

- [12] Patton D, Kiewiet N, Brage M. Infected total ankle arthroplasty: risk factors and treatment options. *Foot Ankle Int.* 2015;36:626-634. doi:10.1177/1071100714568869.
- [13] Jackson WO, Schmalzried TP. Limited role of direct exchange arthroplasty in the treatment of infected total hip replacements. *Clin Orthop Relat Res.* 2000;301:101-105.
- [14] Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. *N Engl J Med.* 2004;351:1645-1654. doi:10.1056/NEJMra040181.
- [15] Parvizi J, Adeli B, Zmistowski B, Restrepo C, Greenwald AS. Management of periprosthetic joint infection: the current knowledge: AAOS exhibit selection. *J Bone Joint Surg Am.* 2012;94:e104. doi:10.2106/JBJS.K.01417.
- [16] Osmon DR, Berbari EF, Berend AR, Lew D, Zimmerli W, Steckelberg JM, et al. Executive summary: diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis.* 2013;56:1-10. doi:10.1093/cid/cis966.
- [17] Senthil S, Munro JT, Pitto RP. Infection in total hip replacement: meta-analysis. *Int Orthop.* 2011;35:253-260. doi:10.1007/s00264-010-1144-z.
- [18] Berend KR, Lombardi AV, Morris MJ, Bergeson AG, Adams JB, Sneller MA. Two-stage treatment of hip periprosthetic joint infection is associated with a high rate of infection control but high mortality. *Clin Orthop Relat Res.* 2013;471:510-518. doi:10.1007/s11999-012-2595-x.
- [19] Romanò CL, Gala L, Logoluso N, Romanò D, Drago L. Two-stage revision of septic knee prosthesis with articulating knee spacers yields better infection eradication rate than one-stage or two-stage revision with static spacers. *Knee Surg Sports Traumatol Arthrosc.* 2012;20:2445-2453. doi:10.1007/s00167-012-1885-x.
- [20] Romanò CL, Romanò D, Albisetti A, Meani E. Preformed antibiotic-loaded cement spacers for two-stage revision of infected total hip arthroplasty. Long-term results. *Hip Int.* 2012;22 Suppl 8:S46-S53. doi:10.5301/HIP.2012.9570.
- [21] Engesaeter LB, Dale H, Schrama JC, Hallan G, Lie SA. Surgical procedures in the treatment of 784 infected THAs reported to the Norwegian Arthroplasty Register. *Acta Orthop.* 2011;82:530-537. doi:10.3109/17453674.2011.623572.
- [22] Wongworawat MD. Clinical faceoff: one- versus two-stage exchange arthroplasty for prosthetic joint infections. *Clin Orthop Relat Res.* 2013;471:1750-1753. doi:10.1007/s11999-013-2882-1.
- [23] Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. *Science.* 1999;284:1318-1322.
- [24] Zoubos AB, Galanakis SP, Soucacos PN. Orthopedics and biofilm—what do we know? A review. *Med Sci Monit.* 2012;18:RA89-RA96.
- [25] Mauffrey C, Herbert B, Young H, Wilson ML, Hake M, Stahel PE. The role of biofilm on orthopaedic implants: the “Holy Grail” of post-traumatic infection management? *Eur J Trauma Emerg Surg.* 2016;42:411-416. doi:10.1007/s00068-016-0694-1.
- [26] Buechel FF, Femino FP, D'Alessio J. Primary exchange revision arthroplasty for infected total knee replacement: a long-term study. *Am J Orthop.* 2004;33:190-198; discussion 198.
- [27] Winkler H, Stoiber A, Kaudela K, Winter F, Menschik F. One stage uncemented revision of infected total hip replacement using cancellous allograft bone impregnated with antibiotics. *J Bone Joint Surg Br.* 2008;90:1580-1584. doi:10.1302/0301-620X.90B12.20742.
- [28] Göksan SB, Freeman MA. One-stage reimplantation for infected total knee arthroplasty. *J Bone Joint Surg Br.* 1992;74:78-82.
- [29] Callaghan JJ, Katz RP, Johnston RC. One-stage revision surgery of the infected hip. A minimum 10-year followup study. *Clin Orthop Relat Res.* 1999;339-343.
- [30] Cordero-Ampuero J, Esteban J, García-Cimbrelo E, Munuera L, Escobar R. Low relapse with oral antibiotics and two-stage exchange for late arthroplasty infections in 40 patients after 2-9 years. *Acta Orthop.* 2007;78:511-519. doi:10.1080/17453670710014167.
- [31] Kurd MF, Ghanem E, Steinbrecher J, Parvizi J. Two-stage exchange knee arthroplasty: does resistance of the infecting organism influence the outcome? *Clin Orthop Relat Res.* 2010;468:2060-2066. doi:10.1007/s11999-010-1296-6.
- [32] Brandt CM, Duffy MC, Berbari EF, Hanssen AD, Steckelberg JM, Osmon DR. Staphylococcus aureus prosthetic joint infection treated with prosthesis removal and delayed reimplantation arthroplasty. *Mayo Clin Proc.* 1999;74:553-558. doi:10.4065/74.6.553.
- [33] Segawa H, Tsukayama DT, Kyle RF, Becker DA, Gustilo RB. Infection after total knee arthroplasty. A retrospective study of the treatment of eighty-one infections. *J Bone Joint Surg Am.* 1999;81:1434-1445.
- [34] Joseph J, Raman R, Macdonald DA. Time interval between first and second stage revision hip arthroplasty for infection, the effect on outcome. *J Bone Joint Surg Br.* 2003;85.
- [35] 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.
- [36] 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.
- [37] 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.

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QUESTION 8: What metrics can be used to determine the optimal timing of reimplantation in patients who have undergone resection arthroplasty as part of a two-stage exchange for infected total ankle arthroplasty (TAA)?

RECOMMENDATION: There is no conclusive data regarding what metrics can be used in order to determine the optimal timing of reimplantation for an infected TAA. We recommend that reimplantation is performed when there are clinical signs of resolution of infection (well-healed wound, lack of erythema, etc.), and the serological markers have substantially declined (> 40%) from baseline (measured at the time of diagnosis of infection).

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Infected TAA is a serious complication that is thought to occur in as many as 5% of patients [1,2]. Management of infected TAA often requires surgical intervention that includes removal of the prosthesis, local and systemic antibiotic treatment, and subsequent reimplantation in a select group of patients. One of the most challenging questions pertains to optimal timing of reimplantation. There is little in the literature regarding the optimal treatment of an infected TAA. Most of the available literature has limitations including low numbers of patients, short duration of follow-up and so on [1-5].

There are a number of publications related to patients with infected TAA who underwent two-stage exchange arthroplasty.

Patton et al. reported on 29 of 966 (3.2%) cases of infected TAA [3]. Among the infected TAA, 13 patients underwent two-stage exchange arthroplasty and antibiotic spacer placement. While infection type and operative cultures were listed, no specific recommendations on timing of reimplantation were made. Similarly, Lee et al. omitted data regarding timing of reimplantation but reported one case of deep infection, out of 50 TAAs (2%) that required implant removal, antibiotic-impregnated spacer placement, and later revision TAA [4].

Thoroughly outlining the timeline, Young et al. detailed a case report of a two-stage TAA revision [5]. Irrigation and debridement (cefazolin 1 gm diluted in 1L 0.9% saline) and antibiotic cement

spacer (80 gm of polymethylmethacrylate impregnated with 2 gm gentamicin) placement was implemented. The blood cultures and intraoperative bone and tissue cultures in the latter infected case isolated *Streptococcus mitis*. As a result, a six-week course of antibiotics with penicillin G was administered. Three months after infection had resolved, the patient had a revision TAA. As demonstrated, the limited TAA infection literature warrants that a treating orthopaedic surgeon applies the basic treatment principles derived from infections of knee and hip arthroplasties [6].

The ultimate decision regarding surgical management of patients with infected TAA in general, and reimplantation of those who have undergone a prior resection in particular, lies with the orthopaedic surgeon with appropriate consultation of other disciplines such as infectious disease specialists, plastic surgeons and so on. A two-stage exchange strategy is commonly indicated in patients who have a chronic infection and are not candidates for a one-stage exchange arthroplasty. Protocols for management of a patient with infected TAA are extrapolated from the available literature for infected hip and knee arthroplasties. Patients undergoing resection arthroplasty typically receive four to six weeks of intravenous or highly bioavailable oral antimicrobial therapy between stages [7,8].

The timing to reimplant usually relies on signs of clinical resolution of infection, such as healing of the wound, absence of erythema and so on, as well as a decline in serological markers of inflammation, namely erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) [9]. To determine infection resolution and predict the presence of infection in patients awaiting reimplantation, numerous serological markers have been evaluated in the past, including interleukin 6 (IL-6) and others [10]. The most widely used serological tests for the diagnosis of periprosthetic joint infection (PJI) are the assessment of ESR and CRP level. A recent publication also suggested the use of serum D-dimer combined with ESR and CRP in order to increase sensitivity and specificity [11].

In data published about hip and knee surgery, time from resection arthroplasty to reimplantation varies significantly from two weeks to several months. In earlier cohort studies, early reimplantation within three weeks after resection resulted in a higher failure rate [12,13]. Some groups have reported satisfactory outcomes when reimplantation occurs two to six weeks after resection while systemic antimicrobials are still being administered in situations when the infection is not due to MRSA, enterococci or any multidrug-resistant gram-negative organisms [14]. Delayed reimplantation after four to six weeks of intravenous antimicrobial therapy and an antibiotic-free period of two to eight weeks has been highly successful and chosen as the “standard” currently [7,15–17]. Recently, synovial fluid biomarkers have been shown to be useful in reaching or refuting the diagnosis of PJI. The combined measurement of synovial fluid alpha-defensin and CRP for the diagnosis of PJI demonstrated a sensitivity of 97% and a specificity of 100% [11,18]. Not only is obtaining synovial fluid invasive and painful to patients, but also there are not infrequent occasions when either an inadequate amount of fluid is available to perform all tests, or, worse, no fluid is retrieved from the joint [11].

Obtaining a pre-revision ESR and CRP is recommended to assess the success of treatment prior to reimplantation [19]. However, as some groups have reported, an elevated CRP level and ESR may not be accurate in predicting persistent infection post-resection, therefore the need for subsequent debridement should be interpreted in the context of the entire clinical picture when deciding on the appropriate timing for reimplantation [20–22].

In the absence of concrete data, and borrowing from the hip and knee infection literature, we recommend that reimplanta-

tion in patients with infected TAA be performed when appropriate antibiotic treatment is completed, clinical signs for resolution of infection are present (healed wound, absent erythema and so on) and the level of inflammatory markers of acute inflammation (ESR, CRP and possibly D-dimer) have declined substantially (> 40%) from their baseline. Further research regarding this issue is desperately is needed.

REFERENCES

- [1] Reuver JM, Dayerizadeh N, Burger B, Elmans L, Hoelen M, Tulp N. Total ankle replacement outcome in low volume centers: short-term followup. *Foot Ankle Int.* 2010;31:1064–1068. doi:10.3113/FAL.2010.1064.
- [2] Gougoulas N, Khanna A, Maffulli N. How successful are current ankle replacements?: a systematic review of the literature. *Clin Orthop Relat Res.* 2010;468:199–208. doi:10.1007/s11999-009-0987-3.
- [3] Patton D, Kiewiet N, Brage M. Infected total ankle arthroplasty: risk factors and treatment options. *Foot Ankle Int.* 2015;36:626–634. doi:10.1177/1071100714568869.
- [4] Lee K-B, Cho S-G, Hur C-I, Yoon T-R. Perioperative complications of HINTEGRA total ankle replacement: our initial 50 cases. *Foot Ankle Int.* 2008;29:978–984. doi:10.3113/FAL.2008.0978.
- [5] Young JL, May MM, Haddad SL. Infected total ankle arthroplasty following routine dental procedure. *Foot Ankle Int.* 2009;30:252–257. doi:10.3113/FAL.2009.0252.
- [6] Alrashidi Y, Galhoum AE, Wiewiorski M, Herrera-Pérez M, Hsu RY, Barg A, et al. How to diagnose and treat infection in total ankle arthroplasty. *Foot Ankle Clin.* 2017;22:405–423. doi:10.1016/j.fcl.2017.01.009.
- [7] Segawa H, Tsukayama DT, Kyle RF, Becker DA, Gustilo RB. Infection after total knee arthroplasty. A retrospective study of the treatment of eighty-one infections. *J Bone Joint Surg Am.* 1999;81:1434–1445.
- [8] 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.
- [9] 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.
- [10] 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.
- [11] 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.
- [12] Rand JA, Bryan RS. Reimplantation for the salvage of an infected total knee arthroplasty. *J Bone Joint Surg Am.* 1983;65:1081–1086.
- [13] Mariaux S, Tabin UF, Borens O. Diagnosis Of persistent infection in prosthetic two-stage exchange: PCR analysis of sonication fluid from bone cement spacers. *J Bone Joint Infect.* 2017;2:218–223. doi:10.7150/jbji.23078.
- [14] Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. *N Engl J Med.* 2004;351:1645–1654. doi:10.1056/NEJMra040181.
- [15] Brandt CM, Duffy MC, Berbari EF, Hanssen AD, Steckelberg JM, Osmon DR. Staphylococcus aureus prosthetic joint infection treated with prosthesis removal and delayed reimplantation arthroplasty. *Mayo Clin Proc.* 1999;74:553–558. doi:10.4065/74.6.553.
- [16] Hanssen AD, Rand JA, Osmon DR. Treatment of the infected total knee arthroplasty with insertion of another prosthesis. The effect of antibiotic-impregnated bone cement. *Clin Orthop Relat Res.* 1994;44–55.
- [17] Westrich GH, Walcott-Sapp S, Bornstein LJ, Bostrom MP, Windsor RE, Brause BD. Modern treatment of infected total knee arthroplasty with a 2-stage reimplantation protocol. *J Arthroplasty* 2010;25:1015–1021. doi:10.1016/j.arth.2009.07.017.
- [18] 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.
- [19] 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.
- [20] 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.
- [21] 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.
- [22] Parvizi J, Gehrke T, Chen AE. Proceedings of the International Consensus on Periprosthetic Joint Infection. *Bone Joint J.* 2013;95-B:1450–1452. doi:10.1302/0301-620X.95B11.33135.