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QUESTION 5: What is the diagnostic accuracy of joint aspiration of a cement spacer in conjunction with clinical evaluation, imaging, serologic tests, and biopsies? Should it routinely be performed prior to reimplantation?

RECOMMENDATION: The diagnostic accuracy of joint aspiration prior to reimplantation is not known. None of the parameters being used to diagnose periprosthetic joint infection (PJI), and their respective thresholds, have been determined for aspiration. The decision to perform aspiration should be made based on the index of suspicion for persistent infection and individualized.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 95%, Disagree: 4%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Until today none of the diagnostic methods for PJI have demonstrated 100% specificity or sensitivity [1]. Therefore, a diagnostic method that involves a combination of clinical evaluation, imaging, serologic tests, as well as aspirate tests and biopsies, needs to be established for confirming the diagnosis of PJI. Two-stage exchange arthroplasty is comparable with one-stage exchange arthroplasty in that all the components are removed at the time of surgery. In contrast to one-stage arthroplasty, in two-stage surgery cases, a temporary antibiotic delivery device (a spacer) is implanted locally, and systemic antibiotics are administered intravenously for four to six weeks, with an antibiotic holiday of two to eight weeks prior to reimplantation for confirming the elimination of the infection [2–4] and to ensure that the samples collected at reimplantation for microbial culture do not give negative results owing to previous antibiotic use [4].

The two-stage reimplantation procedure for managing infected total knee arthroplasty (TKA) was first described by Insall et al. [5] in 1983. According to them, the first stage includes the removal of all the foreign materials from the joint. Thereafter, the debridement of all soft tissues, bone, synovectomy, irrigation and reaming of the medullary canals is performed. After joint preparation, antibiotic-loaded cement beads and/or a static or articulating spacer is inserted, followed by the closure of the soft tissues and the skin. The patient is then prescribed antibiotics for an extended period of time. Intravenous antibiotics are most commonly used and are selected on the basis of the sensitivities of the infecting organisms, as determined from the preoperative and intraoperative microbiologic cultures [5].

In 2000, Mont et al. [6] conducted a prospective study involving 34 patients who had undergone an aspiration before reimplantation, four weeks after antibiotic administration was discontinued. The authors concluded that cultures of knee aspirates had 75% sensitivity, 100% specificity, 100% positive predictive value, and 97% negative predictive value.

Beckerom and Stucky [7] (2006) studied the cultures of aspiration fluid from 68 infected knees in 67 patients; they reported 32 true positives, 17 true negatives, 6 false positives, and 13 false negatives and concluded that preoperative aspiration had a positive predictive value of 71% and a negative predictive value of 74%. They stated that a positive aspiration result may indicate prosthesis infection; however, a negative result does not rule out infection, and one must consider a coagulase-negative Staphylococcus infection in such cases.

Meermans and Haddad [8] (2010) prospectively followed 120 patients with assumed infection of total joint arthroplasty, including 64 with total hip arthroplasties (THAs) and 56 with TKAs. All patients had undergone aspiration with culture and biopsy. They inferred that the sensitivity was 83% for aspiration, 79% for biopsy, and 90% for the combination of both the techniques. The specificity was 100% for aspiration, biopsy and the combination. Their overall accuracies were 84%, 81%, and 90%, respectively. They concluded that routine aspiration should be followed by a biopsy in the workup of septic joints.

Lonner et al. [9] (2001) published a study of 34 infected knee prostheses, where aspiration was performed for the detection of persistent infection prior to reimplantation and after the completion of a four to eight week course of antibiotics. They concluded that knee aspiration following resection arthroplasty had sensitivity and positive predictive value of zero, a negative predictive value of 75%, and a specificity of 92%. They further stated that a negative result of joint aspiration after resection arthroplasty may not necessarily rule out current infection. The average antibiotic-free interval in all patients was 20 days; patients with false-negative results of aspiration had an average antibiotic-free interval of 11.5 days compared with 26 days among all other patients.

In addition, the study performed by Ghanem et al. [10] (2009) reported that a negative result of aspiration of the knee did not rule out infection. They observed false-negative aspiration in 15% of their cases, similar to the report by Lonner [9] et al.

Sanchez-Sotelo et al. [11] (2009) focused on long-term reinfection-free survival and mechanical durability; they retrospectively reviewed 168 patients (169 hips) with infected arthroplasty, all of whom had undergone two-stage reimplantation for an infected THA from 1988 to 1998. In the second stage, the femoral component was fixed with antibiotic-loaded bone cement in 121 hips, while the other femoral components and all the acetabular components were uncemented.

The minimum follow-up time was 2 years (mean, 7 years; range, 2–16 years). At the most recent follow-up, 12 hips (7.1%) had undergone re-operation for reinfection, and 13 hips (7.7%) were revised for aseptic loosening or osteolysis. Aseptic loosening occurred on one or both sides of the joint in 24 hips (14.2%). The 10-year rates for survival without reinfection and mechanical failure were 87.5% and 75.2%, respectively. Nineteen hips dislocated and eight underwent revision surgery for instability. The two-staged procedures included the removal of all the prosthetic components, cement (if present), and all the foreign bodies followed by intravenous antibiotic therapy and delayed reimplantation of THA. They applied a spacer made of antibiotic-loaded polymethyl methacrylate in 31 hips, while the remaining hips underwent resection arthroplasty for the time interval between implant removal and reimplantation.

In the 23 hips with negative intraoperative cultures, infection was diagnosed on the basis of positive intraoperative pathology (13 hips), frank purulence (nine hips, six with positive pathology), positive preoperative aspiration (14 hips, seven with positive pathology)

and/or macroscopic evidence of infection. The average duration of intravenous antibiotic therapy was 6 weeks (range, 3–18 weeks). The median duration of the interval between the resection and reimplantation was 9.4 months (range, 3–18 months). After reimplantation, antibiotics were discontinued when the intraoperative cultures were finalized, except in 16 patients (16 hips) with chronic oral suppression antibiotic therapy.

Kusuma et al. [12] (2011) have determined serology (erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP)) and aspiration (synovial white blood cell (WBC) count) to be predictive parameters for determining the appropriate timing for definitive second-stage reimplantation. These were compared when stopping antibiotic treatment prior to the second-stage procedure. The WBC count in the synovial fluid was found to be the most reliable indicator of infection resolution. However, the researchers were unable to launch any definitive outlines indicative of persistent infection.

Newman et al. [13] retrospectively evaluated 77 hips undergoing aspiration before a second stage reimplantation and found a sensitivity of 30% and specificity of 100% in detecting infection. Similarly, Preininger et al. [14] found that pre-reimplantation aspiration cultures had a high specificity (100%), but low sensitivity (21%).

Although a majority of the studies report a high specificity with respect to cultures, the utility of other aspiration tests is less clear. Shukla et al. [15] found that WBC counts had an area under the curve (AUC) of 0.91 at cut-off of 3,528 cells/μL (sensitivity, 78%; specificity, 96%), whereas polymorphonuclear (PMN) % had an AUC of 0.81 at cut-off of 79% (sensitivity, 78%; specificity, 82%). Newman et al. [13] reported a sensitivity and specificity of 47% and 87% for WBC counts (AUC = 0.67), and 76% and 80% for PMN % (AUC = 0.78), respectively at the MusculoSkeletal Infection Society (MSIS) thresholds of 3,000 cells/μL and 80 PMN %. They also found that when any of the aspiration results were positive for infection (WBC >3,000 cells/μL or PMN % >80 or positive culture), aspiration had a good diagnostic performance (AUC = 0.82). Additionally, they found that lowering the threshold for WBC count significantly improved the diagnostic sensitivity (47 - 76%) while slightly decreasing the specificity (87 - 78%). On the contrary, Hoell et al. [16,17] reported poor diagnostic performances for WBC counts in their two studies (AUCs of 0.37 and 0.56), though the cut-off obtained was close to 1,000 cells/μL. Kheir et al. [18] found that leukocyte esterase (LE) test performed on synovial fluid had a sensitivity and specificity of 26% and 100%, respectively (AUC = 0.56) for detecting persistent infection. They also found that a positive LE test was associated with increased risk of reinfection after the reimplantation surgery.

Most of the studies were performed in a retrospective manner causing an inherent bias in patient selection and were of moderate or low quality [19]. A major concern while interpreting the studies assessing the utility of aspiration is the uncertainty regarding the gold standard test to diagnose persistent infection. Many studies compare the aspiration results to intraoperative cultures, histology or other markers at time of reimplantation, while some studies compare to subsequent failure after reimplantation. Lack of adequate fluid (dry taps) is another concern while performing preoperative aspirations on spacers [13]. Sometimes, saline lavages are performed in an attempt to obtain fluid when such dry taps are encountered. Newman et al. [13] compared the accuracy of aspiration performed with and without a saline lavage, and found that synovial WBC counts and PMN % were noticeably affected by lavage, while culture results were less susceptible to lavage.

In summary, it appears that cultures obtained before the planned second stage are helpful in ruling in persistent infection. A patient with positive culture is likely to benefit from an additional debridement. However, a negative culture does not rule out persistent infection and additional clinical, and laboratory markers should be considered in these patients. WBC counts and PMN % have demonstrated good diagnostic utility, though the WBC cut-off might be lower than the MSIS threshold.

It is well known, that the most important factors in favor of routine aspiration are its reliability, low cost and simplicity of application in an outpatient clinic. Given the studies [8,12] as Level II, diagnostic studies emphasizing the diagnostic accuracy of an aspiration of a cement spacer following a drug-holiday in literature, we conclude that aspiration of a cement spacer in conjunction with clinical evaluation, imaging, serologic tests and biopsies has high diagnostic accuracy and may be performed before reimplantation based on the index of suspicion for persistent infections [20,21].

REFERENCES

[1] Spangehl MJ, Masri BA, O'Connell JX, Duncan CP. Prospective analysis of preoperative and intraoperative investigations for the diagnosis of infection at the sites of two hundred and two revision total hip arthroplasties. J Bone Joint Surg Am. 1999;81:672–683.

[2] Bernard L, Legout L, Zürcher-Pfund L, Stern R, Rohner P, Peter R, et al. Six weeks of antibiotic treatment is sufficient following surgery for septic arthroplasty. J Infect. 2010;61:125–132. doi:10.1016/j.jinf.2010.05.005.

[3] Chen AF, Heller S, Parvizi J. Prosthetic joint infections. Surg Clin North Am. 2014;94:1265–1281. doi:10.1016/j.suc.2014.08.009.

[4] Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013;56:e1–e25. doi:10.1093/cid/cis803.

[5] Insall JN, Thompson FM, Brause BD. Two-stage reimplantation for the salvage of infected total knee arthroplasty. 1983. J Bone Joint Surg Am. 2002;84-A:490.

[6] 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.

[7] Van den Bekerom MPJ, Stuyck J. The value of pre-operative aspiration in the diagnosis of an infected prosthetic knee: a retrospective study and review of literature. Acta Orthop Belg. 2006;72:441–447.

[8] Meermans G, Haddad FS. Is there a role for tissue biopsy in the diagnosis of periprosthetic infection? Clin Orthop Relat Res. 2010;468:1410–1417. doi:10.1007/s11999-010-1245-4.

[9] Lonner JH, Siliski JM, Della Valle C, DiCesare P, Lotke PA. Role of knee aspiration after resection of the infected total knee arthroplasty. Am J Orthop. 2001;30:305–309.

[10] 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.

[11] Sanchez-Sotelo J, Berry DJ, Hanssen AD, Cabanela ME. Midterm to long-term followup of staged reimplantation for infected hip arthroplasty. Clin Orthop Relat Res. 2009;467:219–224. doi:10.1007/s11999-008-0480-4.

[12] 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.

[13] Newman JM, George J, Klika AK, Hatem SF, Barsoum WK, Trevor North W, et al. What is the diagnostic accuracy of aspirations performed on hips with antibiotic cement spacers? Clin Orthop Relat Res. 2017;475:204–211. doi:10.1007/s11999-016-5093-8.

[14] Preininger B, Janz V, von Roth P, Trampuz A, Perka CF, Pfitzner T. Inadequacy of joint aspiration for detection of persistent periprosthetic infection during two-stage septic revision knee surgery. Orthopedics. 2017;40:231–234. doi:10.3928/01477447-20170411-04.

[15] 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.

[16] Hoell S, Moeller A, Gosheger G, Hardes J, Dieckmann R, Schulz D. Two-stage revision arthroplasty for periprosthetic joint infections: what is the value of cultures and white cell count in synovial fluid and CRP in serum before second stage reimplantation? Arch Orthop Trauma Surg. 2016;136:447–452. doi:10.1007/s00402-015-2404-6.

[17] Hoell S, Borgers L, Gosheger G, Dieckmann R, Schulz D, Gerss J, et al. Interleukin-6 in two-stage revision arthroplasty: what is the threshold value to exclude persistent infection before re-implanatation? Bone Joint J. 2015;97-B:71–75. doi:10.1302/0301-620X.97B1.33802.

[18] 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.

[19] American Academy of Orthopaedic Surgeons. Clinical Practice Guideline and Systematic Review Methodology. https://www.aaos.org/uploadedFiles/PreProduction/Quality/Guidelines_and_Reviews/guidelines/Guideline%20and%20Systematic%20Review%20Processes_v2.0_Final.pdf.

[20] Aggarwal VK, Tischler E, Ghanem E, Parvizi J. Leukocyte esterase from synovial fluid aspirate: a technical note. J Arthroplasty. 2013;28:193–195. doi:10.1016/j.arth.2012.06.023.

[21] American Academy of Orthopaedic Surgeons. The diagnosis of periprosthetic joint infections of the hip and knee. Guideline and evidence report. https://www.aaos.org/Research/guidelines/PJIguideline.pdf 2010.

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QUESTION 6: What intraoperative metrics can be utilized at the time of intended reimplantation to help decision-making and reduce the risk of subsequent recurrence?

RECOMMENDATION: Intraoperatively, frozen section and leukocyte esterase (LE) strip test can be used as decision-making metrics for reimplantation.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 66%, Disagree: 25%, Abstain: 9% (Super Majority, Weak Consensus)

RATIONALE

The intraoperative decision-making process for reimplantation must be based on metrics that are fast (due to time constraints), accurate to reduce the risk of recurrence and reliable so that such metrics can be reproduced in many scenarios.

Frozen Section (FS)

Intraoperative FSs have been used as a fast and accurate indicator of infection during reimplantation due to high specificity. Most of the studies recommend withholding reimplantation in the presence of positive results. Nonetheless there is a debate regarding optimal cutoff for the number of polymorphonuclear cells (PMNs) per high-power field and whether this should be a quantitative or qualitative analysis. The primary reason FS is not universally accepted as a decision-making marker is its reliability. FS continues to have a low sensitivity (between 25 - 50%) in the presence of infection [1–5]. FS is also dependent on a highly specialized pathologist with experience, which is evident in a study published by George et al. where even in the presence of a highly trained pathologist, the sensitivity only reached 50% [5]. Gram and fungal stains have very low sensitivity [6–8], and therefore are not recommended.

Leukocyte Esterase (LE)

The LE strip test has the advantages of being a fast, accurate and reliable test. This is supported by several recently published studies and a meta-analysis [9–22]. These publications show that LE has a sensitivity that ranges from 49% up to 95%, and a specificity that ranges from 82 - 100%. Some papers also have shown a positive predictive value (PPV) from 71.5 to 100%.

One of the limitations observed with LE, being a colorimetric assay, was the potential for inaccurate readings in the presence of a bloody sample. A recent study by Li X et al. [23] showed that when a bloody sample is centrifuged, the LE continues to have excellent sensitivity and specificity (92 and 93.1% respectively), making it still a very reliable test for intraoperative decision-making. Another concern when LE started to be widely used was its accuracy in the presence of adverse local tissue reactions (ALTR), namely metallosis. Tischler et al. [12] demonstrated that LE combined with PMN % was reliable in ruling out infection in 92.9% of the cases evaluated.

Alpha-Defensin

The alpha-defensin test as a reliable synovial biomarker for the diagnosis of infection was introduced by Deirmengian et al. [14] Since then, newer techniques have been developed which achieve similar results in a faster fashion. Alpha-defensin lateral-flow immunoassays [24–31]are faster and have a sensitivity that ranges from 64.7 - 94.5%, a specificity with a range of 87 - 99.6%, a positive predictive value (PPV) from 74.6 - 98.1%, and a negative predictive value (NPV) from 83.7 - 98.2%. However, a few studies [29,30] have demonstrated that the immunoassay test performed in the laboratory setting is more accurate than the lateral-flow technique, and provides sensitivity ranges from 83.6 - 97.1%, specificity ranges of 97 - 100%, PPV ranges from 94.9 - 100%, and NPV ranges from 89.9 - 98.2%.

As with LE, other factors can impact the accuracy of Alpha-defensin testing. The specificity and PPV can decrease in the presence of ALTR [24] and crystal deposition arthroplasties [31].

Interleukins

Another lateral-flow immunoassay technique being used for the diagnosis of PJI involves interleukins, specifically Interleukin-6 (IL-6). This intraoperative test allows for a rapid assessment of the cytokines within the synovial fluid. This technique is already in use with an acceptable specificity but relatively low sensitivity. However, when IL-6 is measured in the lab with radioimmunoassay techniques, it is more accurate [32].

Despite having these time-tested and novel techniques, the surgeon continues to rely on a combination of preoperative testing, intraoperative clinical judgment and the interpretation of these intraoperative metrics to decide whether it is safe to proceed with reimplantation and avoid the risk of PJI recurrence.

REFERENCES

[1] Feldman DS, Lonner JH, Desai P, Zuckerman JD. The role of intraoperative frozen sections in revision total joint arthroplasty. J Bone Joint Surg Am. 1995;77:1807–1813.

[2] 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.

[3] 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