biofilm. In contrast, organisms that present with acute infections frequently produce toxins that result in a systemic toxicity and eventually shock. Vasso defined a low-grade infection as one that is not causing systemic illness [10]. Symptoms are sometimes ill-defined. Lab serologies may be slightly elevated and cultures can be difficult to grow. When an organism is isolated it is often a low-virulent organism, such as *Staphylococcus epidermidis* or *Cutibacterium acnes* (formerly *Propionibacterium acnes*). In contrast, a high-grade infection has not been as well-established in the literature [11]. One can deduce that it would be caused by an organism causing systemic illness/sepsis or acting aggressively at the site (i.e., severe pain, swelling, drainage, etc.). Currently, there is no method of qualifying these parameters. Medical advancements, such as 3rd and 4th generation deoxyribonucleic acid (DNA) sequencing, will help make it a possibility to identify genetic sequences that correlate with "organism aggressiveness" and poor outcomes. Only then will we be able to truly "rate" the severity of an invading organism.

Conclusions

In summary, there is substantive data that supports the concept of grading or rating a PJI. The data that supports grading PJI severity is retrospective in nature. There is not yet an international codified system that multiple investigators have agreed upon. Our recommendation is to gather an international workgroup to establish a PJI grading system, utilizing current tools and data available. The system of grading should be reviewed and upgraded every five years, as newer diagnostic tools and outcome data become available. For now, the McPherson schema has taken hold and is used in presentations worldwide over the past three to five years. We suggest using this system (or a modified version) as a starting point until an international workgroup establishes a codified staging system upon which the majority agrees.

REFERENCES

[1] Ong KL, Kurtz SM, Lau E, Bozic KJ, Berry DJ, Parvizi J. Prosthetic joint infection risk after total hip arthroplasty in the Medicare population. J Arthroplasty. 2009;24:105–109. doi:10.1016/j.arth.2009.04.027.

[2] Anagnostakos K, Schmid NV, Kelm J, Grün U, Jung J. Classification of hip joint infections. Int J Med Sci. 2009;6:227–233.

[3] Fehring KA, Abdel MP, Ollivier M, Mabry TM, Hanssen AD. Repeat two-stage exchange arthroplasty for periprosthetic knee infection is dependent on host grade. J Bone Joint Surg Am. 2017;99:19–24. doi:10.2106/JBJS.16.00075.

[4] McPherson EJ, Tontz W, Patzakis M, Woodsome C, Holtom P, Norris L, et al. Outcome of infected total knee utilizing a staging system for prosthetic joint infection. Am J Orthop. 1999;28:161–165.

[5] McPherson EJ, Woodson C, Holtom P, Roidis N, Shufelt C, Patzakis M. Periprosthetic total hip infection: outcomes using a staging system. Clin Orthop Relat Res. 2002:8–15.

[6] Tsukayama DT, Estrada R, Gustilo RB. Infection after total hip arthroplasty. A study of the treatment of one hundred and six infections. J Bone Joint Surg Am. 1996;78:512–523.

[7] Wimmer MD, Randau TM, Friedrich MJ, Ploeger MM, Schmolder J, Strauss AC, et al. Outcome predictors in prosthetic joint infections: validation of a risk stratification score for prosthetic joint infections in 120 cases. Acta Orthop Belg. 2016;82:143–148.

[8] Bryan AJ, Abdel MP, Sanders TL, Fitzgerald SF, Hanssen AD, Berry DJ. Irrigation and debridement with component retention for acute infection after hip arthroplasty: improved results with contemporary management. J Bone Joint Surg Am. 2017;99:2011–2018. doi:10.2106/JBJS.16.01103.

[9] McPherson E, Chowdhry M, Dipane M, Kenney S. Coating of cementless stems with commercially pure antibiotic-loaded calcium sulfate reduces infection rate in revision total hip arthroplasty. Orthopaedic Proceedings 2017;99-B:51–51. doi:10.1302/1358-992X.2017.22.051.

[10] Vasso M, Schiavone Panni A. Low-grade periprosthetic knee infection: diagnosis and management. J Orthop Traumatol. 2015;16:1–7. doi:10.1007/s10195-014-0294-y.

[11] Ettinger M, Calliess T, Kielstein JT, Sibai J, Brückner T, Lichtinghagen R, et al. Circulating biomarkers for discrimination between aseptic joint failure, low-grade infection, and high-grade septic failure. Clin Infect Dis. 2015;61:332–341. doi:10.1093/cid/civ286.

2.2. DIAGNOSIS: ALGORITHM

Authors: Timothy L. Tan, Javad Parvizi, Craig J. Della Valle, Noam Shohat

QUESTION 1: Do you agree with the American Academy of Orthopaedic Surgeons (AAOS) algorithm for the diagnosis of periprosthetic joint infections (PJIs)?

RECOMMENDATION: Yes. However, since the introduction of the AAOS algorithm for diagnosis of PJIs, numerous new tests and diagnostic modalities have become available. The proposed evidence-based and validated algorithm includes the guidelines from AAOS and the 2013 International Consensus Meeting (ICM) on PJIs. A stepwise algorithm first using serological markers followed by more specific and invasive tests continues to be recommended.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 73%, Disagree: 23%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

The guidelines for the diagnosis of PJIs introduced by the AAOS provided useful parameters for clinicians and a framework for diagnosing PJIs [1,2]. These guidelines have been widely adopted and were endorsed at the last ICM on PJIs in 2013 with slight modification [3]. While the existing algorithms are widely accepted, they are not completely evidence-based and have not been validated. Furthermore, several new synovial [4], serum and molecular biomarkers [5–10] have been introduced in recent years, which have increased confusion as many surgeons are unsure how to incorporate these tests into their practice and into the previously established guidelines.

With the introduction of new diagnostic tests and the need for validation of the guidelines, we have been prompted to expand on the prior guidelines and to develop an evidence-based, validated diagnostic algorithm. A multi-institutional study was performed by members of this workgroup, to generate a stepwise approach using random forest and multivariate regression analyses to generate relative weights and to determine which variables should be included

in each step. Ultimately, the algorithm shares many similarities to the previous algorithm as serological testing should be performed first, followed by more invasive tests. This stepwise approach of serological markers prior to joint aspiration has been demonstrated to be the most cost-efficient method of diagnosing PJIs using a multicriteria decision analysis in prior studies [11].

The first step in evaluating for a PJI should include serum testing for C-reactive protein, D-dimer and erythrocyte sedimentation rate. If at least one is elevated, or if there is a high clinical suspicion, clinicians should proceed with synovial fluid testing including a synovial fluid white blood-cell count with differential and leukocyte esterase testing. Intraoperative findings including purulence, histology, next generation sequencing (NGS) or a single positive culture can aid in cases where the diagnosis has not been conclusively ruled in or out prior to revision surgery, or when the aspiration does not yield fluid for analysis (a dry tap). The proposed algorithm was formally validated on a separate cohort of patients and demonstrated a high overall sensitivity (96.9%, 95% confidence interval (CI): 93.8-98.8) and specificity (99.5%, 95% CI: 97.2-100).

In the patient with a painful total joint arthroplasty, it is important to always consider infection. Initially, the first step considers patient risk factors, clinical findings and serum markers; the latter two of which have high sensitivity, but not necessarily high specificity in order to minimize false-negatives. In the multicenter study, approximately 13% of PJIs could be diagnosed with the first step based on a positive sinus tract. It is important to consider clinical suspicion and patient risk factors, (i.e., pretest probability), to optimize sensitivity as serum testing alone is negative in approximately 2.5% of patients who have a PJI [12]. The next step in the investigation of PJIs requires synovial fluid testing which has greater sensitivity and specificity, but is more invasive. The majority of PJIs will be identified following joint aspiration and synovial fluid analysis (approximately 65%). If a diagnosis of PJI cannot be confirmed or excluded at this point, intraoperative findings should be used and approximately 17% of PJIs will be diagnosed after incorporating intraoperative findings including culture, histology, operative appearance and NGS.

It is important to note that it is possible that the diagnosis of PJI may not be made even after reaching the third stage or may be inconclusive after obtaining synovial tests. These patients are often encountered in clinical practice and represent a real diagnostic challenge. Future research and novel tests are certainly needed in this patient population to reduce the gray area in these borderline patients without overt infection. Furthermore, it is important to note that the proposed algorithm and the definition of PJI may be inaccurate and require a modification in the tests utilized for the following conditions: adverse local tissue reactions, crystalline deposition arthropathies, inflammatory arthroplasty flares and infections with slow growing organisms, such as *Cutibacterium acnes* (formerly *Propionibacterium acnes*). Nevertheless, we hope that the introduction of this evidence-based and validated algorithm may simplify a very challenging process and account for recent advancements in the diagnosis of PJIs.

REFERENCES

[1] 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.

[2] Della Valle C, Parvizi J, Bauer TW, DiCesare PE, Evans RP, Segreti J, et al. American Academy of Orthopaedic Surgeons clinical practice guideline on: the diagnosis of periprosthetic joint infections of the hip and knee. J Bone Joint Surg Am. 2011;93:1355–1357. doi:10.2106/JBJS.9314ebo.

[3] Zmistowski B, Della Valle C, Bauer TW, Malizos KN, Alavi A, Bedair H, et al. Diagnosis of periprosthetic joint infection. J Arthroplasty. 2014;29:77–83. doi:10.1016/j.arth.2013.09.040.

[4] 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.

[5] 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.

[6] Saleh A, George J, Faour M, Klika AK, Higuera CA. Serum biomarkers in periprosthetic joint infections. Bone Joint Res. 2018;7:85–93. doi:10.1302/2046-3758.71.BJR-2017-0323.

[7] 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.

[8] Ahmad SS, Hirschmann MT, Becker R, Shaker A, Ateschrang A, Keel MJB, et al. A meta-analysis of synovial biomarkers in periprosthetic joint infection: Synovasure™ is less effective than the ELISA-based alpha-defensin test. Knee Surg Sports Traumatol Arthrosc. 2018;26:3039-3047. doi: 10.1007/s00167-018-4904-8.

[9] 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.

[10] 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.

[11] Diaz-Ledezma C, Lichstein PM, Dolan JG, Parvizi J. Diagnosis of periprosthetic joint infection in Medicare patients: multicriteria decision analysis. Clin Orthop Relat Res. 2014;472:3275–3284. doi:10.1007/s11999-014-3492-2.

[12] Akobeng AK. Understanding diagnostic tests 2: likelihood ratios, pre- and post-test probabilities and their use in clinical practice. Acta Paediatr. 2007;96:487–491. doi:10.1111/j.1651-2227.2006.00179.x.

Authors: Mahmoud Abdel Karim, Derek Ward, Jonathan Danoff

QUESTION 2: Are there any contraindications to knee or hip aspiration prior to revision surgery?

RECOMMENDATION: There are no clearly identified contraindications to aspiration of the knee or hip joint performed as part of the patient workup for infection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 8%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Aspiration of a joint is one of the most important aspects of the workup of a patient suspected of having an infected joint. There are numerous studies that have demonstrated the utility of joint aspiration in aiding diagnosis of periprosthetic joint infections (PJIs). In fact, joint aspiration is one of the initial steps in the workup of a patient for diagnosis of PJI, which is reflected in the algorithm