gini) was used to point out the thresholds for the various markers evaluated that would provide maximal sensitivity and specificity for each marker based on chronicity and the pretest probability. When these thresholds were similar to the previous ICM definition, we used the earlier one to ease its implementation. It should be pointed out that a variety of thresholds have been proposed in the literature and may be different from the ones proposed here. These differences may be attributed to the fact that we wanted to maximize sensitivity in early stages of the workup and to maximize specificity in more advanced stages.
4. The new diagnostic criteria were originally validated on patients from three major orthopaedic institutes in the United States. Additionally, since its introduction earlier this year, the criteria have been validated in patients treated in Japan and Brazil, as well as 84 patients from around the globe using a designated chatbot. They need to be further tested and validated in large volume centers outside the USA to assess whether the preliminary findings presented above are indeed accurate.
5. Several delegates have raised the issue that alpha-defensin is an expensive test that should not be performed routinely. We would like to emphasize that the present scoring system is not designed or intended to be used as a guide for which tests should be ordered; rather, it should be used as a tool to diagnose patients when a panel of tests are already available. Not all tests are needed to use this proposed definition and a preoperative diagnosis can be made without the need for intraoperative findings. To further clarify this issue, we have combined the two tables from the original criteria (separating preoperative and intraoperative findings) into one table.
6. In the present study, we used conventional cultures to diagnose and to define positive growth. We did not use sonication or novel techniques such as Next Generation Sequencing. More sensitive microbiological investigation methods are likely to reveal a potential infection in the absence of elevated serum and/or synovial markers. As these novel methods for isolation of organisms become more widespread, the newly proposed criteria should be validated once again.

7. The proposed definition was developed and validated on both PJI cases of the knee and the hip. While several publications have noted differences in the thresholds for synovial markers in PJI cases of the hip and the knee, we believe the differences are minor. Thus, the new definition has not made a distinction between hip and knee PJI. Nevertheless, future studies should explore such potential difference between these two joints.
8. Newer markers, such as the serum D-dimer, have not been sufficiently studied and while we had sufficient data to analyze the new markers and include them in the definition – more work is needed to further validate their role in the diagnosis of PJIs. Moreover, their role and thresholds in diagnosing acute PJIs still remains unknown.
9. In patients with adverse local tissue reactions (ALTRs), crystalline deposition arthropathy, inflammatory arthropathy flares, infections with slow-growing organisms and patients under antibiotic treatment, the proposed criteria may be inaccurate.
10. There may be other situations when a patient is infected and does not meet the diagnostic criteria and vice versa. Clinical judgment should still prevail and guide physicians in the management of patients.

REFERENCES

[1] Parvizi J, Zmistowski B, Berbari EF, Bauer TW, Springer BD, Della Valle CJ, et al. New definition for periprosthetic joint infection: from the Workgroup of the Musculoskeletal Infection Society. Clin Orthop Relat Res. 2011;469:2992–4694. doi:10.1007/s11999-011-2102-9.

[2] Patel R, Alijanipour P, Parvizi J. Advancements in diagnosing periprosthetic joint infections after total hip and knee arthroplasty. Open Orthop J. 2016;10:654–661. doi:10.2174/1874325001610010654.

[3] Deirmengian C, Kardos K, Kilmartin P, Cameron A, Schiller K, Parvizi J. Diagnosing periprosthetic joint infection: has the era of the biomarker arrived? Clin Orthop Relat Res. 2014;472:3254–3262. doi:10.1007/s11999-014-3543-8.

[4] Lee YS, Koo KH, Kim HJ, Tian S, Kim TY, Maltenfort MG, et al. Synovial fluid biomarkers for the diagnosis of periprosthetic joint infection: a systematic review and meta-analysis. J Bone Joint Surg Am. 2017;99:2077–2084. doi:10.2106/JBJS.17.00123.

[5] Shahi A, Kheir MM, Tarabichi M, Hosseinzadeh HRS, Tan TL, Parvizi J. Serum D-dimer test is promising for the diagnosis of periprosthetic joint infection and timing of reimplantation. J Bone Joint Surg Am. 2017;99:1419–1427. doi:10.2106/JBJS.16.01395.

[6] Tischler EH, Cavanaugh PK, Parvizi J. Leukocyte esterase strip test: matched for musculoskeletal infection society criteria. J Bone Joint Surg Am. 2014;96:1917–1920. doi:10.2106/JBJS.M.01591.

[7] Parvizi J, Jacovides C, Antoci V, Ghanem E. Diagnosis of periprosthetic joint infection: the utility of a simple yet unappreciated enzyme. J Bone Joint Surg Am. 2011;93:2242–2248. doi:10.2106/JBJS.J.01413.

[8] Wyatt MC, Beswick AD, Kunutsor SK, Wilson MJ, Whitehouse MR, Blom AW. The alpha-defensin immunoassay and leukocyte esterase colorimetric strip test for the diagnosis of periprosthetic infection: a systematic review and meta-analysis. J Bone Joint Surg Am. 2016;98:992–1000. doi:10.2106/JBJS.15.01142.

[9] Deirmengian C, Kardos K, Kilmartin P, Cameron A, Schiller K, Parvizi J. Combined measurement of synovial fluid α-defensin and C-reactive protein levels: highly accurate for diagnosing periprosthetic joint infection. J Bone Joint Surg Am. 2014;96:1439–1445. doi:10.2106/JBJS.M.01316.

[10] Omar M, Ettinger M, Reichling M, Petri M, Guenther D, Gehrke T, et al. Synovial C-reactive protein as a marker for chronic periprosthetic infection in total hip arthroplasty. Bone Joint J. 2015;97-B:173–176. doi:10.1302/0301-620X.97B2.34550.

[11] Tarabichi M, Shohat N, Goswami K, Alvand A, Silibovsky R, Belden K, et al. Diagnosis of periprosthetic joint infection: the potential of next-generation sequencing. J Bone Joint Surg Am. 2018;100:147–154. doi:10.2106/JBJS.17.00434.

[12] Sigmund IK, Holinka J, Gamper J, Staats K, Böhler C, Kubista B, et al. Qualitative α-defensin test (synovasure) for the diagnosis of periprosthetic infection in revision total joint arthroplasty. Bone Joint J. 2017;99-B:66–72. doi:10.1302/0301-620X.99B1.BJJ-2016-0295.R1.

[13] Tarabichi M, Shohat N, Goswami K, Parvizi J. Can next generation sequencing play a role in detecting pathogens in synovial fluid? Bone Joint J. 2018;100-B:127–133. doi:10.1302/0301-620X.100B2.BJJ-2017-0531.R2.

[14] Shahi A, Tan TL, Kheir MM, Tan DD, Parvizi J. Diagnosing periprosthetic joint infection: and the winner is? J Arthroplasty. 2017;32:S232–S235. doi:10.1016/j.arth.2017.06.005.

[15] Sousa R, Serrano P, Gomes Dias J, Oliveira JC, Oliveira A. Improving the accuracy of synovial fluid analysis in the diagnosis of prosthetic joint infection with simple and inexpensive biomarkers: C-reactive protein and adenosine deaminase. Bone Joint J. 2017;99-B:351–357. doi:10.1302/0301-620X.99B3.BJJ-2016-0684.R1.

[16] Tarabichi M, Fleischman AN, Shahi A, Tian S, Parvizi J. Interpretation of leukocyte esterase for the detection of periprosthetic joint infection based on serologic markers. J Arthroplasty. 2017;32:S97-S100.e1. doi:10.1016/j.arth.2017.03.045.

[17] Parvizi J, Tan TL, Goswami K, Higuera C, Della Valle C, Chen AF, et al. The 2018 definition of periprosthetic hip and knee infection: an evidence-based and validated criteria. J Arthroplasty. 2018;33:1309-1314.e2. doi:10.1016/j.arth.2018.02.078.

[18] Parvizi J, Della Valle CJ. AAOS Clinical Practice Guideline: diagnosis and treatment of periprosthetic joint infections of the hip and knee. J Am Acad Orthop Surg. 2010;18:771–772.

Authors: Douglas Dennis, Ali Parsa, José Ricardo Pécora

QUESTION 2: What is the definition of septic arthritis in a native knee?

RECOMMENDATION: Native septic arthritis of the knee is a clinical diagnosis supplemented by relevant laboratory data. Signs of septic arthritis include painful effusion, limited range of motion and warmth. Elevated serum inflammatory markers, particularly C-reactive protein (CRP), synovial white blood cell (WBC) counts (50,000 cells/mm^3), polymorphonuclear (PMN) cell count percentages (> 90%) and purulent appearance of the synovial fluid indicate a high likelihood of septic arthritis.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 7%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

Native septic arthritis of the knee classically presents with a painful effusion and limited range of motion. Diagnosis of this clinical entity cannot be made on the basis of laboratory data alone, with infections occurring in the presence of negative cultures and absent in the presence of markedly elevated intra-articular cell counts [1]. The frequency of native knee septic arthritis appears to be increasing and major concerns for serious medical complications and mortality persist [2]. The most robust information on laboratory data diagnostic for septic arthritis is available for the pediatric hip joint [3,4]. However, such high-quality, algorithmically predictive data is lacking for the adult native knee joint.

Septic arthritis in the knee remains a challenging diagnosis to make due to similarities to other entities in clinical presentation and equivocal laboratory results. Clinical impression remains the mainstay of diagnosis, but should be supplemented by relevant laboratory data. Screening inflammatory markers, particularly a