[8] Janz V, Wassilew GI, Kribus M, Trampuz A, Perka C. Improved identification of polymicrobial infection in total knee arthroplasty through sonicate fluid cultures. Arch Orthop Trauma Surg. 2015;135:1453–1457. doi:10.1007/s00402-015-2317-4.
[9] Tunney MM, Patrick S, Gorman SP, Nixon JR, Anderson N, Davis RI, et al. Improved detection of infection in hip replacements. A currently underestimated problem. J Bone Joint Surg Br. 1998;80:568–572.
[10] Trampuz A, Piper KE, Jacobson MJ, Hanssen AD, Unni KK, Osmon DR, et al. Sonication of removed hip and knee prostheses for diagnosis of infection. New Eng J Med. 2007;357:654–663. doi:10.1056/NEJMoa061588.
[11] Hischebeth GTR, Randau TM, Molitor E, Wimmer MD, Hoerauf A, Bekeredjian-Ding I, et al. Comparison of bacterial growth in sonication fluid cultures with periprosthetic membranes and with cultures of biopsies for diagnosing periprosthetic joint infection. Diagn Microbiol Infect Dis. 2016;84:112–115. doi:10.1016/j.diagmicrobio.2015.09.007.
[12] Shen H, Tang J, Wang Q, Jiang Y, Zhang X. Sonication of explanted prosthesis combined with incubation in BD bactec bottles for pathogen-based diagnosis of prosthetic joint infection. J Clin Microbiol. 2015;53:777–781. doi:10.1128/JCM.02863-14.
[13] Nguyen LL, Nelson CL, Saccente M, Smeltzer MS, Wassell DL, McLaren SG. Detecting bacterial colonization of implanted orthopaedic devices by ultrasonication. Clin Orthop Relat Res. 2002:29–37.
[14] Holinka J, Bauer L, Hirschl AM, Graninger W, Windhager R, Presterl E. Sonication cultures of explanted components as an add-on test to routinely conducted microbiological diagnostics improve pathogen detection. J Orthop Res. 2011;29:617–622. doi:10.1002/jor.21286.
[15] Scorzolini L, Lichtner M, Iannetta M, Mengoni F, Russo G, Panni AS, et al. Sonication technique improves microbiological diagnosis in patients treated with antibiotics before surgery for prosthetic joint infections. New Microbiol. 2014;37:321–328.
[16] Piper KE, Jacobson MJ, Cofield RH, Sperling JW, Sanchez-Sotelo J, Osmon DR, et al. Microbiologic diagnosis of prosthetic shoulder infection by use of implant sonication. J Clin Microbiol. 2009;47:1878–1884. doi:10.1128/JCM.01686-08.
[17] Rothenberg AC, Wilson AE, Hayes JP, O'Malley MJ, Klatt BA. Sonication of arthroplasty implants improves accuracy of periprosthetic joint infection cultures. Clin Orthop Relat Res. 2017;475:1827–1836. doi:10.1007/s11999-017-5315-8.
[18] Puig-Verdié L, Alentorn-Geli E, González-Cuevas A, Sorlí L, Salvadó M, Alier A, et al. Implant sonication increases the diagnostic accuracy of infection in patients with delayed, but not early, orthopaedic implant failure. Bone Joint J. 2013;95-B:244–249. doi:10.1302/0301-620X.95B2.30486.
[19] Janz V, Wassilew GI, Hasart O, Matziolis G, Tohtz S, Perka C. Evaluation of sonicate fluid cultures in comparison to histological analysis of the periprosthetic membrane for the detection of periprosthetic joint infection. Int Orthop. 2013;37:931–936. doi:10.1007/s00264-013-1853-1.
[20] Janz V, Wassilew GI, Hasart O, Tohtz S, Perka C. Improvement in the detection rate of PJI in total hip arthroplasty through multiple sonicate fluid cultures. J Orthop Res. 2013;31:2021–2024. doi:10.1002/jor.22451.
[21] Van Diek FM, Albers CGM, Van Hooff ML, Meis JF, Goosen JHM. Low sensitivity of implant sonication when screening for infection in revision surgery. Acta Orthop. 2017;88:294–299. doi:10.1080/17453674.2017.1300021.
[22] Prieto-Borja L, Auñón Á, Blanco A, Fernández-Roblas R, Gadea I, García-Cañete J, et al. Evaluation of the use of sonication of retrieved implants for the diagnosis of prosthetic joint infection in a routine setting. Eur J Clin Microbiol Infect Dis. 2018;37:715–722. doi:10.1007/s10096-017-3164-8.
[23] Trampuz A, Piper KE, Hanssen AD, Osmon DR, Cockerill FR, Steckelberg JM, et al. Sonication of explanted prosthetic components in bags for diagnosis of prosthetic joint infection is associated with risk of contamination. J Clin Microbiol. 2006;44:628–631. doi:10.1128/JCM.44.2.628-631.2006.
[24] Zhai Z, Li H, Qin A, Liu G, Liu X, Wu C, et al. Meta-analysis of sonication fluid samples from prosthetic components for diagnosis of infection after total joint arthroplasty. J Clin Microbiol. 2014;52:1730–1736. doi:10.1128/JCM.03138-13.
[25] Fernandez-Sampedro M, Salas-Venero C, Fariñas-Álvarez C, Sumillera M, Pérez-Carro L, Fakkas-Fernandez M, et al. 26 Postoperative diagnosis and outcome in patients with revision arthroplasty for aseptic loosening. BMC Infect Dis. 2015;15. doi:10.1186/s12879-015-0976-y.
[26] Kempthorne JT, Ailabouni R, Raniga S, Hammer D, Hooper G. Occult infection in aseptic joint loosening and the diagnostic role of implant sonication. Biomed Res Int. 2015;2015:946215. doi:10.1155/2015/946215.
[27] Janz V, Wassilew GI, Perka CF, Bartek B. Increased rate of bacterial colonization on PE-components in total joint arthroplasty: an evaluation through sonication. Technol Health Care. 2017;25:137–142. doi:10.3233/THC-161257.
[28] Portillo ME, Salvadó M, Sorli L, Alier A, Martínez S, Trampuz A, et al. Multiplex PCR of sonication fluid accurately differentiates between prosthetic joint infection and aseptic failure. J Infect. 2012;65:541–548. doi:10.1016/j.jinf.2012.08.018.
[29] Gomez E, Cazanave C, Cunningham SA, Greenwood-Quaintance KE, Steckelberg JM, Uhl JR, et al. Prosthetic joint infection diagnosis using broad-range PCR of biofilms dislodged from knee and hip arthroplasty surfaces using sonication. J Clin Microbiol. 2012;50:3501–3508. doi:10.1128/JCM.00834-12.
[30] Achermann Y, Vogt M, Leunig M, Wüst J, Trampuz A. Improved diagnosis of periprosthetic joint infection by multiplex PCR of sonication fluid from removed implants. J Clin Microbiol. 2010;48:1208–1214. doi:10.1128/JCM.00006-10.
[31] Esteban J, Alonso-Rodriguez N, del-Prado G, Ortiz-Pérez A, Molina-Manso D, Cordero-Ampuero J, et al. PCR-hybridization after sonication improves diagnosis of implant-related infection. Acta Orthop. 2012;83:299–304. doi:10.3109/17453674.2012.693019.
[32] Bereza P, Ekiel A, Augustciak-Duma A, Aptekorz M, Wilk I, Kusz D, et al. Comparison of cultures and 16S rRNA sequencing for identification of bacteria in two-stage revision arthroplasties: preliminary report. BMC Musculoskelet Dis. 2016;17:138. doi:10.1186/s12891-016-0991-1.
[33] Renz N, Feihl S, Cabric S, Trampuz A. Performance of automated multiplex PCR using sonication fluid for diagnosis of periprosthetic joint infection: a prospective cohort. Infection 2017;45:877–884. doi:10.1007/s15010-017-1073-5.

2.5. DIAGNOSIS: REIMPLANTATION

Authors: Carlos A. Higuera, AliSina Shahi

QUESTION 1: Are the MusculoSkeletal Infection Society (MSIS) and Interntional Consensus Meeting (ICM) criteria valid for decision-making before reimplantation?

RECOMMENDATION: The validity of the MSIS and ICM criteria for determination of the timing of reimplantation is unclear.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 7%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

George et al. [1] studied 79 patients undergoing reimplantation and found that MSIS criteria had a high specificity (96%) in predicting persistent infection, though the sensitivity was low (26%). They also found that patients who had positive MSIS criteria were at increased risk for reinfection after reimplantation. Kheir et al. [2] also investigated the MSIS criteria in patients who were undergoing two-stage exchange for periprosthetic joint infection (PJI) and reported a sensitivity of 25% and a specificity of 87% for detecting persistent infection. The authors further investigated the utility of the leucocyte esterase (LE) strip test and found that the LE strip test was positive in 22.2% of culture-positive and 4.4% of culture-negative cases. The LE test was negative in all patients who had not failed at their latest follow-

up, showing a great negative predictive value. In another study of 32 patients undergoing reimplantation, the authors found that the MSIS criteria had a very low sensitivity (0%), though the specificity was high (89%) [18]. Therefore, the MSIS criteria have a limited utility in the setting of reimplantation; nevertheless, it appears to be useful for ruling in infection.

Cultures are an integral part of the MSIS criteria. Multiple studies examining the role of reimplantation microbiology have found that positive cultures were associated with an increased risk for failure [3–10]. Tan et al. [8] reported that the risk of failure due to infection was higher (odds ratio (OR) = 2.5) in those with a positive culture during reimplantation. The study did not show a difference in the reinfection rates between a single and multiple (≥ 2) positive cultures. Although cultures are useful in predicting failure, the results of intraoperative cultures are not available before reimplantation. Prolonged antibiotics are recommended in patients who have positive intraoperative cultures. In a study by Murillo et al. [6], the authors had seven patients with positive intraoperative cultures during reimplantation and treated them all with 6-8 weeks of parenteral antibiotics. Patients were followed for a median of 30 months and none of them had recurrence of infection. The authors concluded that preoperative cultures can help identity patients who can benefit from an additional debridement procedure with spacer exchange. Mont et al. reported that the reinfection rates were lower in patients who underwent an additional debridement procedure if the preoperative cultures were positive prior to reimplantation [11].

Intraoperative frozen sections can help formulate a decision in a timely manner compared to intraoperative cultures. Studies examining the utility of frozen sections have consistently shown that frozen sections had a high specificity and low sensitivity in detecting persistent infection [1,12,13]. Therefore, a positive result should be treated as infection and reimplantation should be delayed, while a negative result may not be able to exclude infection.

Erthrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have been widely used to monitor response to treatment. Currently, there is limited evidence to support a specific cut-off for ESR and CRP. Although some studies have reported that both ESR and CRP decrease between the stages of a two-stage exchange protocol in patients with resolution of infection, their corresponding values are often above the MSIS cut-offs even in patients whose infection has clinically being cleared [14–16].

Synovial markers such as white blood cell (WBC) count and polymorphonuclear leukocytes (PMN) % have shown promising results in determination of reimplantation timing, however the optimal cut-off threshold for WBC count might be lower than the MSIS threshold of 3,000 cells/μL [14,15,17].

One of the major concerns with the studies evaluating the MSIS criteria or its components is the lack of a gold standard for diagnosing PJI or determining persistent infection. Most studies have compared the MSIS criteria with failure after reimplantation or the clinical decision to perform a spacer exchange [1,2,18]. However, it is unclear whether failure after reimplantation is an accurate representation of an undetected persistent infection or a newly acquired PJI. In a multicenter study of 92 patients who developed failure after reimplantation, only 32% of the patients had an identical organism at failure suggesting that many patients may be having a new infection rather than a persistent infection [9]. Another limitation of most studies is the presence of missing data [1,2,18]. As diagnostic tests are often performed in patients with an uncertainty in the diagnosis, it is possible that many patients with obvious infection may not have had all the appropriate tests performed. This can underestimate the utility of the MSIS criteria and maybe partly responsible for the low sensitivity of the MSIS criteria.

In summary, very few studies have evaluated the role of MSIS criteria in determining the reimplantation timing. Therefore, it is unclear whether the MSIS or the ICM criteria are a reliable tool for this matter. Cultures constitute a major part of MSIS criteria and a positive culture at reimplantation has been shown to increase the risk of failure in numerous studies. Frozen sections are reported to have a high specificity, though their sensitivity is limited. Synovial markers such as WBC counts, PMN % and the LE test had better results in diagnosing persistent PJIs compared to serum markers. Although ESR and CRP decrease between the stages of a two-stage exchange treatment, they cannot be reliably used to detect persistent infection at the current thresholds. There is a dire need for an accurate diagnostic test to determine optimal timing of reimplantation in patients undergoing surgical treatment for PJI.

REFERENCES

[1] George J, Kwiecien G, Klika AK, Ramanathan D, Bauer TW, Barsoum WK, et al. Are frozen sections and MSIS criteria reliable at the time of reimplantation of two-stage revision arthroplasty? Clin Orthop Relat Res. 2016;474:1619–1626. doi:10.1007/s11999-015-4673-3.

[2] Kheir MM, Ackerman CT, Tan TL, Benazzo A, Tischler EH, Parvizi J. Leukocyte esterase strip test can predict subsequent failure following reimplantation in patients with periprosthetic joint infection. J Arthroplasty. 2017;32:1976–1979. doi:10.1016/j.arth.2017.01.031.

[3] Akgün D, Müller M, Perka C, Winkler T. A positive bacterial culture during re-implantation is associated with a poor outcome in two-stage exchange arthroplasty for deep infection. Bone Joint J. 2017;99-B:1490–1495. doi:10.1302/0301-620X.99B11.BJJ-2017-0243-R1.

[4] Sorlí L, Puig L, Torres-Claramunt R, González A, Alier A, Knobel H, et al. The relationship between microbiology results in the second of a two-stage exchange procedure using cement spacers and the outcome after revision total joint replacement for infection: the use of sonication to aid bacteriological analysis. J Bone Joint Surg Br. 2012;94:249–253. doi:10.1302/0301-620X.94B2.27779.

[5] Nelson CL, Jones RB, Wingert NC, Foltzer M, Bowen TR. Sonication of antibiotic spacers predicts failure during two-stage revision for prosthetic knee and hip infections. Clin Orthop Rel Res. 2014;472:2208–2214. doi:10.1007/s11999-014-3571-4.

[6] Murillo O, Euba G, Calatayud L, Domínguez MA, Verdaguer R, Pérez A, et al. The role of intraoperative cultures at the time of reimplantation in the management of infected total joint arthroplasty. Eur J Clin Microbiol Infect Dis. 2008;27:805–811. doi:10.1007/s10096-008-0509-3.

[7] Cabo J, Euba G, Saborido A, González-Panisello M, Domínguez MA, Agulló JL, et al. Clinical outcome and microbiological findings using antibiotic-loaded spacers in two-stage revision of prosthetic joint infections. J Infect. 2011;63:23–31. doi:10.1016/j.jinf.2011.04.014.

[8] Tan TL, Gomez MM, Manrique J, Parvizi J, Chen AF. Positive culture during reimplantation increases the risk of subsequent failure in two-stage exchange arthroplasty. J Bone Joint Surg. 2016;98:1313–1319. doi:10.2106/JBJS.15.01469.

[9] Zmistowski B, Tetreault MW, Alijanipour P, Chen AF, Della Valle CJ, Parvizi J. Recurrent periprosthetic joint infection. J Arthroplasty. 2013;28:1486–1489. doi:10.1016/j.arth.2013.02.021.

[10] Tigani D, Trisolino G, Fosco M, Ben Ayad R, Costigliola P. Two-stage reimplantation for periprosthetic knee infection: influence of host health status and infecting microorganism. Knee. 2013;20:9–18. doi:10.1016/j.knee.2012.06.004.

[11] Mont MA, Waldman BJ, Hungerford DS. Evaluation of preoperative cultures before second-stage reimplantation of a total knee prosthesis complicated by infection. A comparison-group study. J Bone Joint Surg Am. 2000;82-A:1552–1557.

[12] Della-Valle CJ, Bogner E, Desai P, Lonner JH, Adler E, Zuckerman JD, et al. Analysis of frozen sections of intraoperative specimens obtained at the time of reoperation after hip or knee resection arthroplasty for the treatment of infection. J Bone Joint Surg Am. 1999;81:684–689.

[13] Bori G, Soriano A, García S, Mallofré C, Riba J, Mensa J. Usefulness of histological analysis for predicting the presence of microorganisms at the time of reimplantation after hip resection arthroplasty for the treatment of infection. J Bone Joint Surg Am. 2007;89:1232–1237. doi:10.2106/JBJS.F.00741.

[14] Shukla SK, Ward JP, Jacofsky MC, Sporer SM, Paprosky WG, Della Valle CJ. Perioperative testing for persistent sepsis following resection arthroplasty of the hip for periprosthetic infection. J Arthroplasty. 2010;25:87–91. doi:10.1016/j.arth.2010.05.006.

[15] Kusuma SK, Ward J, Jacofsky M, Sporer SM, Della Valle CJ. What is the role of serological testing between stages of two-stage reconstruction of the infected prosthetic knee? Clin Orthop Relat Res. 2011;469:1002–1008. doi:10.1007/s11999-010-1619-7.

[16] Ghanem E, Azzam K, Seeley M, Joshi A, Parvizi J. Staged revision for knee arthroplasty infection: what is the role of serologic tests before reimplantation? Clin Orthop Relat Res. 2009;467:1699–1705. doi:10.1007/s11999-009-0742-9.

[17] Newman JM, George J, North WT, Navale SM, Klika AK, Barsoum WK, et al. Hematologic malignancies are associated with adverse perioperative outcomes after total hip arthroplasty. J Arthroplasty. 2017;32. doi:10.1016/j.arth.2017.03.002.

[18] Frangiamore SJ, Siqueira MBP, Saleh A, Daly T, Higuera CA, Barsoum WK. Synovial cytokines and the MSIS criteria are not useful for determining infection resolution after periprosthetic joint infection explantation. Clin Orthop Relat Res. 2016. doi:10.1007/s11999-016-4710-x.

Authors: Arash Aalirezaie, Job Diego Velázquez Moreno, Dirk-Jan Moojen

QUESTION 2: What metrics should be considered to determine the timing of reimplantation after two-stage exchange arthroplasty of the infected hip or knee?

RECOMMENDATION: There are no definitive metrics to allow determination of optimal timing of reimplantation. Thus, timing of reimplantation should consider resolution of clinical signs of infection, down-trend in the serological markers and results of synovial analysis, if aspiration is performed.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 96%, Disagree: 3%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Because optimal timing for reimplantation is unknown, most surgeons prefer to rely on a combination of clinical evaluations, such as clinical evidence of infection control and normalized laboratory values after a period of antibiotic therapy [1]. There is no gold standard that can guide surgeons to determine the optimal time of reimplantation [2]. Various serum and synovial markers have been studied to identify the most accurate test for screening for persistent periprosthetic joint infection (PJI). A common finding of most of the studies is a high specificity, but low sensitivity.

Serum Analysis

Several serum markers have been evaluated for PJI, but only a few prior to reimplantation. Serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have been widely evaluated for diagnosis, monitoring treatment and evaluating their role in identifying the optimal timing of reimplantation [2–9]. Although a decreasing trend in both markers is seen during the interval period, they can still be elevated in patients that are considered to have a treated infection and have also been seen to be normal in persistent infection. In different studies, no cut-off values could be determined and there were no significant differences in average ESR and/or CRP values at time of reimplantation between infected and non-infected cases [3,7].

Interleukin-6 (IL-6) has been recently studied among other biomarkers in PJI. It has been seen that it may have a role in defining persistent infection prior to reimplantation, although stronger evidence is needed [10]. A recent study by Shahi et al. [11], showed promising results in determining the reimplantation time using serum D-dimer test. In their cohort, 29 patients underwent reimplantation surgery for PJI. Five patients had elevated D-dimer levels at the time of reimplantation, two of which had a positive culture from intraoperative specimens (*Staphylococcus epidermidis* in one patient and *Cutibacterium acnes* (*C. acnes*) in the other patient). Both of those patients subsequently experienced failure due to infection. Based on the results of this study, D-dimer outperforms both ESR and CRP for determining the timing of reimplantation. The corresponding CRP and ESR values were falsely negative in both of these patients (a CRP level of 8 mg/L and an ESR of 20 mm/hr in one patient; a CRP level of 1 mg/L and an ESR of 9 mm/hr in the other patient). Ongoing clinical research is currently investigating the utility of D-dimer in determining the timing of reimplantation surgery. D-dimer is an inexpensive and widely available test that can aid in identifying the timing of reimplantation.

Joint Aspiration

Synovial fluid aspiration and analysis for cell count, microbiological culture and biomarkers prior to reimplantation is also widely being used to detect persistent infection. Studies on synovial fluid WBC and differential analysis are contradictory [6–9,12,13]. Kusuma et al. [7], showed that prior to reimplantation, synovial fluid white blood cell (WBC) and differential analysis are poor markers of persistent PJI in the knee. Conversely, Shukla et al. (6) found pre-reimplantation synovial WBC count to be highly diagnostic of persistent infection in the hip. Zmitowski et al. [12], reported elevated synovial WBC count and polymorphonuclear lukocyctes (PMN)% statistically significant in patients with persistent PJI but did not provided useful threshold to identify patients with persistent PJI. Almost all studies evaluating microbiological culture of joint aspirate report a very low sensitivity, which means persistent infections are not detected [8,9,13,14]. In addition, Mühlhofer et al, [8] identified that microbiological synovial fluid analysis can also be misleading due to false positive cultures.

Kheir et al, [15] reported on the use of the leukocyte esterase (LE) as a screening test for persistent infection. This test demonstrated a high specificity (100%), but low sensitivity (25%). A positive LE result had a high predictive value of failure of reimplantation. Frangiamore et al, [16] evaluated synovial fluid cytokines to determine the highest diagnostic accuracy for PJI. IL-6 and IL-1β showed the greatest decrease between first and second stages; these could potentially be used to monitor PJI treatment response. Due to the low sensitivity of these tests, they fail to provide a definite answer as to the infection status.

MusculoSkeletal Infection Society (MSIS) Criteria

The efficacy of MSIS criteria for determining infection resolution in PJI has also been evaluated [15–17]. Despite the clinical importance of these criteria, the lack of sensitivity of these tests do not make them useful in diagnosing persistent infection. Frangiamore et al. reported a specificity of 89% and sensitivity of 0% for MSIS criteria to rule out PJI after the first-stage [16]. Another study by Georges et al. [17], evaluated 97 patients undergoing reimplantation and also demonstrated a high specificity but low sensitivity for MSIS criteria