1.2. PREVENTION: HOST RELATED, GENERAL FACTORS

Authors: Setor Kunutsor, Richard Iorio, James E. Feng, Zlatan Cizmic

QUESTION 1: What modifiable and non-modifiable host factors contribute to an increased risk of surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Modifiable host factors such as body mass index (BMI), smoking and alcohol, as well as certain medical co-morbidities have been shown to increase the risk of SSIs/PJIs. Non-modifiable factors such as increasing age, male gender and black ethnicity have also been shown to increase the risk of SSIs/PJIs.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 98%, Disagree: 1%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

The risk of developing SSIs/PJIs following total joint arthroplasty (TJA) is likely to be influenced by several factors such as the characteristics of the patients, the surgical intervention and the postoperative care (Table 1). However, patient- or host-related factors such as socio-demographic characteristics, body mass index and medical and surgical histories seem to play an important role in the development of SSIs/PJIs. With the exception of factors such as age and sex, many patient factors are modifiable and could potentially be used for the identification of patients at high risk of developing SSIs/PJIs as well as targeting appropriate interventions. The literature has a plethora of studies that have evaluated the associations of these potential host factors and the risk of SSIs/PJIs. However, some of the findings have been inconclusive because of inconsistent results reported. We sought to clarify the evidence by conducting a comprehensive systematic review of the literature.

There is inconsistent evidence on whether age contributes to an increased risk of PJI. The meta-analysis by Chen et al. showed no association between age and risk of infection [1]. In a pooled analysis of eight studies, age (as a continuous exposure) was not associated with the risk of PJI [2]. However, findings from two studies suggested that patients aged 75 years and above had an increased risk of SSI following primary total hip arthroplasty (THA) [3,4].

The effect of gender on the risk of PJI has inconsistently results. While some studies suggest males are at an increased risk of developing PJI following joint arthroplasty, others suggest differently. However, the emerging evidence is more in favor of males being more likely to develop infection compared to females. In a pooled analysis of eight studies, Chen et al. demonstrated that males had a higher risk of infection after total knee arthroplasty (TKA) than females [1]. A recent pooled multivariate analysis of 28 studies confirms this emerging evidence of higher risk in males [2].

Pooled analyses have shown that black populations (compared with white race) have an increased risk of PJI/SSI [5–11]. However, the evidence for Hispanic ethnicity, native Americans, Eskimos and Asian populations is inconsistent and not significant [5–11].

One study reported a decreased risk of PJIs, and another reported an increased risk, comparing patients in rural locations versus non-rural locations [12,13]. Compared with THAs, TKAs were consistently associated with an increased risk of PJI/SSI [14–16].

The evidence for the association between BMI and increased risk of SSI/PJI is consistent. In a pooled analysis of 14 studies, Kerkhoffs et al. reported an increased risk of infection following TKA when obese were compared to non-obese patients [17]. Yuan et al. also reported a two-fold increase risk of surgical site infections for obesity [18]. In a pooled analysis of 29 studies included in the most recent review, high BMI (overweight and obesity) was associated with an increased risk of SSI/PJI [2]. The association was consistent with a dose-response relationship. One study compared underweight (BMI < 18.5 kg/m^2) versus a normal to overweight BMI category but found no association with PJI [19].

The evidence on the association between a history of hypertension and risk of PJI/SSI is inconsistent. A pooled analysis of six studies showed no significant evidence of an association [6,20–24].

A pooled analysis of six studies showed high alcohol consumption or alcohol abuse was associated with a higher risk of PJI/SSI following TJA [5,6,20,23,25,26].

TABLE 1. Summary of risk factors associated with development of SSI/PJI

Modifiable Host Factors	Factors with Limited Evidence of Associations with SSI/PJI
BMI – Strong	Age (as a continuous exposure) – Limited
Smoking – Strong	Hispanic ethnicity – Limited
High alcohol intake (alcohol abuse) – Strong	Native American and Eskimo ethnicity – Limited
Low income - Strong	Asian race – Limited
Malnutrition (low serum albumin) – Strong	History of drug abuse – Limited
History of DM – Strong	Rural location vs. non-rural location – Limited
History of CVD – Moderate	Underweight – Limited
History of CHF – Strong	History of hypertension – Limited

History of cardiac arrhythmia – Strong History of PVD – Strong Chronic pulmonary disease – Strong Chronic obstructive pulmonary disease – Strong History of renal disease – Strong History of liver disease/cirrhosis – Strong History of RA – Strong History of cancer/malignancy – Strong History of osteonecrosis – Strong History of depression – Strong History of psychosis – Strong History of HIV/AIDS – Strong Neurologic disease (hemiplegia, paraplegia) – Moderate History of corticosteroid administration – Strong History of intra-articular corticosteroid injection – Moderate Previous joint surgery – Strong Revision arthroplasty – Strong Previous joint infection – Moderate Frailty – Moderate Preoperative anemia – Strong ASA grade > 2 – Strong Charlson comorbidity index (high) – Strong Preoperative hyperglycemia and high HbA1c – Moderate Allogenic blood transfusion – Strong Prophylaxis with warfarin or low molecular weight heparin – Moderate	History of osteoarthritis – Limited History of post-traumatic arthritis – Limited Low- or high-risk dental procedures – Limited History of UTI – Limited History of dementia – Limited Hypercholesterolemia – Limited Peptic ulcer disease – Limited Valvular disease – Limited Metastatic tumor – Limited History of coagulopathy – Limited History of venous thromboembolism – Limited Pulmonary circulatory disorders – Limited Hypothyroidism – Limited Hepatitis (B or C) – Limited Electrolyte imbalance – Limited Autogenous blood transfusion – Limited
Non-modifiable Host Factors	
Age (≥ 75 years) – Moderate Male sex – Strong Black race – Strong TKA vs. THA – Strong	

ASA, American Society of Anaesthesiologists physical status score; DM, diabetes mellitus; CVD, Cerebro vascular disease; CHF, congestive heart failure; PVD, peripheral vascular disease; RA, rheumatoid arthritis; TKA, total knee arthroplasty; THA, total hip arthroplasty; SSI, surgical site infection; PJI, periprosthetic joint infection; UTI, uninary tract infection

Consistent evidence shows that a low income is associated with an increased risk of PJI/SSI [7,11,27]. Malnutrition (as measured by low serum albumin) was demonstrated to be associated with an increased risk of PJI/SSI in a pooled analysis of five studies [28–32].

An increasing amount of literature has shown that smoking has a negative effect on postoperative outcomes. However, the evidence has been mostly inconsistent regarding the association between smoking and risk of PJI following TJA. However, in a recent pooled analysis of eight studies, smokers were shown to have an increased risk of PJI compared to non-smokers [2]. Robust evidence suggests that smoking cessation before surgery is associated with more than a 50% decrease in the risk of postoperative infection [33].

Consistent evidence suggests that in patients undergoing surgery, diabetes mellitus (DM) is associated with an increased risk for complications. In a pooled analysis of 10 retrospective studies, Tsang and Gaston found DM to be associated with a two-fold increased risk of established SSI after elective THA [34]. Yang et al. in a pooled analysis of eight studies demonstrated the prevalence of DM to be associated with an increased risk of deep infection after elective primary TKA [35]. In another pooled analysis of eight studies, Zhu et al. showed DM to be associated with an increased risk of PJI following TJA [36]. In the most recently pooled analysis of 29 studies, DM was associated with an increased risk of PJI [2].

A pooled analysis of seven studies reported inconsistent findings with respect to the association between a history of cardiovascular disease and PJI/SSI risk after TJA [20,23,37–42]. In a pooled analysis of studies that evaluated congestive heart failure (CHF) and cardiac arrhythmias as risk factors,

significant associations were demonstrated [5,6,20,23,43]. A history of peripheral vascular disease was associated with an increased risk of PJI/SSI in a pooled analysis of six studies [5,6,20,23,43,44].

A pooled analysis of four studies evaluating the associations of chronic pulmonary disease with risk of PJI, showed no significant evidence of an association [5,20,23,43]. However, three of the studies reported consistent significant associations. Chronic obstructive pulmonary disease was associated with an increased risk of PJI/SSI in a pooled analysis of four studies [9,16,22,45].

In a pooled analysis of eight studies, renal disease was significantly associated with an increased risk of PJI/SSI [5,6,20,23,43,46–48]. A history of liver disease or cirrhosis of the liver was associated with an increased risk of PJI/SSI [5,6,20,23,43,44,48]. However, a history of hepatitis B or C infection was not associated with increased risk of PJI/SSI [16,44,48].

A pooled analysis of seven studies showed rheumatoid arthritis (RA) to be associated with an increased risk of PJI following TKA [1]. In another pooled analysis of seven studies, Zhu et al. demonstrated RA to be associated with an increased risk of PJI [36]. Findings of a recent pooled analysis of 13 studies confirms the accumulating evidence [2].

A history of cancer or malignancy was associated with an increased risk of PJI/SSI following arthroplasty in a pooled analysis of seven studies [5,6,16,20,23,28,49] However, evidence on the association between metastatic tumors and risk of PJI/SSI was limited and inconsistent [6,20,23,43].

A history of coagulopathy was not associated with PJI/SSI in a pooled analysis of four studies with inconsistent findings [5,6,20,23]. A single study reported evidence of an association between venous thromboembolism and PJI, but this was based on univariate analysis [15].

A pooled analysis of three studies showed a history of osteonecrosis to be associated with an increased risk of PJI/SSI [10,19,50].

Evidence suggested that histories of depression and psychosis were each associated with an increased risk of PJI following total joint arthroplasty [6,20,23].

A pooled analysis showed a history of HIV/AIDS infection to be associated with an increased risk of PJI/SSI [6,43,44,51].

A history of neurologic disease such as hemiplegia/paraplegia was associated with an increased risk of PJI/SSI in a pooled analysis of four studies with inconsistent findings [5,20,23].

A previous meta-analysis of four studies suggested a history of corticosteroid therapy to be associated with an increased risk of PJI following TKA [1]. Zhu et al. also demonstrated corticosteroid therapy to be associated with an increased risk of PJI following total joint arthroplasty in a pooled analysis of five studies [36]. In the most recent pooled analysis of 10 studies, the findings were consistent with previous evidence [2]. The literature has been inconsistent and weak on whether intra-articular corticosteroid injections administered for osteoarthritis increases the risk of infection following joint arthroplasty. In a previous systematic of nine studies, Pereira et al. found no significant evidence to indicate the presence of an association. In a recent meta-analysis, use of intra-articular corticosteroid injection was not statistically significantly associated with an increased risk of PJI [2]. However, an update of recent evidence which involved pooling of five studies with usable data demonstrated a significant association. Quality of the evidence was moderate.

In a pooled analysis of five studies, a history of previous joint surgery (vs. no previous joint surgery) was associated with about a three-fold increased risk of PJI [2]. When compared with primary arthroplasty, revision arthroplasty was associated with an increased risk of PJI in a pooled analysis of five studies [2]. Two studies reported a history of previous joint infection to be associated with an increased risk of PJI, but the findings were based on univariate analysis [45,52].

A single high-quality study reported an increased risk of PJI comparing frail patients with non-frail patients [12].

Consistent evidence showed that preoperative anemia was associated with an increased risk of PJI/SSI following TJA [20,23,43,53].

An American Society of Anesthesiologists (*ASA*) grade of > 2 was associated with an increased risk of PJI/SSI, and this was consistent across all studies [3,9,10,15,19,54].

Though the exposures were not comparable and therefore could not be pooled, there was consistent evidence showing that a higher Charlson comorbidity index was associated with an increased risk of PJI/SSI [7,8,11].

Pooled evidence from seven studies showed no significant association of osteoarthritis with the risk of PJI following joint arthroplasty [10,19,25,50,55–57].

A pooled analysis of three studies showed no evidence of an association between post-traumatic arthritis and risk of PJI/SSI [10,19,57].

In two studies that evaluated the association of dental procedures with risk of PJI, there was no evidence of any significant associations of PJI with dental procedures [13,58].

There was no evidence of an association between uninary tract infection (UTI) and the risk of PJI/SSI in all studies examined [20,23,38]. This was the same for dementia and PJI/SSI [16,20,23].

None of the studies which evaluated the associations of hypercholesterolemia as well as peptic ulcer disease with the risk of PJI, showed any evidence of associations [6,20,23].

Evidence on the association between valvular disease and risk of PJI/SSI was limited and inconsistent [5,6,20,23]. In a pooled analysis, there was no significant evidence of associations of PJI/SSI with a history of pulmonary circulatory disorders, [5,20,23,43] history of hypothyroidism [6,20,23,59] and a history of drug abuse [6,20,23].

There was no significant evidence of an association between electrolyte imbalance and risk of PJI/SSI [6,60]. The evidence on the association of preoperative hyperglycemia and high HbA1c levels with risk of PJI/SSI was mostly inconsistent and could not be pooled because the exposures were not comparable [14,61–64], but the evidence suggests that these factors might be associated with an increased risk.

Patients who receive allogeneic blood transfusions are at increased risk of SSI/PJI [15,43,65–67]; however, the evidence is limited for autogenous blood transfusions [43]. Prophylaxis with warfarin or low molecular weight heparin for venous thromboembolism was associated with an increased risk of PJI [68,69].

SEARCH STRATEGY

Data sources. Medline, Embase, Web of Science, Cochrane Library and reference lists of relevant studies from inception to February 15, 2018.

Selection criteria. To be included, studies were to be longitudinal studies (observational studies and randomized controlled trials (RCTs)) that have evaluated the associations of patient-related factors and the risk of surgical site infections (SSIs) and/or periprosthetic joint infections (PJIs) in patients undergoing orthopaedic procedures.

Review methods. The relative risk (RR) with 95% confidence intervals was used as the summary measure of association across studies. Study-specific RRs with 95% confidence intervals were meta-analyzed using random effect models.

Results. Of 7,177 potentially relevant citations, 101 studies were finally included in this review. No RCTs relevant to the review topic were identified.

REFERENCES

[1] Chen J, Cui Y, Li X, Miao X, Wen Z, Xue Y, et al. Risk factors for deep infection after total knee arthroplasty: a meta–analysis. Arch Orthop Trauma Surg. . 2013;133:675–687. doi:10.1007/s00402–013–1723–8.

[2] Kunutsor SK, Whitehouse MR, Blom AW, Beswick AD, INFORM Team. Patient–related risk factors for periprosthetic joint infection after total joint arthroplasty: a systematic review and meta–analysis. PLoS One. 2016;11:e0150866. doi:10.1371/journal.pone.0150866.

[3] Ridgeway S, Wilson J, Charlet A, Kafatos G, Pearson A, Coello R. Infection of the surgical site after arthroplasty of the hip. J Bone Joint Surg Br. 2005;87:844–850. doi:10.1302/0301–620X.87B6.15121.

[4] Geubbels ELPE, Grobbee DE, Vandenbroucke–Grauls CMJE, Wille JC, de Boer AS. Improved risk adjustment for comparison of surgical site infection rates. Infect Control Hosp Epidemiol 2006;27:1330–1339. doi:10.1086/509841.

[5] Poultsides LA, Ma Y, Della Valle AG, Chiu YL, Sculco TP, Memtsoudis SG. In–hospital surgical site infections after primary hip and knee arthroplasty—incidence and risk factors. J Arthroplasty. 2013;28:385–389. doi:10.1016/j.arth.2012.06.027.

[6] Tan TL, Rajeswaran H, Haddad S, Shahi A, Parvizi J. Increased risk of periprosthetic joint infections in patients with hypothyroidism undergoing total joint arthroplasty. J Arthroplasty. 2016;31:868–871. doi:10.1016/j.arth.2015.10.028.

[7] Soohoo NF, Farng E, Lieberman JR, Chambers L, Zingmond DS. Factors that predict short–term complication rates after total hip arthroplasty. Clin Orthop Relat Res. 2010;468:2363–2371. doi:10.1007/s11999–010–1354–0.

[8] SooHoo NF, Lieberman JR, Ko CY, Zingmond DS. Factors predicting complication rates following total knee replacement. J Bone Joint Surg Am. 2006;88:480–485. doi:10.2106/JBJS.E.00629.

[9] Ibrahim SA, Stone RA, Han X, Cohen P, Fine MJ, Henderson WG, et al. Racial/ethnic differences in surgical outcomes in veterans following knee or hip arthroplasty. Arthritis Rheum. 2005;52:3143–3151. doi:10.1002/art.21304.

[10] Namba RS, Inacio MCS, Paxton EW. Risk factors associated with deep surgical site infections after primary total knee arthroplasty: an analysis of 56,216 knees. J Bone Joint Surg Am. 2013;95:775–782. doi:10.2106/JBJS.L.00211.

[11] Mahomed NN, Barrett JA, Katz JN, Phillips CB, Losina E, Lew RA, et al. Rates and outcomes of primary and revision total hip replacement in the United States medicare population. J Bone Joint Surg Am. 2003;85–A:27–32.

[12] Ravi B, Jenkinson R, Austin PC, Croxford R, Wasserstein D, Escott B, et al. Relation between surgeon volume and risk of complications after total hip arthroplasty: propensity score matched cohort study. BMJ. 2014;348:g3284.

[13] Wu C, Qu X, Liu F, Li H, Mao Y, Zhu Z. Risk factors for periprosthetic joint infection after total hip arthroplasty and total knee arthroplasty in Chinese patients. PLoS One. 2014;9:e95300. doi:10.1371/journal.pone.0095300.

[14] Chrastil J, Anderson MB, Stevens V, Anand R, Peters CL, Pelt CE. Is hemoglobin A1c or perioperative hyperglycemia predictive of periprosthetic joint infection or death following primary total joint arthroplasty? J Arthroplasty. 2015;30:1197–1202. doi:10.1016/j.arth.2015.01.040.

[15] Pulido L, Ghanem E, Joshi A, Purtill JJ, Parvizi J. Periprosthetic joint infection: the incidence, timing, and predisposing factors. Clin Orthop Relat Res. 2008;466:1710–1715. doi:10.1007/s11999–008–0209–4.

[16] Everhart JS, Andridge RR, Scharschmidt TJ, Mayerson JL, Glassman AH, Lemeshow S. Development and validation of a preoperative surgical site infection risk score for primary or revision knee and hip arthroplasty. J Bone Joint Surg Am. 2016;98:1522–1532. doi:10.2106/JBJS.15.00988.

[17] Kerkhoffs GM, Servien E, Dunn W, Dahm D, Bramer JA, Haverkamp D. The influence of obesity on the complication rate and outcome of total knee arthroplasty: a meta–analysis and systematic literature review. J Bone Joint Surg Am. 2012;94:1839–1844. doi:10.2106/JBJS.K.00820.

[18] Yuan K, Chen HL. Obesity and surgical site infections risk in orthopedics: a meta–analysis. Int J Surg. 2013;11:383–388. doi:10.1016/j.ijsu.2013.02.018.

[19] Namba RS, Inacio MC, Paxton EW. Risk factors associated with surgical site infection in 30,491 primary total hip replacements. J Bone Joint Surg Br. 2012;94:1330–1338. doi:10.1302/0301–620X.94B10.29184.

[20] Bozic KJ, Lau E, Kurtz S, Ong K, Rubash H, Vail TP, et al. Patient–related risk factors for periprosthetic joint infection and postoperative mortality following total hip arthroplasty in Medicare patients. J Bone Joint Surg Am. 2012;94:794–800. doi:10.2106/JBJS.K.00072.

[21] Gou W, Chen J, Jia Y, Wang Y. Preoperative asymptomatic leucocyturia and early prosthetic joint infections in patients undergoing joint arthroplasty. J Arthroplasty. 2014;29:473–476. doi:10.1016/j.arth.2013.07.028.

[22] Bohl DD, Sershon RA, Fillingham YA, Della Valle CJ. Incidence, risk factors, and sources of sepsis following total joint arthroplasty. J Arthroplasty. 2016;31:2875–2879.e2. doi:10.1016/j.arth.2016.05.031.

[23] Bozic KJ, Lau E, Kurtz S, Ong K, Berry DJ. Patient–related risk factors for postoperative mortality and periprosthetic joint infection in medicare patients undergoing TKA. Clin Orthop Relat Res. 2012;470:130–137. doi:10.1007/s11999–011–2043–3.

[24] Pasticci MB, Mancini G, Lapalorcia LM, Morosi S, Palladino N, Zucchini M, et al. Prosthetic infections following total knee arthroplasty: a six–year prospective study (1997–2002). J Orthop Traumatol. 2007;8:25–28. doi:10.1007/s10195–007–0157–x.

[25] Cordero–Ampuero J, de Dios M. What are the risk factors for infection in hemiarthroplasties and total hip arthroplasties? Clin Orthop Relat Res. 2010;468:3268–3277. doi:10.1007/s11999–010–1411–8.

[26] Rotevatn TA, Bøggild H, Olesen CR, Torp–Pedersen C, Mortensen RN, Jensen PF, et al. Alcohol consumption and the risk of postoperative mortality and morbidity after primary hip or knee arthroplasty – a register–based cohort study. PLoS One. 2017;12:e0173083. doi:10.1371/journal.pone.0173083.

[27] Kurtz SM, Ong KL, Lau E, Bozic KJ, Berry D, Parvizi J. Prosthetic joint infection risk after TKA in the Medicare population. Clin Orthop Relat Res. 2010;468:52–56. doi:10.1007/s11999–009–1013–5.

[28] Berbari EF, Hanssen AD, Duffy MC, Steckelberg JM, Ilstrup DM, Harmsen WS, et al. Risk factors for prosthetic joint infection: case–control study. Clin Infect Dis. 1998;27:1247–1254.

[29] Yi PH, Frank RM, Vann E, Sonn KA, Moric M, Della Valle CJ. Is potential malnutrition associated with septic failure and acute infection after revision total joint arthroplasty? Clin Orthop Relat Res. 2015;473:175–182. doi:10.1007/s11999–014–3685–8.

[30] Morey VM, Song YD, Whang JS, Kang YG, Kim TK. Can serum albumin level and total lymphocyte count be surrogates for malnutrition to predict wound complications after total knee arthroplasty? J Arthroplasty. 2016;31:1317–1321. doi:10.1016/j.arth.2015.12.004.

[31] Walls JD, Abraham D, Nelson CL, Kamath AF, Elkassabany NM, Liu J. Hypoalbuminemia more than morbid obesity is an independent predictor of complications after total hip arthroplasty. J Arthroplasty. 2015;30:2290–2295. doi:10.1016/j.arth.2015.06.003.

[32] Nelson CL, Elkassabany NM, Kamath AF, Liu J. Low albumin levels, more than morbid obesity, are associated with complications after TKA. Clin Orthop Relat Res. 2015;473:3163–3172. doi:10.1007/s11999–015–4333–7.

[33] Sørensen LT. Wound healing and infection in surgery. The clinical impact of smoking and smoking cessation: a systematic review and meta–analysis. Arch Surg. 2012;147:373–383. doi:10.1001/archsurg.2012.5.

[34] Tsang ST, Gaston P. Adverse peri–operative outcomes following elective total hip replacement in diabetes mellitus: a systematic review and meta–analysis of cohort studies. Bone Joint J. 2013;95–B:1474–1479. doi:10.1302/0301–620X.95B11.31716.

[35] Yang Z, Liu H, Xie X, Tan Z, Qin T, Kang P. The influence of diabetes mellitus on the post–operative outcome of elective primary total knee replacement: a systematic review and meta–analysis. Bone Joint J. 2014;96–B:1637–1643. doi:10.1302/0301–620X.96B12.34378.
[36] Zhu Y, Zhang F, Chen W, Liu S, Zhang Q, Zhang Y. Risk factors for periprosthetic joint infection after total joint arthroplasty: a systematic review and meta–analysis. J Hosp Infect. 2015;89:82–89. doi:10.1016/j.jhin.2014.10.008.
[37] Dowsey MM, Choong PFM. Obese diabetic patients are at substantial risk for deep infection after primary TKA. Clin Orthop Relat Res. 2009;467:1577–1581. doi:10.1007/s11999–008–0551–6.
[38] Lai K, Bohm ER, Burnell C, Hedden DR. Presence of medical comorbidities in patients with infected primary hip or knee arthroplasties. J Arthroplasty. 2007;22:651–656. doi:10.1016/j.arth.2006.09.002.
[39] Dowsey MM, Choong PF. Obesity is a major risk factor for prosthetic infection after primary hip arthroplasty. Clin Orthop Relat Res. 2008;466:153–158. doi:10.1007/s11999–007–0016–3.
[40] Choong PF, Dowsey MM, Carr D, Daffy J, Stanley P. Risk factors associated with acute hip prosthetic joint infections and outcome of treatment with a rifampinbased regimen. Acta Orthop. 2007;78:755–765. doi:10.1080/17453670710014527.
[41] Babkin Y, Raveh D, Lifschitz M, Itzchaki M, Wiener–Well Y, Kopuit P, et al. Incidence and risk factors for surgical infection after total knee replacement. Scand J Infect Dis. 2007;39:890–895. doi:10.1080/00365540701387056.
[42] Bozic KJ, Lau E, Ong K, Chan V, Kurtz S, Vail TP, et al. Risk factors for early revision after primary total hip arthroplasty in Medicare patients. Clin Orthop Relat Res. 2014;472:449–454. doi:10.1007/s11999–013–3081–9.
[43] Schairer WW, Nwachukwu BU, Mayman DJ, Lyman S, Jerabek SA. Preoperative hip injections increase the rate of periprosthetic infection after total hip arthroplasty. J Arthroplasty. 2016;31:166–169.e1. doi:10.1016/j.arth.2016.04.008.
[44] Jiang SL, Schairer WW, Bozic KJ. Increased rates of periprosthetic joint infection in patients with cirrhosis undergoing total joint arthroplasty. Clin Orthop Relat Res. 2014;472:2483–2491. doi:10.1007/s11999–014–3593–y.
[45] Cordtz RL, Zobbe K, Højgaard P, Kristensen LE, Overgaard S, Odgaard A, et al. Predictors of revision, prosthetic joint infection and mortality following total hip or total knee arthroplasty in patients with rheumatoid arthritis: a nationwide cohort study using Danish healthcare registers. Ann Rheum Dis. 2018;77:281–288. doi:10.1136/annrheumdis–2017–212339.
[46] McCleery MA, Leach WJ, Norwood T. Rates of infection and revision in patients with renal disease undergoing total knee replacement in Scotland. J Bone Joint Surg Br. 2010;92:1535–1539. doi:10.1302/0301–620X.92B11.23870.
[47] Erkocak OF, Yoo JY, Restrepo C, Maltenfort MG, Parvizi J. Incidence of infection and inhospital mortality in patients with chronic renal failure after total joint arthroplasty. J Arthroplasty. 2016;31:2437–2441. doi:10.1016/j.arth.2016.04.031.
[48] Kuo SJ, Huang PH, Chang CC, Kuo FC, Wu CT, Hsu HC, et al. Hepatitis B virus infection is a risk factor for periprosthetic joint infection among males after total knee arthroplasty: a Taiwanese nationwide population–based study. Medicine (Baltimore). 2016;95:e3806. doi:10.1097/MD.000000 0000003806.
[49] Aslam S, Reitman C, Darouiche RO. Risk factors for subsequent diagnosis of prosthetic joint infection. Infect Control Hosp Epidemiol. 2010;31:298–301. doi:10.1086/650756.
[50] Singh JA, Chen J, Inacio MC, Namba RS, Paxton EW. An underlying diagnosis of osteonecrosis of bone is associated with worse outcomes than osteoarthritis after total hip arthroplasty. BMC Musculoskelet Disord. 2017;18:8. doi:10.1186/s12891–016–1385–0.
[51] Bala A, Penrose CT, Visgauss JD, Seyler TM, Randell TR, Bolognesi MP, et al. Total shoulder arthroplasty in patients with HIV infection: complications, comorbidities, and trends. J Shoulder Elbow Surg. 2016;25:1971–1979. doi:10.1016/j.jse.2016.02.033.
[52] Bongartz T, Halligan CS, Osmon DR, Reinalda MS, Bamlet WR, Crowson CS, et al. Incidence and risk factors of prosthetic joint infection after total hip or knee replacement in patients with rheumatoid arthritis. Arthritis Rheum. 2008;59:1713–1720. doi:10.1002/art.24060.
[53] Greenky M, Gandhi K, Pulido L, Restrepo C, Parvizi J. Preoperative anemia in total joint arthroplasty: is it associated with periprosthetic joint infection? Clin Orthop Relat Res. 2012;470:2695–2701. doi:10.1007/s11999–012–2435–z.
[54] Maoz G, Phillips M, Bosco J, Slover J, Stachel A, Inneh I, et al. The Otto Aufranc Award: modifiable versus nonmodifiable risk factors for infection after hip arthroplasty. Clin Orthop Relat Res. 2015;473:453–459. doi:10.1007/s11999–014–3780–x.
[55] Chesney D, Sales J, Elton R, Brenkel IJ. Infection after knee arthroplasty a prospective study of 1509 cases. J Arthroplasty. 2008;23:355–359. doi:10.1016/j.arth.2007.05.052.
[56] Wilson MG, Kelley K, Thornhill TS. Infection as a complication of total knee–replacement arthroplasty. Risk factors and treatment in sixty–seven cases. J Bone Joint Surg Am. 1990;72:878–883.
[57] Kessler B, Sendi P, Graber P, Knupp M, Zwicky L, Hintermann B, et al. Risk factors for periprosthetic ankle joint infection: a case–control study. J Bone Joint Surg Am. 2012;94:1871–1876. doi:10.2106/JBJS.K.00593.
[58] Berbari EF, Osmon DR, Carr A, Hanssen AD, Baddour LM, Greene D, et al. Dental procedures as risk factors for prosthetic hip or knee infection: a hospital–based prospective case–control study. Clin Infect Dis. 2010;50:8–16. doi:10.1086/648676.
[59] Buller LT, Rosas S, Sabeh KG, Roche MW, McLawhorn AS, Barsoum WK. Hypothyroidism Increases 90–day complications and costs following primary total knee arthroplasty. J Arthroplasty.. 2018;33:1003–1007. doi:10.1016/j.arth.2017.10.053.
[60] Pugely AJ, Martin CT, Gao Y, Schweizer ML, Callaghan JJ. The incidence of and risk factors for 30–day surgical site infections following primary and revision total joint arthroplasty. J Arthroplasty. 2015;30:47–50. doi:10.1016/j.arth.2015.01.063.
[61] Jämsen E, Nevalainen P, Kalliovalkama J, Moilanen T. Preoperative hyperglycemia predicts infected total knee replacement. Eur J Intern Med. 2010;21:196–201. doi:10.1016/j.ejim.2010.02.006.
[62] Jämsen E, Nevalainen P, Eskelinen A, Huotari K, Kalliovalkama J, Moilanen T. Obesity, diabetes, and preoperative hyperglycemia as predictors of periprosthetic joint infection: a single–center analysis of 7181 primary hip and knee replacements for osteoarthritis. J Bone Joint Surg Am. 2012;94:e101. doi:10.2106/JBJS.J.01935.
[63] Cancienne JM, Werner BC, Browne JA. Is there a threshold value of hemoglobin a1c that predicts risk of infection following primary total hip arthroplasty? J Arthroplasty. 2017;32:S236–S240. doi:10.1016/j.arth.2017.01.022.
[64] Maradit Kremers H, Lewallen LW, Mabry TM, Berry DJ, Berbari EF, Osmon DR. Diabetes mellitus, hyperglycemia, hemoglobin A1C and the risk of prosthetic joint infections in total hip and knee arthroplasty. J Arthroplasty. 2015;30:439–443. doi:10.1016/j.arth.2014.10.009.
[65] Carroll K, Dowsey M, Choong P, Peel T. Risk factors for superficial wound complications in hip and knee arthroplasty. Clin Microbiol Infect. 2014;20:130–135. doi:10.1111/1469–0691.12209.
[66] Innerhofer P, Klingler A, Klimmer C, Fries D, Nussbaumer W. Risk for postoperative infection after transfusion of white blood cell–filtered allogeneic or autologous blood components in orthopedic patients undergoing primary arthroplasty. Transfusion 2005;45:103–10. doi:10.1111/j.1537–2995.2005.04149.x.
[67] Newman ET, Watters TS, Lewis JS, Jennings JM, Wellman SS, Attarian DE, et al. Impact of perioperative allogeneic and autologous blood transfusion on acute wound infection following total knee and total hip arthroplasty. J Bone Joint Surg Am. 2014;96:279–284. doi:10.2106/JBJS.L.01041.
[68] Huang RC, Parvizi J, Hozack WJ, Chen AF, Austin MS. Aspirin is as effective as and safer than warfarin for patients at higher risk of venous thromboembolism undergoing total joint arthroplasty. J Arthroplasty. 2016;31:83–86. doi:10.1016/j.arth.2016.02.074.
[69] Asensio A, Ramos A, Múñez E, Vilanova JL, Torrijos P, García FJ. Preoperative low molecular weight heparin as venous thromboembolism prophylaxis in patients at risk for prosthetic infection after knee arthroplasty. Infect Control Hosp Epidemiol. 2005;26:903–909. doi:10.1086/505451.

QUESTION 2: Are there any genetic factors that predispose patients to surgical site infection/periprosthetic joint infection (SSI/PJI) or predict the success of the treatment for SSI/PJI?

RECOMMENDATION: The evidence suggests a potential heritable predisposition is possible, but there is a lack of definitive evidence supporting specific genetic risk factors for SSI/PJI after total joint arthroplasty (TJA).

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 2%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

It is hypothesized that individuals may be susceptible to SSIs and PJIs owing to patient-related genetic characteristics. This situation may result from polymorphisms in genes encoding various proteins, receptor intracellular signaling mediators, cytokines, and enzymes vital to the functionality of the host's immune system.

In hopes of allowing for early targeted prevention in high-risk patients, risk calculators have been developed to identify patients at greater risk for developing infection following TJA. However, it has been suggested that these scoring systems are limited in their ability to accurately identify individuals at high risk and very few of them have been externally validated [1,2]. Kunutsor et al. reported that none of the risk scores they reviewed underwent subsequent impact studies to determine their utility for clinical decision-making [2]. Thus, other methods of early identification are needed in order to influence clinical decisions.

Genetic susceptibility testing has broadening interest as a means to identify patients at high risk for infection [3], specifically PJIs [4]. However, such a test has yet to be developed and implemented in the arthroplasty arena. When evaluating the immune response to mycobacterial infections, Blischak et al. reported that the innate immune system may play a role in bacterial infections [5]. Evaluating patients with multiple TJAs, Bedair et al. suggested that some patients may be at greater risk for infection due to subclinical immune deficiencies [6]. In 2013, a large population-based study by Lee et al. reported familial susceptibility to SSI which included, but was not limited to, PJI [7]. Similarly, Anderson et al. demonstrated familial clustering in TJA patients who suffered a PJI [8]. They were able to show an increased risk of PJI following TJA in relatives of patients who have experienced a PJI [8]. These families demonstrated infection rates of 9 to 17% compared to rates of approximately 2.3% in relatives of patients without PJI. Given the current literature, a heritable risk for PJI seems reasonable.

Regarding specific genetic factors, recent reports suggest that genetic variants associated with mannose-binding lectin (MBL) may be associated with an increased risk of infection in general [9,10] and in PJI populations specifically [11,12]. Burgner et al. also reported on several candidate genes identified in the literature that may be related to innate immunity [3]. For example, they noted the association of toll-like receptor (TLR) genes, *TLR2* and *TLR4* and bacterial infections [3]. Sutherland et al. performed a genetic association study on patients admitted to an intensive care unit who had evidence of infection [13]. Ultimately, they reported that the CD14, *MBL* and *TLR2* polymorphisms were associated with a greater prevalence of infection in critically ill adults. However, others report no association between the CD14 polymorphism and the incidence of infection [14]. Agnese et al. were, however, able to associate the *TLR4* mutation with an increased incidence of bacterial infections [14]. Aside from the *MBL* mutations, the CD14, *TLR2*, and *TLR4* have been reported as not being associated with infections in the PJI literature [15]. Furthermore, a recent systematic review on the genetic susceptibility to PJI concluded that although evidence exists supporting a genetic role in PJI, no definitive conclusions can be made given the relatively small amount of data available in the existing literature [15].

In summary, despite the evidence suggesting a heritable risk for infection, there is a scarcity of robust studies providing evidence on genetic risk factors for infection. Additional evidence is needed, perhaps targeting *MBL* variants, in order to consider genetic risk factors and to identify patients at greater risk for infection. Such studies may contribute to our understanding of the pathogenesis of SSI/PJI.

Given the evidence suggesting a genetic susceptibility to SSI/PJI, it seems reasonable that genetic factors may also play a role in the treatment outcomes for infection. Early studies on the ability to predict treatment outcomes of bacterial and fungal infections were not encouraging and relied on antimicrobial susceptibility tests [16–20]. Clinical and genetic risk factors for predicting treatment response has been reported for a variety of diseases [3,21–23]. Furthermore, recent studies evaluating the treatment response in patients with hepatitis and human immunodeficiency viral infections suggest that pre-treatment genetic markers exist which could increase the understanding of the patient's treatment response to anti-viral therapies [24–28]. However, there is little, if any, evidence on the ability of host genetic factors to predict treatment outcomes for surgical site or periprosthetic joint infections.

REFERENCES

[1] Wingert NC, Gotoff J, Parrilla E, Gotoff R, Hou L, Ghanem E. The ACS NSQIP risk calculator is a fair predictor of acute periprosthetic joint infection. Clin Orthop Relat Res. 2016;474:1643–1648. doi:10.1007/s11999–016–4717–3.

[2] Kunutsor SK, Whitehouse MR, Blom AW, Beswick AD. Systematic review of risk prediction scores for surgical site infection or periprosthetic joint infection following joint arthroplasty. Epidemiol Infect. 2017;145:1738–1749. doi:10.1017/S0950268817000486.

[3] Burgner D, Jamieson SE, Blackwell JM. Genetic susceptibility to infectious diseases: big is beautiful, but will bigger be even better? Lancet Infect Dis. 2006;6:653–663. doi:10.1016/S1473–3099(06)70601–6.

[4] Marmor S, Kerroumi Y. Patient–specific risk factors for infection in arthroplasty procedure. Orthop Traumatol Surg Res. 2016;102:S113–119. doi:10.1016/j.otsr.2015.05.012.

[5] Blischak JD, Tailleux L, Mitrano A, Barreiro LB, Gilad Y. Mycobacterial infection induces a specific human innate immune response. Sci Rep. 2015;5:16882. doi:10.1038/srep16882.

[6] Bedair H, Goyal N, Dietz MJ, Urish K, Hansen V, Manrique J, et al. A history of treated periprosthetic joint infection increases the risk of subsequent different site infection. Clin Orthop Relat Res. 2015;473:2300–2304. doi:10.1007/s11999–015–4174–4.

[7] Lee JP, Hopf HW, Cannon–Albright LA. Empiric evidence for a genetic contribution to predisposition to surgical site infection. Wound Repair Regen. 2013;21:211–215. doi:10.1111/wrr.12024.

[8] Anderson MB, Curtin K, Wong J, Pelt CE, Peters CL, Gililland JM. Familial clustering identified in periprosthetic joint infection following primary total joint arthroplasty: a population–based cohort study. J Bone Joint Surg Am. 2017;99:905–913. doi:10.2106/JBJS.16.00514.

[9] Cooke GS, Hill AV. Genetics of susceptibility to human infectious disease. Nat Rev Genet. 2001;2:967–977. doi:10.1038/35103577.

[10] Rashidi E, Fazlollahi MR, Zahedifard S, Talebzadeh A, Kazemnejad A, Saghafi S, et al. Mannose–binding lectin deficiency in patients with a history of recurrent infections. Iran J Allergy Asthma Immunol. 2016;15:69–74.
[11] Navratilova Z, Gallo J, Mrazek F, Lostak J, Petrek M. MBL2 gene variation affecting serum MBL is associated with prosthetic joint infection in Czech patients after total joint arthroplasty. Tissue Antigens. 2012;80:444–451. doi:10.1111/tan.12001.
[12] Malik MH, Bayat A, Jury F, Kay PR, Ollier WE. Genetic susceptibility to total hip arthroplasty failure—positive association with mannose–binding lectin. J Arthroplasty. 2007;22:265–270. doi:10.1016/j.arth.2006.02.163.
[13] Sutherland AM, Walley KR, Russell JA. Polymorphisms in CD14, mannose–binding lectin, and Toll–like receptor–2 are associated with increased prevalence of infection in critically ill adults. Crit Care Med. 2005;33:638–644.
[14] Agnese DM, Calvano JE, Hahm SJ, Coyle SM, Corbett SA, Calvano SE, et al. Human toll–like receptor 4 mutations but not CD14 polymorphisms are associated with an increased risk of gram–negative infections. J Infect Dis. 2002;186:1522–1525. doi:10.1086/344893.
[15] Zhou X, Yishake M, Li J, Jiang L, Wu L, Liu R, et al. Genetic susceptibility to prosthetic joint infection following total joint arthroplasty: a systematic review. Gene. 2015;563:76–82. doi:10.1016/j.gene.2015.03.005.
[16] Zimmerli W, Frei R, Widmer AF, Rajacic Z. Microbiological tests to predict treatment outcome in experimental device–related infections due to Staphylococcus aureus. J Antimicrob Chemother. 1994;33:959–967.
[17] Greenwood D. In vitro veritas? Antimicrobial susceptibility tests and their clinical relevance. J Infect Dis. 1981;144:380–385.
[18] Widmer AF, Frei R, Rajacic Z, Zimmerli W. Correlation between in vivo and in vitro efficacy of antimicrobial agents against foreign body infections. J Infect Dis. 1990;162:96–102.
[19] Odds FC, Van Gerven F, Espinel–Ingroff A, Bartlett MS, Ghannoum MA, Lancaster MV, et al. Evaluation of possible correlations between antifungal susceptibilities of filamentous fungi in vitro and antifungal treatment outcomes in animal infection models. Antimicrob Agents Chemother. 1998;42:282–288.
[20] Moise–Broder PA, Sakoulas G, Eliopoulos GM, Schentag JJ, Forrest A, Moellering RC. Accessory gene regulator group II polymorphism in methicillin–resistant Staphylococcus aureus is predictive of failure of vancomycin therapy. Clin Infect Dis. 2004;38:1700–1705. doi:10.1086/421092.
[21] Cravo M, Ferreira P, Sousa P, Moura–Santos P, Velho S, Tavares L, et al. Clinical and genetic factors predicting response to therapy in patients with Crohn's disease. United European Gastroenterol J. 2014;2:47–56. doi:10.1177/2050640613519626.
[22] Vermeire S, Van Assche G, Rutgeerts P. Role of genetics in prediction of disease course and response to therapy. World J Gastroenterol. 2010;16:2609–2615.
[23] Roberts RL, Barclay ML. Current relevance of pharmacogenetics in immunomodulation treatment for Crohn's disease. J Gastroenterol Hepatol. 2012;27:1546–1554. doi:10.1111/j.1440–1746.2012.07220.x.
[24] Dzekova–Vidimliski P, Nikolov IG, Matevska–Geshkovska N, Boyanova Y, Nikolova N, Romanciuc G, et al. Genetic predictors of the response to the treatment of hepatitis C virus infection. Bosn J Basic Med Sci. 2015;15:55–59.
[25] Thanapirom K, Suksawatamnuay S, Sukeepaisarnjaroen W, Tangkijvanich P, Treeprasertsuk S, Thaimai P, et al. Vitamin D–related gene polymorphism predict treatment response to pegylated interferon–based therapy in Thai chronic hepatitis C patients. BMC Gastroenterol. 2017;17:54. doi:10.1186/s12876–017–0613–x.
[26] Guo X, Yang G, Yuan J, Ruan P, Zhang M, Chen X, et al. Genetic variation in interleukin 28B and response to antiviral therapy in patients with dual chronic infection with hepatitis B and C viruses. PLoS One. 2013;8:e77911. doi:10.1371/journal.pone.0077911.
[27] Hou J, van Oord G, Groothuismink ZMA, Claassen MAA, Kreefft K, Zaaraoui–Boutahar F, et al. Gene expression profiling to predict and assess the consequences of therapy–induced virus eradication in chronic hepatitis C virus infection. J Virol. 2014;88:12254–64. doi:10.1128/JVI.00775–14.
[28] Chapman SJ, Hill AVS. Human genetic susceptibility to infectious disease. Nat Rev Genet. 2012;13:175–188. doi:10.1038/nrg3114.

Authors: John J. Callaghan, Matthew Austin, Matthew Kheir, Nicholas A. Bedard, David E. DeMik, Max Greenky

QUESTION 3: Does current tobacco use increase the risk of surgical site infection/periprosthetic joint infection (SSI/PJI) recurrence?

RECOMMENDATION: Yes. Current tobacco use appears to increase the risk of SSI/PJI in patients undergoing orthopaedic procedures.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 94%, Disagree: 3%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

PJI is a devastating potential complication after total joint arthroplasty (TJA) procedures. Studies have shown that this complication occurs approximately 1 to 2% of the time following primary TJA, and is even more common following revision surgery [1–3]. Surgical treatments of PJI, with the goal of infection eradication, include irrigation and debridement with implant retention, one-stage revision and two-stage revision procedures. There are no standard definitions for successful treatment but most physicians would agree that the goal of these interventions is to eradicate the infection. Reported success rates of the aforementioned procedures vary and there exists abundant literature focusing on the impact of various patient, surgical and infectious factors on treatment success. Despite the large number of studies on factors contributing to the recurrence of PJI following surgical treatment, relatively little has been published looking at the impact of current tobacco use on PJI recurrence.

An extensive systematic review was performed to identify all studies reporting the success of surgical treatments for hip or knee PJI. This literature review identified 20 published studies that specifically reported or evaluated tobacco use in the study population or in relation to the surgical treatment of SSI/PJI [4–23]. Using the methodology for evaluating evidence as outlined by the American Academy of Orthopaedic Surgeons Clinical Practice Guideline and Systematic Review Methodology Version 2.0 [24], 17 of these studies were graded as being low-quality [4,5,7,8,10–12,14–23], and three studies were graded as being very low-quality [6,9,13].

Of the 20 studies evaluated, 14 studies evaluated two-stage revisions; two studies evaluated irrigation and debridement, and five studies evaluated patients with either of those two procedures for PJI. Univariate statistical analysis evaluating the association between tobacco use and recurrence of PJI was performed in 19 of the studies. Smoking was associated with a significantly increased risk for PJI recurrence in three of these studies [4,8,9]. Further multivariate analysis was performed in two of these studies [4,9]. Hoell et al. retrospectively evaluated 59 patients who underwent two-stage revision for PJI and identified smoking as an independent risk factor for failure to cure infection (odds ratio (OR): 21.5, 95% confidence interval (CI) 2.6 to 178) [9]. Cancienne et al. utilized the Medicare administrative claims dataset to evaluate 18,533 patients who underwent antibiotic spacer placement for infected

total knee arthroplasty and found tobacco use to be independently associated with the need for a repeat debridement without reimplantation within one year (OR 1.10, p = 0.003) [4].

Given that many of the studies had relatively small cohorts and may have been underpowered to detect an association between smoking and PJI recurrence, pooled analysis on the studies was performed. Of the 20 studies, 12 provided sufficient data to be included in the pooled analysis [5,6,8,10–14,18–21]. The remainder either did not report raw data on the number of patients who used tobacco or did not report on how many tobacco users had a recurrence of PJI. If there were multiple studies from the same institution, only the most recent study with the largest cohort was included. This was done to prevent the unintentional inclusion of the same patient data multiple times. This left ten studies, representing 1,124 patients with PJI, to be included in the pooled analysis [5,6,8,10,12–14,19–21]. Heterogeneity across studies was present as determined using the Q and I^2 statistics or likelihood ratio test. Therefore, inverse-variance weighted random-effects models were used to evaluate the pooled estimates using R software. Forest plots were also generated to display the odds ratios and 95% confidence intervals for each study, as well as the overall random-effects pooled estimate and its confidence interval. Pooled analysis demonstrated that tobacco users were significantly more likely to experience recurrence of PJI after surgical treatment than non-tobacco users, with an OR of 1.53 (1.06 to 2.21) (see Fig. 1). Furthermore, this finding remained significant when only including patients treated with two-stage revision (OR: 1.59, 1.03 to 2.47).

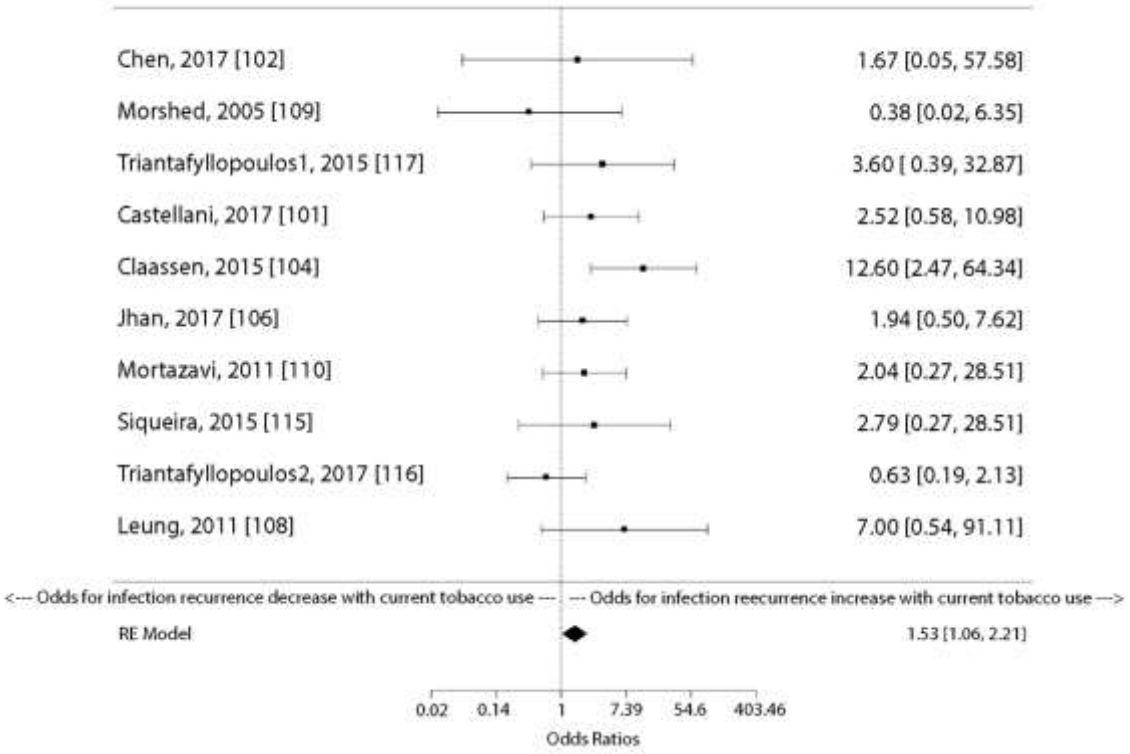

FIGURE 1. Odds ratios for infection recurrence with current tobacco use versus no tobacco use.

The findings from these studies and the results of the pooled analysis suggest that current tobacco use increases the risk of PJI recurrence after surgical treatment of hip and knee PJI. The strength of this conclusion is limited by the available studies being of low or very low quality and primarily including small numbers of patients. However, there is higher quality literature that associates current tobacco use with an increased risk of PJI following primary TJA [25–30]. There are also established adverse effects of tobacco use on wound healing. It is therefore reasonable to conclude that the findings from these studies and the results of the pooled analyses likely represent a true association. There is a need for additional, high-quality research to confirm this association and to assess whether cessation of tobacco use can increase the success of infection remission following surgical treatment for PJI.

REFERENCES

[1] Kurtz SM, Lau E, Schmier J, Ong KL, Zhao K, Parvizi J. Infection burden for hip and knee arthroplasty in the United States. J Arthroplasty. 2008;23:984–991. doi:10.1016/j.arth.2007.10.017.

[2] Peersman G, Laskin R, Davis J, Peterson M. Infection in total knee replacement: a retrospective review of 6489 total knee replacements. Clin Orthop Relat Res. 2001:15–23.

[3] Pulido L, Ghanem E, Joshi A, Purtill JJ, Parvizi J. Periprosthetic joint infection: the incidence, timing, and predisposing factors. Clin Orthop Relat Res. 2008;466:1710–1715. doi:10.1007/s11999–008–0209–4.

[4] Cancienne JM, Granadillo VA, Patel KJ, Werner BC, Browne JA. Risk factors for repeat debridement, spacer retention, amputation, arthrodesis, and mortality after removal of an infected total knee arthroplasty with spacer placement. J Arthroplasty. 2018;33:515–520. doi:10.1016/j.arth.2017.08.037.

[5] Castellani L, Daneman N, Mubareka S, Jenkinson R. Factors associated with choice and success of one– versus two–stage revision arthroplasty for infected hip and knee prostheses. HSS J. 2017;13:224–231. doi:10.1007/s11420–017–9550–z.
[6] Chen KH, Tsai SW, Wu PK, Chen CF, Wang HY, Chen WM. Partial component–retained two–stage reconstruction for chronic infection after uncemented total hip arthroplasty: results of sixteen cases after five years of follow–up. Int Orthop. 2017;41:2479–2486. doi:10.1007/s00264–017–3505–3.
[7] Chen SY, Hu CC, Chen CC, Chang YH, Hsieh PH. Two–stage revision arthroplasty for periprosthetic hip infection: mean follow–up of ten years. Biomed Res Int. 2015;2015:345475. doi:10.1155/2015/345475.
[8] Claassen L, Plaass C, Daniilidis K, Calliess T, von Lewinski G. Two–stage revision total knee arthroplasty in cases of periprosthetic joint infection: an analysis of 50 cases. Open Orthop J. 2015;9:49–56. doi:10.2174/1874325001509010049.
[9] Hoell S, Sieweke A, Gosheger G, Hardes J, Dieckmann R, Ahrens H, et al. Eradication rates, risk factors, and implant selection in two–stage revision knee arthroplasty: a mid–term follow–up study. J Orthop Surg Res. 2016;11:93. doi:10.1186/s13018–016–0428–4.
[10] Jhan SW, Lu YD, Lee MS, Lee CH, Wang JW, Kuo FC. The risk factors of failed reimplantation arthroplasty for periprosthetic hip infection. BMC Musculoskelet Disord. 2017;18:255. doi:10.1186/s12891–017–1622–1.
[11] 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.
[12] Leung F, Richards CJ, Garbuz DS, Masri BA, Duncan CP. Two–stage total hip arthroplasty: how often does it control methicillin–resistant infection? Clin Orthop Relat Res. 2011;469:1009–1015. doi:10.1007/s11999–010–1725–6.
[13] Morshed S, Huffman GR, Ries MD. Extended trochanteric osteotomy for 2–stage revision of infected total hip arthroplasty. J Arthroplasty. 2005;20:294–301.
[14] Mortazavi SMJ, Vegari D, Ho A, Zmistowski B, Parvizi J. Two–stage exchange arthroplasty for infected total knee arthroplasty: predictors of failure. Clin Orthop Relat Res. 2011;469:3049–3054. doi:10.1007/s11999–011–2030–8.
[15] Narayanan R, Anoushiravani AA, Elbuluk AM, Chen KK, Adler EM, Schwarzkopf R. Irrigation and debridement for early periprosthetic knee infection: is it effective? J Arthroplasty. 2018;33:1872–1878. doi:10.1016/j.arth.2017.12.039.
[16] Parvizi J, Azzam K, Ghanem E, Austin MS, Rothman RH. Periprosthetic infection due to resistant staphylococci: serious problems on the horizon. Clin Orthop Relat Res. 2009;467:1732–1739. doi:10.1007/s11999–009–0857–z.
[17] Pelt CE, Grijalva R, Anderson L, Anderson MB, Erickson J, Peters CL. Two–stage revision tka is associated with high complication and failure rates. Adv Orthop. 2014;2014:659047. doi:10.1155/2014/659047.
[18] Sakellariou VI, Poultsides LA, Vasilakakos T, Sculco P, Ma Y, Sculco TP. Risk factors for recurrence of periprosthetic knee infection. J Arthroplasty. 2015;30:1618–1622. doi:10.1016/j.arth.2015.04.005.
[19] Siqueira MB, Saleh A, Klika AK, O'Rourke C, Schmitt S, Higuera CA, et al. Chronic suppression of periprosthetic joint infections with oral antibiotics increases infection–free survivorship. J Bone Joint Surg Am. 2015;97:1220–1232. doi:10.2106/JBJS.N.00999.
[20] Triantafyllopoulos GK, Memtsoudis SG, Zhang W, Ma Y, Sculco TP, Poultsides LA. Periprosthetic infection recurrence after 2–stage exchange arthro-plasty: failure or fate? J Arthroplasty. 2017;32:526–531. doi:10.1016/j.arth.2016.08.002.
[21] Triantafyllopoulos GK, Poultsides LA, Zhang W, Sculco PK, Ma Y, Sculco TP. Periprosthetic knee infections treated with irrigation and debridement: outcomes and preoperative predictive factors. J Arthroplasty. 2015;30:649–657. doi:10.1016/j.arth.2014.10.026.
[22] Watts CD, Wagner ER, Houdek MT, Osmon DR, Hanssen AD, Lewallen DG, et al. Morbid obesity: a significant risk factor for failure of two–stage revision total knee arthroplasty for infection. J Bone Joint Surg Am. 2014;96:e154. doi:10.2106/JBJS.M.01289.
[23] Wilke B, Wagner E, Trousdale R. Long–term survival of a semi–constrained implant following revision for infection. J Arthroplasty. 2015;30:808–812. doi:10.1016/j.arth.2014.10.037.
[24] 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 n.d.
[25] Duchman KR, Gao Y, Pugely AJ, Martin CT, Noiseux NO, Callaghan JJ. The effect of smoking on short–term complications following total hip and knee arthroplasty. J Bone Joint Surg Am. 2015;97:1049–1058. doi:10.2106/JBJS.N.01016.
[26] Møller AM, Pedersen T, Villebro N, Munksgaard A. Effect of smoking on early complications after elective orthopaedic surgery. J Bone Joint Surg Br. 2003;85:178–181.
[27] Sahota S, Lovecchio F, Harold RE, Beal MD, Manning DW. The effect of smoking on thirty–day postoperative complications after total joint arthroplasty: a propensity score–matched analysis. J Arthroplasty. 2018;33:30–35. doi:10.1016/j.arth.2017.07.037.
[28] Singh JA, Houston TK, Ponce BA, Maddox G, Bishop MJ, Richman J, et al. Smoking as a risk factor for short–term outcomes following primary total hip and total knee replacement in veterans. Arthritis Care Res (Hoboken). 2011;63:1365–1374. doi:10.1002/acr.20555.
[29] Singh JA, Schleck C, Harmsen WS, Jacob AK, Warner DO, Lewallen DG. Current tobacco use is associated with higher rates of implant revision and deep infection after total hip or knee arthroplasty: a prospective cohort study. BMC Med. 2015;13:283. doi:10.1186/s12916–015–0523–0.
[30] Tischler EH, Matsen Ko L, Chen AF, Maltenfort MG, Schroeder J, Austin MS. Smoking increases the rate of reoperation for infection within 90 days after primary total joint arthroplasty. J Bone Joint Surg Am. 2017;99:295–304. doi:10.2106/JBJS.16.00311.

Authors: Jorge Manrique, Andrew Battenberg, João Mauricio Barretto

QUESTION 4: Do underweight patients (body mass index (BMI) < 18.5Kg/m2) have a higher risk of surgical site infection/periprosthetic joint infection (SSI/PJI) following orthopaedic procedures? If yes, does increasing the BMI in underweight patients reduce the risk of SSI/PJI?

RECOMMENDATION: Yes. Underweight patients (BMI < 18.5K/m2) have a higher risk of SSI/PJI following orthopaedic procedures. However, there is no current evidence indicating that an increase in the BMI of an underweight individual has an effect on reducing the risk of SSI/PJI.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 4%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

BMI abnormalities have been associated with worse outcomes in surgical patients. Most studies have focused on comparisons between obese patients and those of normal weight (NW) in finding that higher BMI is associated with a higher incidence of infections [1–6]. Underweight (UW) patients are

typically defined as having a BMI of less than 18.5 kg/m^2 [7]. UW patients make up 2.3% of the United States population and up to 3.66% of patients in European nations [8,9]. In the field of general surgery, UW patients have been shown to have higher complication rates compared to overweight and obese patients [7,10–12]. Similarly, UW total joint arthroplasty (TJA) patients have also been identified as having a higher incidence of infection, transfusion, dislocation, readmission and mortality [1,3,13,14]. No studies have been identified that evaluate the risk reduction when increasing the BMI in these patients.

Saucedo et al. [1] evaluated readmission risk in cohorts of both total knee arthroplasty (TKA) and total hip arthroplasty (THA) patients. Compared to NW patients (defined as BMI 18.5 to 24.9 kg/m^2 in this study), UW status was a significant risk factor for readmission at 30 and 90 days postoperatively (16.4 and 11.6%, respectively) with postoperative infection being the leading cause for readmission [1]. A separate study evaluating infection risk factors in patients with rheumatoid arthritis showed that UW status also had an increased risk of infection, (odds ratio (OR) 6.0, 95% confidence interval (CI) 1.2 to 30.9, p = 0.033) [13]. Also, a study by Nafiu et al. demonstrated worse TJA outcomes and higher SSI rates in UW minorities [11]. When patients were stratified based on BMI, the study found SSI rates of 3% in the UW group, 1.3% in the NW group, 1.4% in the overweight group, 1.5% in the obese group and 1.7% in severely obese patients, respectively (p < 0.001) [11].

When specifically evaluating TKA, similar results have been found. Manrique et al. compared UW TKA patients to a cohort of NW TKA patients and found that UW individuals had a higher rate of SSI (11.1%) than did NW individuals (0%) (p = 0.01) [15]. UW patients also had an increased risk of SSI (OR: 23.3; 95% CI 1.2 to 466, p = 0.04) compared to NW patients. This study and others utilized the SSI definition specified by the Centers for Disease Control (CDC) criteria [16]. The CDC SSI criteria was used instead of the Musculoskeletal Infection Society (MSIS) and International Consensus Meeting (ICM) definitions for periprosthetic joint infection (PJI) [17] because the MSIS and ICM criteria were not available at the time of publication.

While there is evidence that UW status increases risk of SSI/PJI, there are a few database studies that contradict these findings. Using the New Zealand joint registry, Murgatroyd et al. showed no increased risk of deep infection at a maximum of two-year follow-up [18]. Of the 5,357 patients, 131 were UW (2.4%). However, UW was defined as BMI < 20 kg/m^2 in this study [18]. All seven reported deep infections occurred in the overweight and obese groups with zero in the UW group at two years [18]. SSI and wound infections were not reported.

Another registry study, utilizing the Clinical Practice Research Datalink of 31,817 patients, found six-month wound infection rates of 1.5% (BMI < 18.5 kg/m^2), 2.2% (BMI = 18.5 to 25 kg/m^2), 3.0% (BMI = 25 to 30 kg/m^2), 3.3% (BMI = 30 to 35 kg/m^2) and 3.1% (BMI > 35 kg/m^2) respectively, with UW patients having the lowest wound infection rate [19]. Deep infection rates were not reported. In addition, discharge data from the National Inpatient Sample found that UW individuals (BMI < 18.5 kg/m^2 in this study) had a decreased rate of postoperative infection (OR 0.23, 95% CI 0.09 to 0.61) [20]. Importantly, all three of these studies possessed the limitations inherent to the analysis of large administrative databases (i.e., errors in data collection, incomplete data sets and observer bias) particularly with the diagnoses of postoperative infection, SSI and PJI.

Overall, there is an established association between low BMI and poorer surgical outcomes, specifically infection, in a variety of disciplines, including TJA in orthopaedics [10–12,19–26]. Furthermore, higher transfusion rates were also observed among UW patients after surgical intervention [11,13,15]. Postoperative allogeneic transfusion has been demonstrated to be an independent risk factor for developing SSI and PJI [27]. A lower BMI may be an indirect measure of nutritional status, as lower BMI patients have been shown to have lower levels of albumin, prealbumin, and protein- all of which can be used to evaluate nutritional status [28]. Low BMI patients have decreased reserves and an inability to accurately react to stress secondary to their suppressed immune systems [29]. Low BMI has also been associated with higher morbidity and mortality rates possibly reflecting an altered physiological state [30]. A potential optimization of this status resulting in a BMI increase in UW patients could be beneficial by decreasing their risk of adverse events. Increasing BMI to mitigate SSI and PJI risk in UW individuals is an area for future study.

REFERENCES

[1] Saucedo JM, Marecek GS, Wanke TR, Lee J, Stulberg SD, Puri L. Understanding readmission after primary total hip and knee arthroplasty: who's at risk? J Arthroplasty. 2014;29:256–260. doi:10.1016/j.arth.2013.06.003.

[2] Zhang Z, Zhao X, Kang Y, Zhang Z, Yang Z, He A, et al. The influence of body mass index on life quality and clinical improvement after total hip arthroplasty. J Orthop Sci. 2012;17:219–225. doi:10.1007/s00776–012–0197–9.

[3] Alfonso DT, Howell RD, Caceres G, Kozlowski P, Di Cesare PE. Total hip arthroplasty in the underweight. J Arthroplasty. 2008;23:956–959. doi:10.1016/j.arth.2007.09.008.

[4] Workgroup A, Surgeons K, Evidence A, Committee B, Hip O, Carolina N. Obesity and total joint arthroplasty: a literature based review. J Arthroplasty. 2013;28:714–721. doi:10.1016/j.arth.2013.02.011.

[5] Wolfe F, Michaud K. Effect of body mass index on mortality and clinical status in rheumatoid arthritis. Arthritis Care Res. 2012;64:1471–1479. doi:10.1002/acr.21627.

[6] Lash H, Hooper G, Hooper N, Frampton C. Should a patients BMI status be used to restrict access to total hip and knee arthroplasty? Functional outcomes of arthroplasty relative to BMI – single centre retrospective review. Open Orthop J. 2013;7:594–599. doi:10.2174/1874325001307010594.

[7] Flegal KM, Kit BK, Graubard BI. Body mass index categories in observational studies of weight and risk of death. Am J Epidemiol. 2014;180:288–296. doi:10.1093/aje/kwu111.

[8] Costa–Font J, Jofre–Bonet M. Anorexia, body image and peer effects: evidence from a sample of European women. Economica. 2013;80:44–64. doi:10.1111/j.1468–0335.2011.00912.x.

[9] Fryar CD, Carroll MD, Ogden CL. Prevalence of underweight among adults aged 20 and over: United States, 1960–1962 through 2011–2012. CDC/NCHS. 2014:1960–2962.

[10] Batsis JA, Huddleston JM, Melton LJ, Huddleston PM, Lopez–Jimenez F, Larson DR, et al. Body mass index and risk of adverse cardiac events in elderly patients with hip fracture: a population–based study. J Am Geriatr Soc. 2009;57:419–426. doi:10.1111/j.1532–5415.2008.02141.x.

[11] Nafiu OO, Ramachandran SK, Wagner DS, Campbell DA Jr, Stanley JC. Contribution of body mass index to postoperative outcome in minority patients. J Hosp Med. 2012;7:117–123. doi:10.1002/jhm.958.

[12] Atalan N, Fazlioğulları O, Kunt AT, Başaran C, Gürer O, Şitilci T, et al. Effect of body mass index on early morbidity and mortality after isolated coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth. 2012;26:813–817. doi:10.1053/j.jvca.2012.01.033.

[13] Somayaji R, Barnabe C, Martin L. Risk factors for infection following total joint arthroplasty in rheumatoid arthritis. Open Rheumatol J. 2013;7:119–124. doi:10.2174/1874312920131210005.

[14] Ringbäck Weitoft G, Eliasson M, Rosén M. Underweight, overweight and obesity as risk factors for mortality and hospitalization. Scand J Public Health. 2008;36:169–176. doi:10.1177/1403494807085080.

[15] Manrique J, Chen AF, Gomez MM, Maltenfort MG, Hozack WJ. Surgical site infection and transfusion rates are higher in underweight total knee arthroplasty patients. Arthroplast Today. 2017;3:57–60. doi:10.1016/j.artd.2016.03.005.

[16] Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. Am J Infect Control. 1999;27:97–132; quiz 133–134; discussion 96. doi:10.1016/S0196–6553(99)70088–X.

[17] Parvizi J, Gehrke T. Definition of periprosthetic joint infection. J Arthroplasty. 2014;29:1331. doi:10.1016/j.arth.2014.03.009.

[18] Murgatroyd SE, Frampton CM, Wright MS. The effect of body mass index on outcome in total hip arthroplasty: early analysis from the New Zealand joint registry. J Arthroplasty. 2014;29:1884–1888. doi:10.1016/j.arth.2014.05.024.

[19] Allen JG, Arnaoutakis GJ, Weiss ES, Merlo CA, Conte JV, Shah AS. The impact of recipient body mass index on survival after lung transplantation. J Heart Lung Transplant. 2010;29:1026–1033. doi:10.1016/j.healun.2010.05.005.
[20] Ndrepepa G, Keta D, Byrne RA, Schulz S, Mehilli J, Seyfarth M, et al. Impact of body mass index on clinical outcome in patients with acute coronary syndromes treated with percutaneous coronary intervention. Heart Vessels. 2010;25:27–34. doi:10.1007/s00380–009–1160–3.
[21] Giles K a, Hamdan AD, Pomposelli FB, Wyers MC, Siracuse JJ, Schermerhorn ML. Body mass index: surgical site infections and mortality after lower extremity bypass from the National Surgical Quality Improvement Program 2005–2007. Ann Vasc Surg. 2010;24:48–56. doi:10.1016/j.avsg.2009.05.003.
[22] Lederer DJ, Wilt JS, D'Ovidio F, Bacchetta MD, Shah L, Ravichandran S, et al. Obesity and underweight are associated with an increased risk of death after lung transplantation. Am J Respir Crit Care Med. 2009;180:887–895. doi:10.1164/rccm.200903–0425OC.
[23] Smith BG, Hakim–Zargar M, Thomson JD. Low body mass index: a risk factor for superior mesenteric artery syndrome in adolescents undergoing spinal fusion for scoliosis. J Spinal Disord Techn. 2009;22:144–148. doi:10.1097/BSD.0b013e31816b6b9a.
[24] Suemitsu R, Sakoguchi T, Morikawa K, Yamaguchi M, Tanaka H, Takeo S. Effect of body mass index on perioperative complications in thoracic surgery. Asian Cardiovasc Thorac Ann. 2008;16:463–467. doi:10.1177/021849230801600607.
[25] van Venrooij LM, de Vos R, Borgmeijer–Hoelen MM, Haaring C, de Mol BA. Preoperative unintended weight loss and low body mass index in relation to complications and length of stay after cardiac surgery. Am J Clin Nutr. 2008;87:1656–1661.
[26] Sharma S, Fraser M, Lovell F, Reece A, McLellan AR. Characteristics of males over 50 years who present with a fracture: epidemiology and underlying risk factors. J Bone Joint Surg Br. 2008;90:72–77. doi:10.1302/0301–620X.90B1.18773.
[27] Pulido L, Ghanem E, Joshi A, Purtill JJ, Parvizi J. Periprosthetic joint infection: the incidence, timing, and predisposing factors. Clin Orthop Relat Res. 2008;466:1710–1715. doi:10.1007/s11999–008–0209–4.
[28] Horwich TB, Kalantar–Zadeh K, MacLellan RW, Fonarow GC. Albumin levels predict survival in patients with systolic heart failure. Am Heart J. 2008;155:883–889. doi:10.1016/j.ahj.2007.11.043.
[29] Buzby GP, Mullen JL, Matthews DC, Hobbs CL, Rosato EF. Prognostic nutritional index in gastrointestinal surgery. Am J Surg 1980;139:160–167.
[30] Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. JAMA. 2005 Apr 20;293(15):1861-1867.

Authors: Stuart Goodman, Ruben Limas, Derek F. Amanatullah, Katherine Hwang

QUESTION 5: (A) What upper body mass index (BMI) threshold is associated with an increased risk of surgical site infection/periprosthetic joint infection (SSI/PJI)? (B) Does implementation of these cutoffs reduce the incidence of SSI/PJI?

RECOMMENDATION:

A) Obesity increases the risk of SSI/PJI after total joint arthroplasty (TJA). The risk increases gradually throughout the full range of BMI rather than surging at a certain cutoff point. A substantially increased risk is noticed in patients with a BMI > 40 Kg/m^2 and the risks of surgery must be carefully weighed against its benefits in these patients.

B) Weight reduction prior to surgery may have a benefit in mitigating risk for SSI/PJI for all patients with a BMI above normal.

LEVEL OF EVIDENCE: A) Strong, B) Consensus

DELEGATE VOTE: Agree: 95%, Disagree: 2%, Abstain: 3% (Unanimous, Strongest Consensus)

RATIONALE

Obesity has been shown to play a negative role throughout the natural history of osteoarthritis, from the development and progression of the disease to the occurrence of postoperative complications [1–5]. Among the range of complications that can occur following TJA, infection has proven to be a significant source of morbidity and mortality in its own right [6–9]. Numerous studies have examined the association between obesity and infection following TJA [10–13]. While the importance of these studies in ascertaining the importance of BMI as a potentially modifiable risk factor is acknowledged, there is a lack of a distinct threshold to be used in the preoperative period.

We conducted a systematic review to evaluate the threshold above which BMI is associated with SSI/PJI and found 17 studies meeting the inclusion criteria to answer this question. Most studies compared patients above and below BMI of 30 Kg/m^2 and limited their analysis to this dichotomous group. A recent meta-analysis examining the influence of obesity on complications following TKA concluded that patients with BMI ≥ 30 Kg/m^2 are at increased risk for infection [14]. Re-infection is also increased in obese patients who undergo revision for an infection of their primary or revised implant [13,15]. Lübbeke et al. [16] categorized patients into five groups based on their BMI levels in an attempt to specify which group had the highest risk for PJI. These investigators concluded that a BMI ≥ 35 Kg/m^2 should serve as a cutoff for increased risk for PJI. However, recent evidence suggests that a cutoff of 40 kg/m^2 [17,18] and even 50 kg/m^2 [19,20] should serve as the threshold above which the risk for PJI increases substantially.

The highest evidence to answer this question stems from two recent studies that used their large institutional databases (approximately 20,000 patients in each institution) to show a 10% increased risk for PJI for each BMI unit above normal (25 Kg/m^2) [17,18]. In both studies, the risk became progressively more pronounced for the group of patients with BMI values above 40 kg/m^2 with a three-times higher risk for SSI/PJI. The study by Shohat et al. [18] specifically aimed to determine whether there is a distinct BMI threshold above which the risk for infection increases substantially. The authors reported a linear increased risk with higher BMI with no distinct cutoff performing better than random chance.

To our knowledge there are no prospective randomized studies that directly address the subject of implementation of these BMI cutoffs (the majority of studies are retrospective reviews of databases or registries). While bariatric surgery did not seem to reduce complications following TKA, [21] it did

show a reduction in complications after THA [22]. A recent systematic review of five studies with a total of 23,348 TJA patients showed no statistically significant difference in infection rates (superficial or deep) after bariatric surgery [23]. There are ongoing studies following obese patients undergoing bariatric surgery versus those who decline bariatric surgery, but no definitive conclusions are available on this subject at this time.

Our results suggest that the risk for infection increases gradually throughout the full range of BMI above 30 kg/m^2, and patients with a BMI above 40 kg/m^2 are at substantial (three-times) risk for infection. These results should encourage surgeons to encourage all overweight patients to reduce weight prior to surgery with a special emphasis on patients who have a BMI above 40 kg/m^2. Further studies should prospectively examine the influence of BMI reduction on reducing the risk for infection.

REFERENCES

[1] Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis. The Framingham Study. Ann Intern Med. 1988;109:18–24.

[2] D'Apuzzo MR, Novicoff WM, Browne JA. The John Insall Award: Morbid obesity independently impacts complications, mortality, and resource use after TKA. Clin Orthop Relat Res. 2015;473:57–63. doi:10.1007/s11999–014–3668–9.

[3] Haverkamp D, Klinkenbijl MN, Somford MP, Albers GH, van der Vis HM. Obesity in total hip arthroplasty—does it really matter? A meta–analysis. Acta Orthop. 2011;82:417–422. doi:10.3109/17453674.2011.588859.

[4] Wagner ER, Kamath AF, Fruth KM, Harmsen WS, Berry DJ. Effect of body mass index on complications and reoperations after total hip arthroplasty. J Bone Joint Surg Am. 2016;98:169–179. doi:10.2106/JBJS.O.00430.

[5] Werner BC, Evans CL, Carothers JT, Browne JA. Primary total knee arthroplasty in super–obese patients: dramatically higher postoperative complication rates even compared to revision surgery. J Arthroplasty. 2015;30:849–853. doi:10.1016/j.arth.2014.12.016.

[6] Blumenfeld TJ. Does the infection or the treatment kill the patient?: Commentary on an article by Benjamin Zmistowski, BS, et al.: "Periprosthetic joint infection increases the risk of one–year mortality." J Bone Joint Surg Am. 2013;95:e200(1–2). doi:10.2106/JBJS.M.01085.

[7] Zmistowski B, Karam JA, Durinka JB, Casper DS, Parvizi J. Periprosthetic joint infection increases the risk of one–year mortality. J Bone Joint Surg Am. 2013;95:2177–2184. doi:10.2106/JBJS.L.00789.

[8] Son MS, Lau E, Parvizi J, Mont MA, Bozic KJ, Kurtz S. What are the frequency, associated factors, and mortality of amputation and arthrodesis after a failed infected TKA? Clin Orthop Relat Res. 2017;475:2905–2913. doi:10.1007/s11999–017–5285–x.

[9] Gundtoft PH, Pedersen AB, Varnum C, Overgaard S. Increased mortality after prosthetic joint infection in primary THA. Clin Orthop Relat Res. 2017;475:2623–2631. doi:10.1007/s11999–017–5289–6.

[10] Bozic KJ, Lau E, Kurtz S, Ong K, Berry DJ. Patient–related risk factors for postoperative mortality and periprosthetic joint infection in medicare patients undergoing TKA. Clin Orthop Relat Res. 2012;470:130–137. doi:10.1007/s11999–011–2043–3.

[11] Namba RS, Paxton L, Fithian DC, Stone ML. Obesity and perioperative morbidity in total hip and total knee arthroplasty patients. J Arthroplasty. 2005;20:46–50. doi:10.1016/j.arth.2005.04.023.

[12] Dowsey MM, Choong PF. Obese diabetic patients are at substantial risk for deep infection after primary TKA. Clin Orthop Relat Res. 2009;467:1577–1581. doi:10.1007/s11999–008–0551–6.

[13] Houdek MT, Wagner ER, Watts CD, Osmon DR, Hanssen AD, Lewallen DG, et al. Morbid obesity: a significant risk factor for failure of two–stage revision total hip arthroplasty for infection. J Bone Joint Surg Am. 2015;97:326–332. doi:10.2106/JBJS.N.00515.

[14] Kerkhoffs GM, Servien E, Dunn W, Dahm D, Bramer JA, Haverkamp D. The influence of obesity on the complication rate and outcome of total knee arthroplasty: a meta–analysis and systematic literature review. J Bone Joint Surg Am. 2012;94:1839–1844. doi:10.2106/JBJS.K.00820.

[15] Watts CD, Wagner ER, Houdek MT, Lewallen DG, Mabry TM. Morbid obesity: increased risk of failure after aseptic revision TKA. Clin Orthop Relat Res. 2015;473:2621–2627. doi:10.1007/s11999–015–4283–0.

[16] Lübbeke A, Zingg M, Vu D, Miozzari HH, Christofilopoulos P, Uçkay I, et al. Body mass and weight thresholds for increased prosthetic joint infection rates after primary total joint arthroplasty. Acta Orthop. 2016;87:132–138. doi:10.3109/17453674.2015.1126157.

[17] Wagner ER, Kamath AF, Fruth K, Harmsen WS, Berry DJ. Effect of body mass index on reoperation and complications after total knee arthroplasty. J Bone Joint Surg Am. 2016;98:2052–2060. doi:10.2106/JBJS.16.00093.

[18] Shohat N, Fleischman A, Tarabichi M, Tan TL, Parvizi J. Weighing in on body mass index and infection after total joint arthroplasty: is there evidence for a body mass index threshold? Clin Orthop Relat Res. 2018;Publish Ahead of Print.

[19] Meller MM, Toossi N, Gonzalez MH, Son MS, Lau EC, Johanson N. Surgical risks and costs of care are greater in patients who are super obese and undergoing THA. Clin Orthop Relat Res. 2016;474:2472–2481. doi:10.1007/s11999–016–5039–1.

[20] Werner BC, Higgins MD, Pehlivan HC, Carothers JT, Browne JA. Super obesity is an independent risk factor for complications after primary total hip arthroplasty. J Arthroplasty. 2017;32:402–406. doi:10.1016/j.arth.2016.08.001.

[21] Martin JR, Watts CD, Taunton MJ. Bariatric surgery does not improve outcomes in patients undergoing primary total knee arthroplasty. Bone Joint J. 2015;97–B:1501–1505. doi:10.1302/0301–620X.97B11.36477.

[22] Watts C, Martin JR, Houdek M, Abdel M, Lewallen D, Taunton M. Prior bariatric surgery may decrease the rate of re–operation and revision following total hip arthroplasty. Bone Joint J. 2016;98–B:1180–1184. doi:10.1302/0301–620X.98B9.37943.

[23] Smith TO, Aboelmagd T, Hing CB, MacGregor A. Does bariatric surgery prior to total hip or knee arthroplasty reduce post–operative complications and improve clinical outcomes for obese patients? Systematic review and meta–analysis. Bone Joint J. 2016;98–B:1160–1166. doi:10.1302/0301–620X.98B9.38024.

Authors: Mitchell R. Klement, Ngai Nung, Neil Sheth, Suraya Zainul-Abidin, Kae Sian Tay, Ajay Premkumar

QUESTION 6: Does bariatric surgery reduce the risk of surgical site infection/periprosthetic joint infection (SSI/PJI) in patients with obesity?

RECOMMENDATION: The evidence is inconclusive at present. Thus, preoperative bariatric surgery cannot be routinely recommended.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 85%, Disagree: 7%, Abstain: 8% (Super Majority, Strong Consensus)

RATIONALE

Obesity, defined as body mass index (BMI) > 30 kg/m^2, has reached alarming proportions in the United States (US), the United Kingdom (UK) and globally, with no signs of decline [1,2]. The national prevalence of obesity in US men and women from 2013 to 2014 has been reported as 35% and 40.4%, respectively [3]. In addition, it has been predicted that by 2025, 47% of men and 36% of women (aged between 21 and 60 years old) in the UK will be obese [2]. Obesity has also been linked to the development of osteoarthritis and joint disease [4]. As a result, a higher portion of obese patients will present to orthopaedic surgeons seeking total knee arthroplasty (TKA) or total hip arthroplasty (THA). George et al. reported that obese patients constituted 52% of THAs and 70% of TKA patients in 2011 [5].

Although obese patients can achieve high satisfaction and pain relief following arthroplasty [5], obesity has also been associated with increased risk of surgical site infection (SSI) and periprosthetic joint infection (PJI) [6–8]. As a result, obesity is viewed as a modifiable risk factor and the American Association of Hip and Knee Surgeons (AAHKS) workgroup on obesity concluded that the risks associated with a BMI > 40 kg/m^2 outweigh the functional benefit of an arthroplasty [9]. Therefore, many centers and providers will delay arthroplasty until the patient can reduce their weight below this threshold. ho

Bariatric surgery is often viewed as a safe, effective means to help morbidly obese patients achieve weight reduction [10]. It has also been shown to be more effective in helping patients reduce weight than nonsurgical methods [11]. Bariatric surgery is considered the most effective treatment for weight loss in patients with severe obesity, and it is indicated in patients with a BMI ≥ 40 kg/m^2 or patients with a BMI ≥ 35 kg/m^2 and at least one important comorbidity who have failed clinical management for weight loss [11,12]. Some orthopaedic surgeons advocate for bariatric surgery prior to hip, knee or ankle arthroplasty in order to lower the risk of postoperative SSI and PJI. Parvizi et al. demonstrated that patients who undergo bariatric surgery prior to total hip or knee arthroplasty experience significant functional improvements following surgery with an acceptably low complication rate [13].

Springer et al. described bariatric surgery as an effective and durable treatment for obesity. They reported that patients lost up to 50 to 70% of their excess weight (a BMI reduction of 10 to 15kg/m^2) following bariatric procedures [14]. However, there is limited evidence that supports that bariatric surgery is associated with reduced rates of SSI/PJI following total joint arthroplasty. Despite the lack of level I or level II evidence, nine retrospective studies have investigated the potential beneficial influence of bariatric surgery on SSI/PJI in obese patients undergoing total joint arthroplasty. The results are conflicting. Kulkarni et al. compared 90 patients who underwent bariatric surgery prior to total joint arthroplasty (TJA) to 53 patients who underwent bariatric surgery following TJA. They found that the infection rates following joint arthroplasty surgery were 1.1 to 3.7%, respectively. There was no statistical difference between the two groups (p = 0.55) [15]. In addition, six additional studies have demonstrated that undergoing bariatric surgery either prior to or after undergoing TJA does not influence the incidence of subsequent SSI/PJI [16–21].

Only two studies have demonstrated reductions of SSI/PJI in patients who underwent TJA following bariatric surgery [22,23]. One was a large cohort study using the Medicare database (bariatric prior vs. obese only patients, (odds ratio (OR) 0.36, 95% confidence interval (CI) 0.13 to 0.96, p = 0.049) [23] and the second used the New York State database (2.4% bariatric vs.1.3% obese TKA patients, p = 0.003, no difference for THA) [22]. Also, a meta-analysis published in 2015 demonstrated a reduction in postoperative infection in the bariatric group (OR 0.36, 95% CI 0.15 to 0.90, p = 0.03). However, no differences in infection were found when the results were stratified by superficial or deep infection [24]. The authors concluded that the analyses of postoperative complications following bariatric surgery were assessed as “very low” quality of evidence using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach. In addition, they reported very little confidence in these findings due to inconsistency, imprecision and the risk of bias. They concluded that bariatric surgery prior to hip or knee arthroplasty does not improve clinical outcomes or reduce complication rates for patients who are obese [24].

The existing literature has important limitations in attempting to answer the proposed question. Many of the aforementioned studies are retrospective in nature. There is a lack of prospective or randomized trials. There is also a lack of data on the nutritional status of obese patients undergoing bariatric surgery and TJA. This is important in that post-bariatric surgery patients may remain in a malnourished state following bariatric surgery [25]. Because malnutrition has been previously associated with an increased rate of PJI [26], the lack of data on the nutritional status of these patients prior to and after bariatric surgery can potentially confound results. The small sample sizes and the use of registry databases does not allow for subgroup analysis on the types of bariatric surgeries received. There are differences in weight loss and nutritional status between different types of bariatric surgery, and this may influence the rate of infection following arthroplasty [11]. In addition, the time interval between bariatric surgery and arthroplasty was often unreported or inconsistent across the different studies. In addition, given the relatively low rate of PJI in TJA, many of the current studies may be too underpowered to address this clinical question. Furthermore, the criteria for definition of SSI or PJI, particularly in the large database studies, were not consistently reported.

In conclusion, in the absence of strong evidence and a lack of studies with detailed data pertinent to the subject, we feel that subjecting obese patients to bariatric surgery prior to TJA for the sake of reducing subsequent SSI or PJI is not warranted.

REFERENCES

[1] Seidell JC, Halberstadt J. Obesity: The obesity epidemic in the USA – no end in sight? Nat Rev Endocrinol. 2016;12:499–500. doi:10.1038/nrendo.2016.121.

[2] World Health Organization. Global database on body mass index (BMI). http://www.who.int/nutrition/databases/bmi/en/. Accessed July 12, 2018.

[3] Flegal KM, Kruszon–Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. JAMA 2016;315:2284–2291. doi:10.1001/jama.2016.6458.

[4] Jiang L, Tian W, Wang Y, Rong J, Bao C, Liu Y, et al. Body mass index and susceptibility to knee osteoarthritis: a systematic review and meta–analysis. Joint Bone Spine. 2012;79:291–297. doi:10.1016/j.jbspin.2011.05.015.

[5] George J, Klika AK, Navale SM, Newman JM, Barsoum WK, Higuera CA. Obesity epidemic: Is its impact on total joint arthroplasty underestimated? An analysis of national trends. Clin Orthop Relat Res. 2017;475:1798–1806. doi:10.1007/s11999–016–5222–4.

[6] Kerkhoffs GM, Servien E, Dunn W, Dahm D, Bramer JA, Haverkamp D. The influence of obesity on the complication rate and outcome of total knee arthroplasty: a meta–analysis and systematic literature review. J Bone Joint Surg Am. 2012;94:1839–1844. doi:10.2106/JBJS.K.00820.

[7] Wagner ER, Kamath AF, Fruth KM, Harmsen WS, Berry DJ. Effect of body mass index on complications and reoperations after total hip arthroplasty. J Bone Joint Surg Am. 2016;98:169–179. doi:10.2106/JBJS.O.00430.

[8] Malinzak RA, Ritter MA, Berend ME, Meding JB, Olberding EM, Davis KE. Morbidly obese, diabetic, younger, and unilateral joint arthroplasty patients have elevated total joint arthroplasty infection rates. J Arthroplasty. 2009;24:84–88. doi:10.1016/j.arth.2009.05.016.

[9] Workgroup of the American Association of Hip and Knee Surgeons Evidence Based Committee. Obesity and total joint arthroplasty: a literature based review. J Arthroplasty. 2013;28:714–721. doi:10.1016/j.arth.2013.02.011.

[10] Maciejewski ML, Arterburn DE, Van Scoyoc L, Smith VA, Yancy WS, Weidenbacher HJ, et al. Bariatric surgery and long–term durability of weight loss. JAMA Surg 2016;151:1046–1055. doi:10.1001/jamasurg.2016.2317.
[11] Colquitt JL, Pickett K, Loveman E, Frampton GK. Surgery for weight loss in adults. Cochrane Database Syst Rev 2014:CD003641. doi:10.1002/14651858.CD003641.pub4.
[12] Kingsberg JG, Halpern AA, Hill BC. A bariatric surgery primer for orthopedic surgeons. Am J Orthop. 2016;45:E1–6.
[13] Parvizi J, Trousdale RT, Sarr MG. Total joint arthroplasty in patients surgically treated for morbid obesity. J Arthroplasty. 2000;15:1003–1008. doi:10.1054/arth.2000.9054.
[14] Springer BD, Carter JT, McLawhorn AS, Scharf K, Roslin M, Kallies KJ, et al. Obesity and the role of bariatric surgery in the surgical management of osteoarthritis of the hip and knee: a review of the literature. Surg Obes Relat Dis. 2017;13:111–118. doi:10.1016/j.soard.2016.09.011.
[15] Kulkarni A, Jameson SS, James P, Woodcock S, Muller S, Reed MR. Does bariatric surgery prior to lower limb joint replacement reduce complications? Surgeon 2011;9:18–21. doi:10.1016/j.surge.2010.08.004.
[16] Inacio MC, Paxton EW, Fisher D, Li RA, Barber TC, Singh JA. Bariatric surgery prior to total joint arthroplasty may not provide dramatic improvements in post–arthroplasty surgical outcomes. J Arthroplasty. 2014;29:1359–1364. doi:10.1016/j.arth.2014.02.021.
[17] Martin JR, Watts CD, Taunton MJ. Bariatric surgery does not improve outcomes in patients undergoing primary total knee arthroplasty. Bone Joint J. 2015;97–B:1501–1505. doi:10.1302/0301–620X.97B11.36477.
[18] Nearing EE, Santos TM, Topolski MS, Borgert AJ, Kallies KJ, Kothari SN. Benefits of bariatric surgery before elective total joint arthroplasty: is there a role for weight loss optimization? Surg Obes Relat Dis. 2017;13:457–462. doi:10.1016/j.soard.2016.11.005.
[19] Nickel BT, Klement MR, Penrose CT, Green CL, Seyler TM, Bolognesi MP. Lingering risk: bariatric surgery before total knee arthroplasty. J Arthroplasty. 2016;31:207–211. doi:10.1016/j.arth.2016.02.075.
[20] Severson EP, Singh JA, Browne JA, Trousdale RT, Sarr MG, Lewallen DG. Total knee arthroplasty in morbidly obese patients treated with bariatric surgery: a comparative study. J Arthroplasty. 2012;27:1696–1700. doi:10.1016/j.arth.2012.03.005.
[21] Watts CD, Martin JR, Houdek MT, Abdel MP, Lewallen DG, Taunton MJ. Prior bariatric surgery may decrease the rate of re–operation and revision following total hip arthroplasty. Bone Joint J. 2016;98–B:1180–1184. doi:10.1302/0301–620X.98B9.37943.
[22] McLawhorn AS, Levack AE, Lee YY, Ge Y, Do H, Dodwell ER. Bariatric surgery improves outcomes after lower extremity arthroplasty in the morbidly obese: a propensity score–matched analysis of a New York statewide database. J Arthroplasty. 2018;33:2062–2069.e4. doi:10.1016/j.arth.2017.11.056.
[23] Werner BC, Kurkis GM, Gwathmey FW, Browne JA. Bariatric surgery prior to total knee arthroplasty is associated with fewer postoperative complications. J Arthroplasty. 2015;30:81–85. doi:10.1016/j.arth.2014.11.039.
[24] Smith TO, Aboelmagd T, Hing CB, MacGregor A. Does bariatric surgery prior to total hip or knee arthroplasty reduce post–operative complications and improve clinical outcomes for obese patients? Systematic review and meta–analysis. Bone Joint J. 2016;98–B:1160–1166. doi:10.1302/0301–620X.98B9.38024.
[25] Xanthakos SA. Nutritional deficiencies in obesity and after bariatric surgery. Pediatr Clin North Am. 2009;56:1105–1121. doi:10.1016/j.pcl.2009.07.002.
[26] Huang R, Greenky M, Kerr GJ, Austin MS, Parvizi J. The effect of malnutrition on patients undergoing elective joint arthroplasty. J Arthroplasty. 2013;28:21–24. doi:10.1016/j.arth.2013.05.038.

Authors: Mohammad Ali Enayatollahi, Lipalo Mokete, Marisa Sanchez, Jurek R.T. Pietrzak

QUESTION 7: Does human immunodeficiency virus (HIV) predispose patients to surgical site infection/periprosthetic joint infection (SSI/PJI)? If so, what optimization should be undertaken prior to operating on patients with HIV?

RECOMMENDATION: Human immunodeficiency virus (HIV) infection is known to be a risk factor for surgical site infection (SSI) and periprosthetic joint infection (PJI). However, in patients who are medically optimized, with highly active antiretroviral therapy (HAART), the magnitude of the risk is small and comparable to HIV-negative patients. Patients must be optimized for underlying conditions including malnutrition, renal and liver disease, cluster of differentiation (CD4) count and viral load.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 96%, Disagree: 2%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

HIV has led to more than 70 million people currently infected and about 35 million HIV-related mortalities. An estimated 0.8% of adults aged 15 to 49 years worldwide are living with HIV [1]. Between 1979 and 1985, many hemophilic patients were exposed to HIV through administration of unscreened blood products [2]. The advent of HAART in 1997 changed the nature of HIV infection from a life-threatening condition into a well-controlled chronic disease, with patients achieving a near normal lifespan [3–8]. As the HIV-infected population ages, these patients may develop advanced age-specific morbidities such as degenerative joint disease [3]. Therefore, the demand for total joint arthroplasty (TJA) in HIV-infected patients is on the rise and concerns about proper treatment strategies and the outcomes of this procedure in this patient population are emerging [2,3,9,10].

Studies performed before initiation of HAART have reported infection-related complication rates as high as 50% [2,9,11]. These patients, in most cases, were hemophiliacs who had been co-infected with HIV [12] or had comorbidities such as intravenous drug abuse [13]. Later studies on HIV-infected patients without hemophilia had better outcomes and lower rates of periprosthetic joint infection (PJI), even equal to a healthy population [6–8,14–17]. This inconsistency in the literature reflects small sample sizes and the inclusion of confounding conditions such as hemophilia, which in itself increases complication risks, and the use of HAART [11]. (Table 1 and Table 2 consist of most representative papers describing demographics and PJI rates in HIV-infected patients without hemophilia and with hemophilia, respectively) [3].

Confounding Factors (e.g., Hemophilia and Intravenous Drug Use)

There are conditions that have a strong effect on joint arthroplasty outcomes in HIV-infected patients. Lehman et al. analyzed data on 41 hip and knee arthroplasties performed on intravenous drug users, some of whom were HIV-positive, and they showed that drug use was an independent risk factor for infection after total joint arthroplasty [13]. This study and similar other studies have shown that comorbidities in patients, particularly hemophilia and intravenous (IV) drug abuse, are potential independent risk factors for developing PJI [13,26,33,35–38]. Some of these patients also

demonstrated minimal benefit from the use of HAART [12,13]. A thorough social history and urine toxicology should be obtained to screen for current IV drug users. Ongoing illegal drug abuse is a strong contraindication for elective TJA [39]. Nevertheless, factors such as nutritional status, liver and renal function, CD4 cell count and viral load (VL), are correctable and need to be addressed in the perioperative period in HIV-infected patients [3,40].

We identified 15 studies suitable for inclusion in a systematic review to answer the posed question for hemophiliac patients [12,13,19,28,41–44]. Eight of the studies had an HIV-negative comparator group [19,42,43]. There were 47 PJIs/SSIs in 332 arthroplasties (0.142, 95% CI:0.106 to 0.184).

The relative risk of PJI/SSI based on a combination of the seven studies with a control group was 170, (95% CI: 0.93 to 3.1) indicating that the risk was not significantly elevated in the HIV-infected hemophiliac arthroplasty patients compared to the HIV-negative hemophiliacs (see Fig. 1).

Features common to most of the above studies on hemophiliacs are small numbers of study patients and long periods of follow-up with inclusion of a large proportion of patients who received joint arthroplasties before the HAART era.

CD4 count

The importance of CD4 count and its relation to the severity of the infection in patients with HIV has been previously confirmed [45,46]. However, the optimal threshold for CD4 count in patients undergoing elective arthroplasty has not been established. Limited data has shown some association between CD4 count and PJI in HIV-positive patients. In a retrospective study with a mean follow-up of 10.2 years, Parvizi et al. [9] noted a PJI rate of 28.5% (6 out of 21) and showed a significant association between the immune status of the patient and the incidence of PJI. The CD4 count at the time of arthroplasty was not available for four of six of these patients. However, the CD4 count was significantly lower at an average 239 cells/ml at latest follow-up for patients with deep infection versus 523 cells/ml for the study population as a whole ($p < .001$).

In the field of orthopaedic trauma procedures, there is evidence that patients with CD4 cell counts less than 200 have higher rates of complications than patients with higher counts. Other studies showed that risk factors for wound infection in the orthopaedic trauma setting include HIV clinical category B, CD4 counts of < 500 cells/ml, contaminated wounds and low serum albumin [47–49].

Viral load

The viral load, that is the number of copies of viral RNA in a patient's blood, is another test used to monitor HIV infection. It remains to be seen if the level of viral load can be used to predict the rates of PJI in HIV-positive patients who undergo TJA [3]. Horberg et al. [50] found that in HIV-infected patients undergoing surgical procedures (including both orthopaedic and non-orthopaedic procedures), HIV viral loads of > 500 copies/mL were associated with minimal complications, whereas HIV viral loads of > 30,000 copies/mL were associated with an increased risk of complications. If CD4 counts are > 400 cells/ml with undetectable viral loads, the patient might benefit from TJA as the risk of PJI may be decreased [51]. In a retrospective study, Falakassa et al. [24] suggested that well-controlled HIV patients on HAART therapy with undetectable viral loads and CD4 > 200 are at similar risk of PJI as the average population. Based on some indirect evidence, a CD4 count of > 400 cell/ml and a viral load of < 50 copies/ml could be ideal thresholds for elective TJA [50].

TABLE 1. Demographics of representative studies on PJI in patients with HIV, but not hemophilia

Study	TJA Number	PJI Number	Number of Patients	Number of Male Patients	Mean Follow-Up	Mean Age (Years)
Capogna [8] 2013	69	3	57	Unclear (Only 58% of HIV cases presented)	609 days	44.8
Chokotho [15] 2013	15	0	12	Unclear – HIV patients not separated	Unclear	47.1 (not useable)
Cummins [7] 2014	8	0	7	3 (Not useable as operations not clear)	25 months (1–68 months)	35 (not useable)
Graham [6] 2014	43	0	29	19	3 years, 6 months (5 months–8 years and 2 months)	47 years, 7 months (21–59 + 5 months)
Joon Yoo [18] 2010	5	0	3	3	16.6 months (4–37 months)	38.6 (not separated by operation)
Lin [19] 2014	22	2	20	20	4.6 years (2–8.6 years)	49 (+/-17.8)
Lubega [14] 2009	18	0	18	Unclear	Unclear	52 (not useable)
Mahoney [20] 2005	54	1	40	31	2.3 years (1–7 years)	44.4 years (+/-9.3)
Snir [21] 2014	41	1	31	22	33 months (4–116)	49.6 (32–75)
Tornero [22] 2012	18	0	13	11	3.3 years (+/- 2.5)	44.3 (+/- 9.1)
Wang [23] 2012	8	0	5	Unclear	38.6 months (4–84)	44.5 (36–54)

Falakassa [24] 2014	32	0	24	17	14 months (1.5–60)	50 (31–74)
Issa [25] 2013	44	2	34	23	7 years (4–11 years)	48 (Range 34–80)
Lehman [13] 2001	4	0	NA	NA	Unclear	Unclear
Issa [16] 2017	50	0	45	31	6 years	57 years (38–72)

HIV, human immunodeficiency virus; NA, not available; PJI, periprosthetic joint infection; TJA, total joint arthroplasty.

TABLE 2. Demographics of representative studies on PJI in patients with HIV and hemophilia [3]

Study	TJA Number	PJI Number	Number of Patients	Number of Male Patients	Mean Follow-Up	Mean Age (Years)
Goddard [26] 2010	17	1	16	Unclear	9.2 years (2–23)	43 (25–70)
Haberman [27] 2008	?53	?	41	37	81 months (2–14 years)	46 (34–68)
Hicks [12] 2001	91	17	Unclear	Unclear	5.7 years (0.1–20.8)	39 (22–60)
Lehman [13] 2001	18	3	14	Unclear	62 months (24–152)	33 (25–48)
Norian [28] 2002	40	4	29	Unclear	110 months (24–246)	33.7 (+/-8.2)
Thomason [29] 1999	12	4	12 (not useable)	Unclear		Unclear
Powell [30] 2005	30	3	19	19	80 months (2–323)	33 (20–61)
Ragni [31] 1995	34	8	34 (not useable)	Unclear	Unclear	36 (+/- 3.1)
Rodriguez [32] 2011	21	2	21	Unclear	8.5 years (1–13)	36.5 (24–52)
Rodriguez [33] 2007	19	1	19	Unclear	7.5 years (1–10)	31 (24–42)
Unger [34] 1995	26	0	15	Unclear	6.4 years (1–9)	33 (25–42)

HIV, human immunodeficiency virus; PJI, periprosthetic joint infection; TJA, total joint arthroplasty.

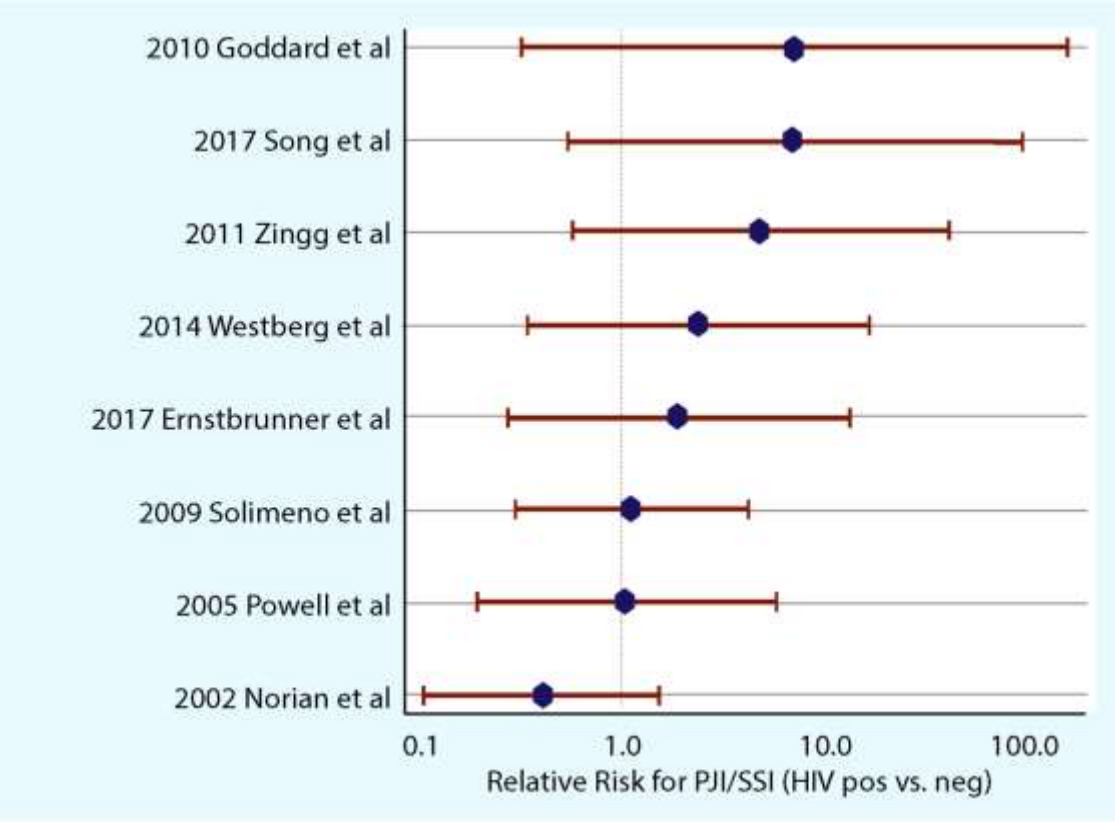

FIGURE 1. Forest plot of relative risk of PJI/SSI in HIV-infected hemophiliacs vs. HIV-negative hemophiliacs.

HAART

HAART therapy reduces HIV transmission, restores immune function, reduces HIV- related morbidity and mortality and improves survival [39,48]. Some studies have shown that HAART therapy could stabilize CD4 count within normal limits which is assumed to be correlated with better outcomes in patients undergoing orthopaedic procedures [39].

In a systematic review, Enayatollahi et al. [3] suggested that HIV-positive patients who are medically optimized with HAART and controlled for their comorbidities have an acceptable rate of PJI after TJA that approaches that of HIV-negative patients.

Malnutrition, Liver and Renal Disease

Malnutrition is strongly associated with a multitude of complications following TJA, including prolonged hospitalization, delayed wound healing, persistent wound drainage and subsequent susceptibility to infection. The nutritional status is assessed by the level of serum albumin (normal 3.5 to 5 g/dl), serum transferrin (normal 204 to 360 mg/dl), serum prealbumin (normal 15 to 35 mg/dl) and total lymphocyte count (800 to 2,000/ml) [49]. Although thresholds for these tests have not been established, any deviation of these parameters might be associated with increased complications. It is reasonable to expect that HIV-positive patients may suffer a higher risk of postoperative complications due to underlying malnutrition [52], abnormal weight loss, fluid and electrolyte imbalance and renal disease [10,11,19,43,53].

Using a nationwide database between 2005 and 2012, Kildow et al. [53] concluded that HIV-positive patients co-infected with hepatitis C virus (HCV) or hepatitis B virus (HBV) are at increased risk of PJI at two years, and the risk of revision after total hip arthroplasty is also increased at 90 days and 2 years.

Conclusion

The advent of HAART has transformed HIV infection to a well-controlled chronic disease and HIV-positive patients are expected to have a near normal life span. Elective arthroplasty is a safe procedure and could benefit this patient population should they be medically optimized with HAART and establish appropriate CD4 count and viral load, while addressing their comorbidities including malnutrition, liver and renal disease, hemophilia and IV drug abuse in the perioperative period.

REFERENCES

[1] World Health Organization. Global Health Observatory (GHO) data: HIV/AIDS. http://www.who.int/gho/hiv/en. Accessed May 1, 2015.
[2] Swensen S, Schwarzkopf R. Total joint arthroplasty in human immunodeficiency virus positive patients. Orthop Surg. 2012;4:211–215. doi:10.1111/os.12001.
[3] Enayatollahi MA, Murphy D, Maltenfort MG, Parvizi J. Human immunodeficiency virus and total joint arthroplasty: the risk for infection is reduced. J Arthroplasty. 2016;31:2146–2151. doi:10.1016/j.arth.2016.02.058.
[4] Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med. 1998;338:853–860. doi:10.1056/NEJM199803263381301.

[5] The CASCADE Collaboration. Survival after introduction of HAART in people with known duration of HIV–1 infection. The CASCADE Collaboration. Concerted Action on SeroConversion to AIDS and Death in Europe. Lancet 2000;355:1158–1159.
[6] Graham SM, Lubega N, Mkandawire N, Harrison WJ. Total hip replacement in HIV–positive patients. Bone Joint J. 2014;96–B:462–466. doi:10.1302/0301–620X.96B4.33213.
[7] Cummins F, Ramasubbu B, McCarthy T, Bergin C, Grieve PP. Surgery of the femur in HIV positive patients: a retrospective review from 2005 to 2011. Ir J Med Sci. 2015;184:505–510. doi:10.1007/s11845–014–1156–6.
[8] Capogna BM, Lovy A, Blum Y, Kim SJ, Felsen UR, Geller DS. Infection rate following total joint arthroplasty in the HIV population. J Arthroplasty. 2013;28:1254–1258. doi:10.1016/j.arth.2012.12.021.
[9] Parvizi J, Sullivan TA, Pagnano MW, Trousdale RT, Bolander ME. Total joint arthroplasty in human immunodeficiency virus–positive patients: An alarming rate of early failure. J Arthroplasty. 2003;18:259–264. doi:10.1054/arth.2003.50094.
[10] Lin CA, Kuo AC, Takemoto S. Comorbidities and perioperative complications in HIV–positive patients undergoing primary total hip and knee arthroplasty. J Bone Joint Surg Am. 2013;95:1028–1036. doi:10.2106/JBJS.L.00269.
[11] Boylan MR, Basu N, Naziri Q, Issa K, Maheshwari AV, Mont MA. Does HIV infection increase the risk of short–term adverse outcomes following total knee arthroplasty? J Arthroplasty. 2015;30:1629–1632. doi:10.1016/j.arth.2015.03.018.
[12] Hicks JL, Ribbans WJ, Buzzard B, Kelley SS, Toft L, Torri G, et al. Infected joint replacements in HIV–positive patients with haemophilia. J Bone Joint Surg Br. 2001;83:1050–1054.
[13] Lehman CR, Ries MD, Paiement GD, Davidson AB. Infection after total joint arthroplasty in patients with human immunodeficiency virus or intravenous drug use. J Arthroplasty. 2001;16:330–335. doi:10.1054/arth.2001.21454.
[14] Lubega N, Mkandawire NC, Sibande GC, Norrish AR, Harrison WJ. Joint replacement in Malawi: establishment of a National Joint Registry. J Bone Joint Surg Br. 2009;91:341–343. doi:10.1302/0301–620X.91B3.21706.
[15] Chokotho L, Harrison WJ, Lubega N, Mkandawire NC. Avascular necrosis of the femoral head in HIV positive patients–an assessment of risk factors and early response to surgical treatment. Malawi Med J. 2013;25:28–32.
[16] Issa K, Pierce TP, Harwin SF, Scillia AJ, Festa A, Mont MA. No decrease in knee survivorship or outcomes scores for patients with hiv infection who undergo TKA. Clin Orthop Relat Res. 2017;475:465–471. doi:10.1007/s11999–016–5122–7.
[17] Zhao CS, Li X, Zhang Q, Sun S, Zhao RG, Cai J. Early outcomes of primary total hip arthroplasty for osteonecrosis of the femoral head in patients with human immunodeficiency virus in China. Chin Med J (Engl). 2015;128:2059–2064. doi:10.4103/0366–6999.161364.
[18] Yoo JJ, Chun SH, Kwon YS, Koo KH, Yoon KS, Kim HJ. Operations about hip in human immunodeficiency virus–positive patients. Clin Orthop Surg. 2010;2:22–27. doi:10.4055/cios.2010.2.1.22.
[19] Lin CA, Takemoto S, Kandemir U, Kuo AC. Mid–term outcomes in HIV–positive patients after primary total hip or knee arthroplasty. J Arthroplasty. 2014;29:277–282. doi:10.1016/j.arth.2013.06.015.
[20] Mahoney CR, Glesby MJ, Dicarlo EF, Peterson MG, Bostrom MP. Total hip arthroplasty in patients with human immunodefciency virus infection: Pathologic findings and surgical outcomes. Acta Orthopaedica. 2005;76:198–203. doi:10.1080/00016470510030571.
[21] Snir N, Wolfson TS, Schwarzkopf R, Swensen S, Alvarado CM, Hamula M, et al. Outcomes of Total hip arthroplasty in human immunodeficiency virus–positive patients. J Arthroplasty. 2014;29:157–161. doi:10.1016/j.arth.2013.04.023.
[22] Tornero E, García S, Larrousse M, Gallart X, Bori G, Riba J, et al. Total hip arthroplasty in HIV–infected patients: a retrospective, controlled study. HIV Med. 2012;13:623–629. doi:10.1111/j.1468–1293.2012.01017.x.
[23] Wang TI, Chen CF, Chen WM, Chiang CC, Huang CK, Liu CL, et al. Joint replacement in human immunodeficiency virus–infected patients. J Chin Med Assoc. 2012;75:595–599. doi:10.1016/j.jcma.2012.08.021.
[24] Falakassa J, Diaz A, Schneiderbauer M. Outcomes of total joint arthroplasty in HIV patients. Iowa Orthop J. 2014;34:102–106.
[25] Issa K, Naziri Q, Rasquinha V, Maheshwari AV, Delanois RE, Mont MA. Outcomes of cementless primary THA for osteonecrosis in hiv–infected patients. J Bone Joint Surg Am. 2013;95:1845–1850. doi:10.2106/JBJS.L.01583.
[26] Goddard NJ, Mann HA, Lee CA. Total knee replacement in patients with end–stage haemophilic arthropathy: 25–year results. J Bone Joint Surg Br. 2010;92:1085–1089. doi:10.1302/0301–620X.92B8.23922.
[27] Habermann B, Eberhardt C, Kurth AA. Total joint replacement in HIV positive patients. J Infect. 2008;57:41–46. doi:10.1016/j.jinf.2008.01.045.
[28] Norian JM, Ries MD, Karp S, Hambleton J. Total knee arthroplasty in hemophilic arthropathy. J Bone Joint Surg Am. 2002;84–A:1138–1141.
[29] Thomason HC, Wilson FC, Lachiewicz PF, Kelley SS. Knee arthroplasty in hemophilic arthropathy. Clin Orthop Relat Res. 1999:169–173.
[30] Powell DL, Whitener CJ, Dye CE, Ballard JO, Shaffer ML, Eyster ME. Knee and hip arthroplasty infection rates in persons with haemophilia: a 27 year single center experience during the HIV epidemic. Haemophilia. 2005;11:233–239. doi:10.1111/j.1365–2516.2005.01081.x.
[31] Ragni MV, Crossett LS, Herndon JH. Postoperative infection following orthopaedic surgery in human immunodeficiency virus–infected hemophiliacs with CD4 counts ≤ 200/mm3. J Arthroplasty. 1995;10:716–721. doi:10.1016/S0883–5403(05)80065–8.
[32] Rodriguez–Merchan EC, Gomez–Cardero P, Jimenez–Yuste V. Infection after total knee arthroplasty in haemophilic arthropathy with special emphasis on late infection: letter to the editor. Haemophilia. 2011;17:e831–e832. doi:10.1111/j.1365–2516.2011.02530.x.
[33] Rodriguez–Merchan EC. Total knee replacement in haemophilic arthropathy. J Bone Joint Surg Br. 2007;89:186–188. doi:10.1302/0301–620X.89B2.18682.
[34] Unger AS, Kessler CM, Lewis RJ. Total knee arthroplasty in human immunodeficiency virus–infected hemophiliacs. J Arthroplasty. 1995;10:448–452. doi:10.1016/S0883–5403(05)80144–5.
[35] Cohen I, Heim M, Martinowitz U, Chechick A. Orthopaedic outcome of total knee replacement in haemophilia A. Haemophilia. 2000;6:104–109.
[36] Gregg–Smith SJ, Pattison RM, Dodd CA, Giangrande PL, Duthie RB. Septic arthritis in haemophilia. J Bone Joint Surg Br. 1993;75:368–370.
[37] Trieb K, Panotopoulos J, Wanivenhaus A. Risk of infection after total knee arthroplasty in HIV–positive hemophilic patients. J Bone Joint Surg Am. 2003;85–A:969; author reply 969–970.
[38] Beeton K, Rodriguez–Merchan EC, Alltree J. Total joint arthroplasty in haemophilia. Haemophilia. 2000;6:474–481.
[39] Shah KN, Truntzer JN, Touzard Romo F, Rubin LE. Total joint arthroplasty in patients with human immunodeficiency virus. J Bone Joint Surg Rev. 2016;4. doi:10.2106/JBJS.RVW.15.00117.
[40] Pretell–Mazzini J, Subhawong T, Hernandez VH, Campo R. HIV and orthopaedics: musculoskeletal manifestations and outcomes. J Bone Joint Surg Am. 2016;98:775–786. doi:10.2106/JBJS.15.00842.
[41] Günthard HF, Saag MS, Benson CA, del Rio C, Eron JJ, Gallant JE, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the international antiviral society–USA panel. JAMA. 2016;316:191–210. doi:10.1001/jama.2016.8900.
[42] Rezapoor M, Parvizi J. Prevention of Periprosthetic Joint Infection. J Arthroplasty. 2015;30:902–907. doi:10.1016/j.arth.2015.02.044.
[43] Naziri Q, Boylan MR, Issa K, Jones LC, Khanuja HS, Mont MA. Does HIV infection increase the risk of perioperative complications after THA? A nationwide database study. Clin Orthop Relat Res. 2015;473:581–586. doi:10.1007/s11999–014–3855–8.
[44] Kildow BJ, Politzer CS, DiLallo M, Bolognesi MP, Seyler TM. Short and long–term postoperative complications following total joint arthroplasty in patients with human immunodeficiency virus, hepatitis B, or hepatitis C. J Arthroplasty. 2018;33:S86–S92 e1. doi:10.1016/j.arth.2017.10.061.
[45] Govender S, Harrison WJ, Lukhele M. Impact of HIV on bone and joint surgery. Best Pract Res Clin Rheumatol. 2008;22:605–619. doi:10.1016/j.berh.2008.05.002.
[46] Gilks CF, Walker AS, Munderi P, Kityo C, Reid A, Katabira E, et al. A single CD4 test with 250 cells/mm3 threshold predicts viral suppression in HIV–infected adults failing first–line therapy by clinical criteria. PLoS One. 2013;8. doi:10.1371/journal.pone.0057580.
[47] Abalo A, Patassi A, James YE, Walla A, Sangare A, Dossim A. Risk factors for surgical
wound infection in HIV–positive patients undergoing surgery for orthopaedic trauma. J Orthop Surg (Hong Kong). 2010;18:224–227. doi:10.1177/230949901001800218.
[48] Guild GN, Moore TJ, Barnes W, Hermann C. CD4 count is associated with postoperative infection in patients with orthopaedic trauma who are HIV positive. Clin Orthop Relat Res. 2012;470:1507–1512. doi:10.1007/s11999–011–2223–1.
[49] Bahebeck J, Eone DH, Nonga BN, Kingue TN, Sosso M. Implant orthopaedic surgery in HIV asymptomatic carriers: Management and early outcome. Injury. 2009;40:1147–1150. doi:10.1016/j.injury.2008.12.012.

[50] Horberg MA, Hurley LB, Klein DB, Follansbee SE, Quesenberry C, Flamm JA, et al. Surgical outcomes in human immunodeficiency virus–infected patients in the era of highly active antiretroviral therapy. Arch Surg. 2006;141:1238–1245. doi:10.1001/archsurg.141.12.1238.
[51] Aggarwal VK, Tischler EH, Lautenbach C, Williams GR, Abboud JA, Altena M, et al. Mitigation and education. J Arthroplasty. 2014;29:19–25. doi:10.1016/j.arth.2013.09.028.
[52] Santos ACO dos, Almeida AMR. Nutritional status and CD4 cell counts in patients with HIV/AIDS receiving antiretroviral therapy. Rev Soc Bras Med Trop. 2013;46:698–703. doi:10.1590/0037–8682–0125–2013.
[53] McCleery MA, Leach WJ, Norwood T. Rates of infection and revision in patients with renal disease undergoing total knee replacement in Scotland. J Bone Joint Surg Br. 2010;92:1535–1539. doi:10.1302/0301–620X.92B11.23870.

Authors: Susan Goodman, Bryan D. Springer, Jasvinder Singh, Adolph J. Yates

QUESTION 8: Do immunomodulatory disease-modifying medications (e.g., methotrexate or antitumor necrosis factor (anti-TNF) agents) need to be withheld preoperatively to reduce the risk for subsequent surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION:

For adults with inflammatory arthritis (rheumatoid arthritis (RA), psoriatic arthritis (PsA), adults with juvenile idiopathic arthritis (JA), ankylosing spondylitis (AS) or systemic lupus erythematosus (SLE)), all biologic anti-rheumatic medications including TNF inhibitors and IL-6 blockers (see Table 1 for complete list) should be withheld for a full dosing cycle prior to total hip (THA) and total knee arthroplasty (TKA), and the surgery should be timed to the week following the withheld dose. These medications can be restarted no less than two weeks after surgery if the wound is healing well, all sutures are out and there are no non-surgical site infections.

For adults with inflammatory arthritis or SLE, synthetic disease-modifying anti-rheumatic drugs (DMARDs; see Table 1), including methotrexate, can be continued through the perioperative period.

For adults with severe SLE, immunomodulatory medications (see Table 1) can be continued through the perioperative period.

For adults with mild SLE, immunomodulating medications (with the exception of tacrolimus) should be withheld prior to surgery and restarted at a minimum of 14 days after surgery if the wound is healing well and all sutures are out and there is no surgical site or non-surgical site infection.

For adults with RA, SLE, AS, PsA and JIA receiving glucocorticoids (GCs) for treatment of their rheumatic disease, who did not receive GCs during development and are not receiving replacement therapy, we recommend that the usual daily GC dose be given on the day of surgery rather than supra-physiologic ("stress dose") GCs.

LEVEL OF EVIDENCE: Limited, based on moderate to low-quality indirect evidence

DELEGATE VOTE: Agree: 87%, Disagree: 3%, Abstain: 10% (Super Majority, Strong Consensus)

RATIONALE

While arthroplasty provides important benefits for those with inflammatory arthritis and SLE, these patients are at increased risk of complications including infection [1–3]. To provide guidance, the American Association of Hip and Knee Surgeons (AAHKS) and the American College of Rheumatology (ACR) convened a panel of stakeholders including rheumatologists, orthopaedists, patients, infectious disease experts and methodologists. We systematically reviewed the relevant literature in Embase (1974 +), the Cochrane Library and PubMed (mid-1960s +) from January 1, 1980 through March 6, 2016 and synthesized the evidence, reaching consensus on the recommendations listed above, to balance the risk of infection against the risk of disease flare [4]. An additional literature search was conducted from March 1, 2016 through February 28, 2018 and additional relevant articles were added to this discussion.

For synthetic non-biologic DMARDs there is evidence from randomized controlled trials revealing no increase in infection when these medications are continued through the perioperative period. Although there are no surgical trials directly comparing infection and flare for biologic anti-rheumatic medications including TNF inhibitors and IL-6 blockers, there are numerous trials that demonstrate an increase in infection associated with these medications in non-surgical settings. Because patients with mild SLE can be carefully monitored after surgery and medications can be restarted for flares, we recommend withholding all immunomodulating medications at the time of surgery. For patients with severe or potentially life or organ-threatening SLE, perioperative complications may be linked to active disease, so we recommended continuing immunomodulating medications through surgery, in consultation with the patient's rheumatologist.

TABLE 1. Medications included in this guideline

DMARDs: CONTINUE these medications through surgery.	Dosing Interval	Continue/Withhold
Methotrexate	Weekly	Continue
Sulfasalazine	Once or twice daily	Continue

Hydroxychloroquine	Once or twice daily	Continue
Leflunomide (Arava)	Daily	Continue
Doxycycline	Daily	Continue
BIOLOGICS: STOP these medications prior to surgery and schedule surgery at the end of the dosing cycle. RESUME medications at minimum 14 days after surgery in the absence wound healing problems, surgical site infection or systemic infec tion.	**Dosing Interval**	**Schedule Surgery (relative to last biologic dose administered)**
Adalimumab (Humira) 40 mg	Every 2 weeks	Week 3
Etanercept (Enbrel) 50 mg or 25 mg	Weekly or twice weekly	Week 2
Golimumab (Simponi) 50 mg	Every 4 weeks (SQ) or Every 8 weeks (IV)	Week 5 Week 9
Infliximab (Remicade) 3 mg/kg	Every 4, 6 or 8 weeks	Week 5, 7 or 9
Abatacept (Orencia) weight-based 500 mg; IV 1000 mg; SQ 125 mg	Monthly (IV) or weekly (SQ)	Week 5 Week 2
Rituximab (Rituxan) 1000 mg	2 doses 2 weeks apart every 4-6 months	Month 7
Tocilizumab (Actemra) IV 4 mg/kg; SQ 162 mg	Every week (SQ) or Every 4 weeks (IV)	Week 3 Week 5
Anakinra (Kineret) SQ 100 mg	Daily	Day 2
Secukinumab (Cosentyx) 150 mg	Every 4 weeks	Week 5
Ustekinumab (Stelara) 45 mg	Every 12 weeks	Week 13
Belimumab (Benlysta) 10 mg/kg	Every 4 weeks	Week 5
Tofacitinib (Xeljanz) 5 mg: STOP this medication 7 days prior to surgery.	Daily or twice daily	7 days after last dose
SEVERE SLE-SPECIFIC MEDICATIONS: CONTINUE these medications in the perioperative period.	**Dosing Interval**	**Continue/Withhold**

Mycophenolate	Twice daily	Continue
Azathioprine	Daily or twice daily	Continue
Cyclosporine	Twice daily	Continue
Tacrolimus	Twice daily (IV and PO)	Continue
NOT-SEVERE SLE: DISCONTINUE these medications in the perioperative period.	**Dosing Interval**	**Continue/Withhold**
Mycophenolate	Twice daily	Withhold
Azathioprine	Daily or twice daily	Withhold
Cyclosporine	Twice daily	Withhold
Tacrolimus	Twice daily (IV and PO)	Continue
Dosing intervals obtained from prescribing information provided online by pharmaceutical companies. *2016 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Anti-rheumatic Medication in Patients with Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty		

IV, intravenous; SQ, subcutaneous; PO, oral
Reproduced with permission [4].

Tofacitinib is a unique oral immunomodulator that increases infection risk, so we recommended withholding tofacitinib for seven days prior to surgery. Immunocompromised status is linked to high-dose biologic therapy, so we based the period of drug withholding on the dose interval, to reflect the period of effective immunosuppression that is not reflected in the serum pharmacokinetic half-life. For example, rituximab has a serum half-life of 18 to 32 days, yet B-lymphocyte depletion may persist ≥ 6 months after an infusion. This suggests that the optimal time for surgery is at the end of the dosing cycle at the drug immunosuppressive nadir.

Glucocorticoids (GCs) are typically administered at supra-physiologic doses ("stress-dose corticosteroids") to patients receiving long-term GCs at the time of THA and TKA, despite the consistent association with increased infection, out of concern for hemodynamic instability. Based on randomized control trials as well as observational studies that do not demonstrate hypotension when usual dose GCs are administered, we recommended continuing the usual dose rather than "stress-dose corticosteroids." This recommendation applies only when the GCs are given for a rheumatic conditions and not to those who received GCs during development or those receiving GCs as replacement therapy for other medical conditions.

Since this publication, the background assumption of increased infection risk for patients with RA has been confirmed in a large registry-based THA/TKA cohort study of 3,913 patients with RA compared with 120,499 patients with osteoarthritis (OA) [5]. Patients with RA had an increased risk of PJI (subhazard ratio (SHR): 1.46, 95% confidence interval (CI) 1.13 to 1.88). Biologics were administered within 90 days of surgery in 345 of 1,946 patients but did not increase the risk of PJI (SHR: 1.61, CI 0.70 to 3.69). A second retrospective cohort study analyzed surgeries in 4,288 patients with inflammatory bowel disease and inflammatory arthritis on chronic infliximab who received an infusion within 6 months of THA and TKA [6]. Exploiting the precision of infusion billing records, they determined that infliximab when given within four weeks of surgery compared to infliximab given > six months prior to surgery did not increase the risk of serious infection within 30 days after surgery (odds ratio (OR): 0.90, CI 0.60 to 1.34) or PJI within one year (OR: 0.98, CI 0.52, 1.87). Glucocorticoid dose > 10 mg significantly increased the risk of 30 day infection (OR: 2.11, CI 1.30 to 3.40) and PJI (HR: 2.70, CI 1.30 to 5.60). In a retrospective case control study using data from a large commercial database, 55,861 patients with OA or RA undergoing arthroplasty were identified, including 1,127 infected TJA cases that were matched to 1,106 controls. RA patients were 47% more likely to have a postoperative infection than OA patients (OR: 1.47, CI 1.04 to 2.08). Use of perioperative immunosuppressive medications did not increase the risk (OR: 1.12, CI 0.84 to 1.50). Perioperative prednisone use was again found to be a significant risk factor for infection (OR: 1.59, CI 1.28 to 1.97) [7].

These observational studies indicate that addressing infection risk for rheumatic disease patients remains important, and support our recommendation to give the usual dose of GCs, not supraphysiologic doses, at the time of THA and TKA. While biologics were not a risk factor for infection after surgery, unmeasured confounders may play a role in observational studies. These studies provide further justification for needed research in the future.

REFERENCES

[1] Lin JA, Liao CC, Lee YJ, Wu CH, Huang WQ, Chen –L. Adverse outcomes after major surgery in patients with systemic lupus erythematosus: a nationwide population–based study. Ann Rheum Dis. 2014;73:1646–1651. doi:10.1136/annrheumdis–2012–202758.

[2] Ravi B, Croxford R, Hollands S, Paterson JM, Bogoch E, Kreder H, et al. Increased risk of complications following total joint arthroplasty in patients with rheumatoid arthritis. Arthritis Rheumatol (Hoboken, NJ). 2014;66:254–263. doi:10.1002/art.38231.

[3] Singh JA, Inacio MCS, Namba RS, Paxton EW. Rheumatoid arthritis is associated with higher ninety–day hospital readmission rates compared to osteoarthritis after hip or knee arthroplasty: a cohort study. Arthritis Care Res (Hoboken). 2015;67:718–724. doi:10.1002/acr.22497.

[4] Goodman SM, Springer B, Guyatt G, Abdel MP, Dasa V, George M, et al. 2017 American College of Rheumatology/American Association of Hip and Knee Surgeons guideline for the perioperative management of antirheumatic medication in patients with rheumatic diseases undergoing elective total hip or total knee arthroplasty. J Arthroplasty. 2017;32:2628–2638. doi:10.1016/j.arth.2017.05.001.

[5] Cordtz RL, Zobbe K, Højgaard P, Kristensen LE, Overgaard S, Odgaard A, et al. Predictors of revision, prosthetic joint infection and mortality following total hip or total knee arthroplasty in patients with rheumatoid arthritis: a nationwide cohort study using Danish healthcare registers. Ann Rheum Dis. 2018;77:281–288. doi:10.1136/annrheumdis–2017–212339.

[6] George MD, Baker JF, Hsu JY, Wu Q, Xie F, Chen L, et al. Perioperative timing of infliximab and the risk of serious infection after elective hip and knee arthroplasty. Arthritis Care Res (Hoboken). 2017;69:1845–1854. doi:10.1002/acr.23209.

[7] Salt E, Wiggins AT, Rayens MK, Morris BJ, Mannino D, Hoellein A, et al. Moderating effects of immunosuppressive medications and risk factors for post–operative joint infection following total joint arthroplasty in patients with rheumatoid arthritis or osteoarthritis. Semin Arthritis Rheum. 2017;46:423–429. doi:10.1016/j.semarthrit.2016.08.011.

Authors: Chi Xu, Yuhan Chang, Wadih Y. Matar, Daniel Varin, Jui Ping Chen

QUESTION 9: Does liver disease (hepatitis C, cirrhosis, etc.) predispose patients to surgical site infection/periprosthetic joint infection (SSI/PJI)? If so, what optimization should be undertaken prior to operating on patients with liver disease?

RECOMMENDATION: Yes. Patients with liver disease such as hepatitis or cirrhosis have a higher risk of infection. These patients are at increased risk of intraoperative and postoperative bleeding. All efforts should be made to ensure such complications are minimized.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 98%, Disagree: 1%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Hepatitis C virus (HCV) affects more than 185 million people worldwide, and approximately 80% of infected individuals progress to chronic infection, with 20% developing cirrhosis within 25 years [1–4]. As medical therapy continues to improve the life expectancy of patients with liver disease, there is an increasing demand for orthopaedic procedures in this population [5–8]. Earlier studies evaluating postoperative complications in this patient population were of small sample sizes and were not conclusive [6,9,10]. However, recent studies have predominantly demonstrated that, indeed, SSI and PJI occur at much higher rates among these patients [11].

PJIs can occur at a higher frequency among patients with liver cirrhosis compared with those without liver cirrhosis undergoing elective knee arthroplasty (2.7 vs. 0.8%), elective hip arthroplasty (3.66 vs. 0.69%) and hip fracture patients (6.30 vs. 1.10%), as shown by Jiang et al. by analyzing the data from the Nationwide Inpatient Sample and the State Inpatient Database. The study found that liver cirrhosis was an independent risk factor for PJI (odds ratio (OR): 2.4, confidence interval (CI) 1.87 to 3.12), as was a diagnosis of HCV without cirrhosis (OR: 2.3, CI 1.97 to 2.76) [5]. Another retrospective cohort study of primary total hip arthroplasty (THA) or total knee arthroplasty (TKA) patients within the Danish National Patient Registry also supported a higher rate of PJI within one year of surgery in patients with liver cirrhosis [12]. It is important to note that HCV itself may increase complication rates even in the absence of liver cirrhosis.

Pour et al. observed an increased rate of surgical complications, including PJI, in patients with non-cirrhotic HCV undergoing THA but not TKA [10]. The study by Issa et al. included 6,343 patients with HCV and 19,029 matched controls and demonstrated an increased rate of early postoperative surgical complications following THA or TKA in patients with chronic HCV [6]. The cohort also had a higher rate of 90-day complication and readmission [13]. Best et al. used the National Hospital Discharge Survey to compare 26,444 patients with HCV undergoing THA or TKA with a control cohort of 8,336,882 patients without HCV. They reported higher rates of PJI in patients with HCV undergoing total joint arthroplasty (TJA) (HCV: 0.84%, controls: 0.09%, OR: 9.5, CI 8.3 to 10.8) [14]. Studies by Cancienne et al. using the PearlDiver patient record database showed significant OR of 1.7 to 2.1 for infection in total knee, hip [15] and shoulder [16] arthroplasty at 3, 6 and 12 months after surgery. These 3 groups had respectively 15,383, 8,380 and 1,466 cases with HCV that were compared to, respectively 146,541, 48,440 and 21,502 matched control patients. Kildow et al. have demonstrated that by matching control group with age, gender and Charlson comorbidity index (CCI), patients with HCV had higher rates of complications in a 30-day, 90-day or two-year period after TJA [17].

In addition, hepatitis B virus has been recognized as an independent risk factor for PJI after total knee arthroplasty [18]. The risk of PJI at 90 days and two years after total hip and knee arthroplasty were also significantly increased [17]. As compared to control patients, those with liver cirrhosis have more blood loss, higher complications and higher mortality rates. Among cirrhosis patients, alcohol-related cirrhosis carried the highest rate of perioperative complications [19,20].

There are several different explanations for the higher PJI risk in liver cirrhosis patients. One explanation is that liver disease may impair platelet function and cause thrombocytopenia that increases the risk of intraoperative and postoperative bleeding [21–23]. HCV could suppress the immune system, damage the endothelial cells, and lead to severe medical and surgical complications [6,24,25]. Intraoperative blood loss and the need for concentrated red blood cell transfusions reduce the immunological condition of these patients even further. Moreover, the formation of a hematoma

around the surgical wound in the days following the intervention is yet another risk factor for developing a PJI. Also, patients with HCV may have beta-islet cell dysfunction and subsequently may develop diabetes mellitus that may result in an increased prevalence of wound complications and the potential for infection [21]. Also, another possible reason is that patients with liver disease had a decreased ability to activate the reticuloendothelial system, lymphoproliferation, neutrophil mobilization and phagocytic activity, all of which diminish their bactericidal activity and have been suggested as important contributing factors to this predisposition towards bacterial infection [16,26,27].

Orthopaedic surgeons should be increasingly aware of this association which should influence the shared decision-making process of performing TJA in patients with liver disease [12,20]. We believe that it is in these patients that preventative measures should be heightened against infection and that strict postoperative control should be followed to proceed aggressively if the infection is suspected. The hemostatic balance should be corrected before surgery according to established procedures such as vitamin K administration or concentrated plasma transfusions to avoid excessive bleeding or perhaps patients with advanced stage of disease should not subject to elective arthroplasty [28,29]. Also, the immune-compromised status of patients with liver disease should be more stringently monitored before surgery [26].

After correlating the seroprevalence rate and underdiagnosed rate, Cheng et al. have concluded that routine screening for HCV infection is not cost-effective [30]. The other study made the same conclusion by comparing the cost and the transmission rate of HCV through percutaneous contact with blood [31].

Given the presence of overwhelming evidence in the literature, we conclude that liver disease such as hepatitis or cirrhosis predisposes patients to SSI/PJI. The hemostatic balance and immune compromised status should be corrected before surgery in patients with liver disease. There are presently no proposed guidelines to better prepare patients with liver disease for orthopaedic surgery. Future research should address care optimization for these patients. Hepatitis will increase the rate of complication after elective arthroplasty. The advantage of operation and disadvantage of possible complications should be carefully evaluated and discussed with the patient.

REFERENCES

[1] Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age–specific antibody to HCV seroprevalence. Hepatology. 2013;57:1333–1342. doi:10.1002/hep.26141.

[2] Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage–specific fibrosis progression rates in chronic hepatitis C virus infection: a meta–analysis and meta–regression. Hepatology. 2008;48:418–431. doi:10.1002/hep.22375.

[3] World Health Organization. Hepatitis C. http://www.who.int/news–room/fact–sheets/detail/hepatitis–c. Accessed May 17, 2018.

[4] Centers for Disease Control Division of Viral Hepatitis. Hepatitis C: FAQs for the public. https://www.cdc.gov/hepatitis/hcv/cfaq.htm. Accessed May 17, 2018.

[5] Jiang SL, Schairer WW, Bozic KJ. Increased rates of periprosthetic joint infection in patients with cirrhosis undergoing total joint arthroplasty. Clin Orthop Relat Res. 2014;472:2483–2491. doi:10.1007/s11999–014–3593–y.

[6] Issa K, Boylan MR, Naziri Q, Perfetti DC, Maheshwari AV, Mont MA. The impact of hepatitis C on short–term outcomes of total joint arthroplasty. J Bone Joint Surg Am. 2015;97:1952–1957. doi:10.2106/JBJS.O.00183.

[7] Truntzer JN, Shah KN, Jenkins DR, Rubin LE. Total joint arthroplasty in patients with chronic infectious liver disease. Arthroplast Today. 2016;2:69–76. doi:10.1016/j.artd.2015.07.001.

[8] Calore BL, Cheung RC, Giori NJ. Prevalence of hepatitis C virus infection in the veteran population undergoing total joint arthroplasty. J Arthroplasty. 2012;27:1772–1776. doi:10.1016/j.arth.2012.05.016.

[9] Orozco F, Post ZD, Baxi O, Miller A, Ong A. Fibrosis in hepatitis C patients predicts complications after elective total joint arthroplasty. J Arthroplasty. 2014;29:7–10. doi:10.1016/j.arth.2013.03.023.

[10] Pour AE, Matar WY, Jafari SM, Purtill JJ, Austin MS, Parvizi J. Total joint arthroplasty in patients with hepatitis C. J Bone Joint Surg Am. 2011;93:1448–1454. doi:10.2106/JBJS.J.00219.

[11] Schwartz FH, Lange J. Factors that affect outcome following total joint arthroplasty: a review of the recent literature. Curr Rev Musculoskelet Med. 2017;10:346–355. doi:10.1007/s12178–017–9421–8.

[12] Deleuran T, Vilstrup H, Overgaard S, Jepsen P. Cirrhosis patients have increased risk of complications after hip or knee arthroplasty. Acta Orthop. 2015;86:108–113. doi:10.3109/17453674.2014.961397.

[13] Chowdhury R, Chaudhary MA, Sturgeon DJ, Jiang W, Yau AL, Koehlmoos TP, et al. The impact of hepatitis C virus infection on 90–day outcomes following major orthopaedic surgery: a propensity–matched analysis. Arch Orthop Trauma Surg. 2017;137:1181–1186. doi:10.1007/s00402–017–2742–7.

[14] Best MJ, Buller LT, Klika AK, Barsoum WK. Increase in perioperative complications following primary total hip and knee arthroplasty in patients with hepatitis C without cirrhosis. J Arthroplasty. 2015;30:663–668. doi:10.1016/j.arth.2014.11.013.

[15] Cancienne JM, Kandahari AM, Casp A, Novicoff W, Browne JA, Cui Q, et al. Complication rates after total hip and knee arthroplasty in patients with hepatitis C compared with matched control patients. J Am Acad Orthop Surg. 2017;25:e275–281. doi:10.5435/JAAOS–D–16–00920.

[16] Cancienne JM, Dempsey IJ, Holzgrefe RE, Brockmeier SF, Werner BC. Is hepatitis C infection associated with a higher risk of complications after total shoulder arthroplasty? Clin Orthop Relat Res. 2016;474:2664–2669. doi:10.1007/s11999–016–4979–9.

[17] Kildow BJ, Politzer CS, DiLallo M, Bolognesi MP, Seyler TM. Short and long–term postoperative complications following total joint arthroplasty in patients with human immunodeficiency virus, hepatitis B, or hepatitis C. J Arthroplasty. 2018;33:S86–S92. doi:10.1016/j.arth.2017.10.061.

[18] Kuo SJ, Huang PH, Chang CC, Kuo FC, Wu CT, Hsu HC, et al. Hepatitis B virus infection is a risk factor for periprosthetic joint infection among males after total knee arthroplasty: a Taiwanese nationwide population–based study. Medicine (Baltimore). 2016;95:e3806. doi:10.1097/MD.0000000000003806.

[19] Shih LY, Cheng CY, Chang CH, Hsu KY, Hsu RW, Shih HN. Total knee arthroplasty in patients with liver cirrhosis. J Bone Joint Surg Am. 2004;86–A:335–341.

[20] Newman JM, Schiltz NK, Mudd CD, Szubski CR, Klika AK, Barsoum WK. Impact of cirrhosis on resource use and inpatient complications in patients undergoing total knee and hip arthroplasty. J Arthroplasty. 2016;31:2395–2401. doi:10.1016/j.arth.2016.04.011.

[21] Mayo MJ. Extrahepatic manifestations of hepatitis C infection. Am J Med Sci. 2003;325:135–148.

[22] Olariu M, Olariu C, Olteanu D. Thrombocytopenia in chronic hepatitis C. J Gastrointestin Liver Dis. 2010;19:381–385.

[23] Cines DB, Liebman H, Stasi R. Pathobiology of secondary immune thrombocytopenia. Semin Hematol. 2009;46:S2–S14. doi:10.1053/j.seminhematol.2008.12.005.

[24] Fuster D, Sanvisens A, Bolao F, Rivas I, Tor J, Muga R. Alcohol use disorder and its impact on chronic hepatitis C virus and human immunodeficiency virus infections. World J Hepatol. 2016;8:1295–1308. doi:10.4254/wjh.v8.i31.1295.

[25] González–Reimers E, Quintero–Platt G, Martín–González C, Pérez–Hernández O, Romero–Acevedo L, Santolaria–Fernández F. Thrombin activation and liver inflammation in advanced hepatitis C virus infection. World J Gastroenterol. 2016;22:4427–4437. doi:10.3748/wjg.v22.i18.4427.

[26] Garcia–Tsao G, Wiest R. Gut microflora in the pathogenesis of the complications of cirrhosis. Best Pract Res Clin Gastroenterol. 2004;18:353–372. doi:10.1016/j.bpg.2003.10.005.

[27] Fiuza C, Salcedo M, Clemente G, Tellado JM. In vivo neutrophil dysfunction in cirrhotic patients with advanced liver disease. J Infect Dis. 2000;182:526–533. doi:10.1086/315742.

[28] Hsieh PH, Ueng SW, Lee MS, Shih HN, Huang KC. Prosthetic hip infection in patients with liver cirrhosis: an outcome analysis. Int J Infect Dis. 2010;14:e1054–1059. doi:10.1016/j.ijid.2010.06.018.

[29] Moon YW, Kim YS, Kwon SY, Kim SY, Lim SJ, Park YS. Perioperative risk of hip arthroplasty in patients with cirrhotic liver disease. J Korean Med Sci. 2007;22:223–226. doi:10.3346/jkms.2007.22.2.223.

[30] Cheng T, Zhang XL, Hu JJ, Li B, Wang Q. The role of routine screening in blood–borne pathogens in Chinese patients undergoing joint arthroplasty. Bone Joint Res. 2017;6:566–571. doi:10.1302/2046–3758.69.BJR–2017–0066.R2.
[31] Winkelmann M, Sorrentino JN, Klein M, Macke C, Mommsen P, Brand S, et al. Is there a benefit for health care workers in testing HIV, HCV and HBV in routine before elective arthroplasty? Orthop Traumatol Surg Res. 2016;102:513–516. doi:10.1016/j.otsr.2016.02.012.

Authors: Efrain Diaz-Borjon, Navin Fernando, Kerri Bell, Ruben Alejandro Morales Maldonado

QUESTION 10: Is there a link between opioid consumption and an increased risk for surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Yes. The utilization of opioids prior to surgery has been associated with an increased risk of developing SSIs/PJIs.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 71%, Disagree: 17%, Abstain: 12% (Super Majority, Strong Consensus)

RATIONALE

In both in vitro studies and in animal models, opioids have been shown to have immunosuppressive effects, modulating both the adaptive and innate immune systems [1–6]. Opioids have been implicated in the development of various infections including human immunodeficiency virus (HIV), hepatitis C virus (HCV) and opportunistic bacterial infections [4,5,7,8].

Despite the increased interest in opioid research, few studies within the arthroplasty literature have examined the effect of preoperative opioid consumption and the subsequent development of infection. With respect to surgical site infections, Menendez et al. found that preoperative opioid utilization was associated with higher patient morbidity, including an increased risk of surgical site infections [9]. For PJI, Cancienne et al. found in a national database review that preoperative narcotic use was associated with a higher risk of PJI within one year [10]. Similarly, Bell et al. reported in a retrospective case-control study that preoperative opioid usage was independently associated with an increased risk of PJI within two years [11]. Furthermore, preoperative opioid usage has been implicated as a risk factor for early revision surgery [12–14]. Neither of the two database surveys in the literature, however, performed further sub-analyses on type of revision. Therefore, the relationship between preoperative opioids and septic revisions remains unknown.

In conclusion, limited evidence exists to support the role of opioids as a risk factor for development of SSI/PJI. Given the scope of the danger posed by these medications, there is a need for further studies to develop more concrete recommendations for potential risk factor modification.

REFERENCES

[1] Sacerdote P. Opioids and the immune system. Palliat Med. 2006;20:9–15. doi:10.1191/0269216306pm1124oa.
[2] Egydio F, Ruiz FS, Tomimori J, Tufik S, Andersen ML. Can morphine interfere in the healing process during chronic stress? Arch Dermatol Res. 2012;304:413–420. doi:10.1007/s00403–012–1261–1.
[3] Liang X, Liu R, Chen C, Ji F, Li T. Opioid system modulates the immune function: a review. Transl Perioper Pain Med. 2016;1:5–13.
[4] Wang X, Zhang T, Ho W–Z. Opioids and HIV/HCV Infection. J Neuroimmune Pharmacol. 2011;6:477–489. doi:10.1007/s11481–011–9296–1.
[5] Roy S, Ninkovic J, Banerjee S, Charboneau RG, Das S, Dutta R, et al. Opioid drug abuse and modulation of immune function: consequences in the susceptibility to opportunistic infections. J Neuroimmune Pharmacol. 2011;6:442–465. doi:10.1007/s11481–011–9292–5.
[6] Breslow JM, Monroy MA, Daly JM, Meissler JJ, Gaughan J, Adler MW, et al. Morphine, but not trauma, sensitizes to systemic acinetobacter baumannii infection. J Neuroimmune Pharmacol. 2011;6:551–565. doi:10.1007/s11481–011–9303–6.
[7] Mora AL, Salazar M, Pablo–Caeiro J, Frost CP, Yadav Y, DuPont HL, et al. Moderate to high use of opioid analgesics are associated with an increased risk of clostridium difficile infection. Am J Med Sci. 2012;343:277–280. doi:10.1097/MAJ.0b013e31822f42eb.
[8] Schwacha MG, McGwin G, Hutchinson CB, Cross JM, MacLennan PA, Rue LW. The contribution of opiate analgesics to the development of infectious complications in burn patients. Am J Surg. 2006;192:82–86. doi:10.1016/j.amjsurg.2006.01.001.
[9] Menendez ME, Ring D, Bateman BT. Preoperative opioid misuse is associated with increased morbidity and mortality after elective orthopaedic surgery. Clin Orthop Relat Res. 2015;473:2402–2412. doi:10.1007/s11999–015–4173–5.
[10] Cancienne JM, Patel KJ, Browne JA, Werner BC. Narcotic use and total knee arthroplasty. J Arthroplasty. 2018;33:113–118. doi:10.1016/j.arth.2017.08.006.
[11] Bell K, Shohat N, Goswami K, Tan T, Kalbian I, Parvizi J. Preoperative opioids increases the risk of periprosthetic joint infection after total joint arthroplasty. J Arthroplasty. 2018 Oct;33:3246-3251.
[12] Bedard NA, DeMik DE, Dowdle SB, Owens JM, Liu SS, Callaghan JJ. Does preoperative opioid use increase the risk of early revision total hip arthroplasty? J Arthroplasty. 2018;33:S154–S156. doi:10.1016/j.arth.2018.01.018.
[13] Ben–Ari A, Chansky H, Rozet I. Preoperative opioid use is associated with early revision after total knee arthroplasty: a study of male patients treated in the Veterans Affairs system. J Bone Joint Surg Am. 2017;99:1–9. doi:10.2106/JBJS.16.00167.
[14] Starr J, Rozet I, Ben–Ari A. A risk calculator using preoperative opioids for prediction of total knee revision arthroplasty. Clin J Pain. 2018;34:328–331. doi:10.1097/AJP.0000000000000544.

Authors: Alexander Rondon, Samuel Wellman, Camila Novaes de Santana

QUESTION 11: Does the presence of anxiety/depression and mood disorders increase the risk of surgical site infections/periprosthetic joint infections (SSIs/PJIs)? If so, what are the considerations that should be implemented to reduce the risk of SSIs/PJIs?

RECOMMENDATION: There is emerging evidence to suggest that affective disorders, such as depression and anxiety, increase the risk for PJIs. Although both physiological and psychological explanations for this association have been offered, it is not clear whether modulating or treating these disorders prior to surgery results in a reduction in the risk of PJIs.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 88%, Disagree: 4%, Abstain: 8% (Super Majority, Strong Consensus)

RATIONALE

Recent studies suggest that affective disorders, such as depression and anxiety, can increase the risk for SSIs/PJIs [1]. There are both physiological and psychological reasons for this association. Depression has been shown to stimulate production of pro-inflammatory cytokines, such as IL-6, as well as promote the down-regulation of the cellular immune response (natural killer cell activation and T-helper cell replication) [2,3]. Promotion of IL-6 stimulates the secretion of corticotrophin-releasing hormone (CRH), which increases the production of plasma adrenocorticotropic hormone (ACTH) and cortisol, and thus inhibits certain aspects of the immune response [2,4]. Patients with depression and anxiety disorders are also likely to suffer self-neglect, that places them at higher risk of SSI/PJI [5,6]. Patients with affective disorders are likely to be smokers, suffer from malnutrition and consequently can be anemic, consume alcohol or live in social isolation, all of which places them at higher risk of SSIs/PJIs [7–12].

While the link between depression and PJI still warrants investigation, depression has been shown to be an independent risk factor for PJI following primary TJA in several national registry studies [13–16]. Browne et al. reported the incidence of depression in the arthroplasty population to be 10.0% [14]. This same study found depression to be associated with greater risk of postoperative infection (odds ratio (OR): 1.33) [14]. A case-control retrospective study by Bozic et al. found depression to be independently associated with an increased risk of PJI in total hip arthroplasty patients (hazard ratio (HR): 1.28) [17]. Similarly, another single center retrospective study of primary total hip arthroplasty (THA) found depression to be significantly related to PJI [18]. Furthermore, a systematic review and meta-analysis of 66 observational studies (23 prospective, 43 retrospective) pooled variably adjusted relative risks demonstrated depression produced a significantly increased risk of PJI (RR: 1.48, 95% CI 1.13 to 1.95) after total knee arthroplasty (TKA) or THA [19].

Other mental health disorders, such as bipolar disorder and schizophrenia, have also demonstrated an association with PJI. Kheir et al. demonstrated patients with psychosis and depression had increased odds of developing PJI at 90 days (OR: 3.334, $p = 0.049$), two years (OR: 3.94, $p = 0.004$) and at any time point (OR: 4.32, $p = 0.002$) [20]. Furthermore, Klement et al. demonstrated that patients with any psychiatric illness (bipolar disorder, depression and schizophrenia) undergoing elective primary TKA and primary THA, were at increased risk for PJI (TKA OR: 2.17, $p < 0.001$, THA OR: 2.26, $p < 0.001$) [15,16].

While there is substantial evidence that depression is an independent risk factor for PJI, there is limited evidence that controlling or treating depression results in a reduction or normalization of the PJI risk. A recent retrospective study of over 20,000 arthroplasty patients by Yao et al. demonstrated no association between the use of perioperative antidepressants and increased risk of revision or PJI; however, selective serotonin reuptake inhibitor (SSRI) users did experience lower risk of all-cause revision and aseptic revisions [21]. A retrospective study of 140 patients undergoing anterior cervical discectomy and fusion found similar self-reported surgical outcomes in patients pretreated with antidepressants for at least six months prior to surgery compared to the control group that had no prior history of depression [22]. However, future prospective interventional studies investigating the influence of depression treatment modalities on PJI risk in arthroplasty patients are warranted.

REFERENCES

[1] Eka A, Chen AF. Patient–related medical risk factors for periprosthetic joint infection of the hip and knee. Ann Transl Med. 2015;3:233. doi:10.3978/j.issn.2305–5839.2015.09.26.

[2] Kiecolt–Glaser JK, Glaser R. Depression and immune function: central pathways to morbidity and mortality. J Psychosom Res. 2002;53:873–876.

[3] Leonard BE. The immune system, depression and the action of antidepressants. Prog Neuropsychopharmacol Biol Psychiatry. 2001;25:767–780.

[4] Rezapoor M, Parvizi J. Prevention of periprosthetic joint infection. J Arthroplasty. 2015;30:902–907. doi:10.1016/j.arth.2015.02.044.

[5] DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta–analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med. 2000;160:2101–2107.

[6] Lysaker PH, Dimaggio G, Buck KD, Callaway SS, Salvatore G, Carcione A, et al. Poor insight in schizophrenia: links between different forms of metacognition with awareness of symptoms, treatment need, and consequences of illness. Compr Psychiatry. 2011;52:253–260. doi:10.1016/j.comppsych.2010.07.007.

[7] Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, et al. Prevalence and co–occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry. 2004;61:807–816. doi:10.1001/archpsyc.61.8.807.

[8] Conway KP, Compton W, Stinson FS, Grant BF. Lifetime comorbidity of DSM–IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2006;67:247–257.

[9] Pratt LA, Brody DJ. Depression and smoking in the U.S. household population aged 20 and over, 2005–2008. NCHS Data Brief. 2010:1–8.

[10] Hawton A, Green C, Dickens AP, Richards SH, Taylor RS, Edwards R, et al. The impact of social isolation on the health status and health–related quality of life of older people. Qual Life Res. 2011;20:57–67. doi:10.1007/s11136–010–9717–2.

[11] Smoliner C, Norman K, Wagner KH, Hartig W, Lochs H, Pirlich M. Malnutrition and depression in the institutionalised elderly. Br J Nutr. 2009;102:1663–1667. doi:10.1017/S0007114509990900.

[12] Stewart R, Hirani V. Relationship between depressive symptoms, anemia, and iron status in older residents from a national survey population. Psychosom Med. 2012;74:208–213. doi:10.1097/PSY.0b013e3182414f7d.

[13] Bozic KJ, Lau E, Kurtz S, Ong K, Berry DJ. Patient–related risk factors for postoperative mortality and periprosthetic joint infection in medicare patients undergoing TKA. Clin Orthop Relat Res. 2012;470:130–137. doi:10.1007/s11999–011–2043–3.

[14] Browne JA, Sandberg BF, D'Apuzzo MR, Novicoff WM. Depression is associated with early postoperative outcomes following total joint arthroplasty: a nationwide database study. J Arthroplasty. 2014;29:481–483. doi:10.1016/j.arth.2013.08.025.
[15] Klement MR, Nickel BT, Penrose CT, Bala A, Green CL, Wellman SS, et al. Psychiatric disorders increase complication rate after primary total knee arthroplasty. Knee. 2016;23:883–886. doi:10.1016/j.knee.2016.05.007.
[16] Klement MR, Bala A, Blizzard DJ, Wellman SS, Bolognesi MP, Seyler TM. Should we think twice about psychiatric disease in total hip arthroplasty? J Arthroplasty. 2016;31:221–226. doi:10.1016/j.arth.2016.01.063.
[17] Bozic KJ, Ward DT, Lau EC, Chan V, Wetters NG, Naziri Q, et al. Risk factors for periprosthetic joint infection following primary total hip arthroplasty: a case control study. J Arthroplasty. 2014;29:154–6. doi:10.1016/j.arth.2013.04.015.
[18] Radtke K, Tetzlaff T, Vaske B, Ettinger M, Claaßen L, Flörkemeier T, et al. Arthroplasty–center related retrospective analysis of risk factors for periprosthetic joint infection after primary and after revision total hip arthroplasty. Technol Health Care. 2016;24:721–728. doi:10.3233/THC–161158.
[19] Kunutsor SK, Whitehouse MR, Blom AW, Beswick AD, INFORM Team. patient–related risk factors for periprosthetic joint infection after total joint arthroplasty: a systematic review and meta–analysis. PLoS One. 2016;11:e0150866. doi:10.1371/journal.pone.0150866.
[20] Kheir MM, Kheir YN, Tan TL, Ackerman CT, Rondon AJ, Chen AF. Increased complications for schizophrenia and bipolar disorder patients undergoing total joint arthroplasty. J Arthroplasty. 2018;33:1462–1466. doi:10.1016/j.arth.2017.12.006.
[21] Yao JJ, Maradit Kremers H, Kremers WK, Lewallen DG, Berry DJ. Perioperative inpatient use of selective serotonin reuptake inhibitors is associated with a reduced risk of THA and TKA revision. Clin Orthop Relat Res. 2018;476:1191–1197. doi:10.1007/s11999.0000000000000098.
[22] Elsamadicy AA, Adogwa O, Cheng J, Bagley C. Pretreatment of depression before cervical spine surgery improves patients' perception of postoperative health status: a retrospective, single institutional experience. World Neurosurg. 2016;87:214–219. doi:10.1016/j.wneu.2015.11.067.

Authors: Andrew Battenberg, Kier Blevins

QUESTION 12: Does vitamin D deficiency (VDD) increase the risk of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs) in patients undergoing orthopaedic procedures?

RECOMMENDATION: Unknown. VDD may increase the risk of subsequent SSIs and/or PJIs in patients undergoing orthopaedic procedures by diminishing vitamin D-mediated innate and adaptive immune responses.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 82%, Disagree: 5%, Abstain: 13% (Super Majority, Strong Consensus)

RATIONALE

The exact mechanism of how vitamin D affects immune function is unknown. Numerous studies have demonstrated its regulation of both the innate and adaptive immune responses [1–6]. Vitamin D has been shown to activate the innate immune system to kill bacteria through intracrine regulation of monocytes, as well as by modulating production of anti-microbial peptides (AMPs) and cytokines [1,2]. Vitamin D activates the adaptive immune response through paracrine regulation in dendritic cells, T cells and B cells [1].

Clinical evidence of VDD and risk of SSI/PJI in the orthopaedic literature is limited. In a prospective study, measuring serum 25-hydroxyvitamin D levels, VDD was found in 64% of patients presenting for primary total joint arthroplasty (TJA), 52% of patients presenting with aseptic loosening, and 86% of patients presenting with PJI – a statistically significant difference for PJI compared to the other groups [7]. A retrospective case-control study of revision TJAs had similar findings, with PJI patients being more likely to have VDD than patients being revised for aseptic indications (72.7 vs.48.4%, respectively) [8]. Additionally, prevalence of VDD was 55% in the revision TJA population compared with 39% in the primary TJA population. Importantly, when controlling for other nutritional parameters such as albumin and transferrin, VDD remained predictive of PJI as the reason for revision surgery [8].

To date, there are no clinical studies on the effect of vitamin D supplementation and the risk for SSI/PJI. In a PJI mouse model, VDD mice were shown to have an increased bacterial burden when compared to VDD mice that received "rescue" vitamin D supplementation [9]. Bacterial burden was similarly decreased between normal mice and the VDD "rescue" mice receiving supplementation.

VDD is common, with rates reported to be 42% in adults in the United States, and 24 to 65% in TJA patients [10–14]. As a potential modifiable risk factor for SSI and PJI, VDD is an important area for future study.

REFERENCES

[1] Hewison M. Vitamin D and innate and adaptive immunity. Vitam Horm. 2011;86:23–62. doi:10.1016/B978–0–12–386960–9.00002–2.
[2] Youssef DA, Miller CW, El–Abbassi AM, Cutchins DC, Cutchins C, Grant WB, et al. Antimicrobial implications of vitamin D. Dermatoendocrinol. 2011;3:220–229. doi:10.4161/derm.3.4.15027.
[3] Fabri M, Stenger S, Shin DM, Yuk JM, Liu PT, Realegeno S, et al. Vitamin D is required for IFN–gamma–mediated antimicrobial activity of human macrophages. Sci Transl Med. 2011;3:104ra102. doi:10.1126/scitranslmed.3003045.
[4] Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. Toll–like receptor triggering of a vitamin D–mediated human antimicrobial response. Science. 2006;311:1770–1773. doi:10.1126/science.1123933.
[5] van Etten E, Decallonne B, Bouillon R, Mathieu C. NOD bone marrow–derived dendritic cells are modulated by analogs of 1,25–dihydroxyvitamin D3. J Steroid Biochem Mol Biol. 2004;89–90:457–459. doi:10.1016/j.jsbmb.2004.03.017.
[6] van Etten E, Mathieu C. Immunoregulation by 1,25–dihydroxyvitamin D3: basic concepts. J Steroid Biochem Mol Biol. 2005;97:93–101. doi:10.1016/j.jsbmb.2005.06.002.
[7] Maier GS, Horas K, Seeger JB, Roth KE, Kurth AA, Maus U. Is there an association between periprosthetic joint infection and low vitamin D levels? Int Orthop. 2014;38:1499–1504. doi:10.1007/s00264–014–2338–6.
[8] Traven SA, Chiaramonti AM, Barfield WR, Kirkland PA, Demos HA, Schutte HD, et al. Fewer complications following revision hip and knee arthroplasty in patients with normal vitamin D levels. J Arthroplasty. 2017;32:S193–S196. doi:10.1016/j.arth.2017.02.038.

[9] Hegde V, Dworsky EM, Stavrakis AI, Loftin AH, Zoller SD, Park HY, et al. Single–dose, preoperative vitamin–D supplementation decreases infection in a mouse model of periprosthetic joint infection. J Bone Joint Surg Am. 2017;99:1737–1744. doi:10.2106/JBJS.16.01598.
[10] Forrest KYZ, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. Nutr Res. 2011;31:48–54. doi:10.1016/j.nutres.2010.12.001.
[11] Nawabi DH, Chin KF, Keen RW, Haddad FS. Vitamin D deficiency in patients with osteoarthritis undergoing total hip replacement: a cause for concern? J Bone Joint Surg Br. 2010;92:496–499. doi:10.1302/0301–620X.92B3.23535.
[12] Jansen JA, Haddad FS. High prevalence of vitamin D deficiency in elderly patients with advanced osteoarthritis scheduled for total knee replacement associated with poorer preoperative functional state. Ann R Coll Surg Engl. 2013;95:569–572. doi:10.1308/rcsann.2013.95.8.569.
[13] Lavernia CJ, Villa JM, Iacobelli DA, Rossi MD. Vitamin D insufficiency in patients with THA: prevalence and effects on outcome. Clin Orthop Relat Res. 2014;472:681–686. doi:10.1007/s11999–013–3172–7.
[14] Naylor B, King A, Voges S, Blackwell T, Huff R, Schutte H. Exploration of serum 25–hydroxy vitamin D in total joint arthroplasty within a subtropical climate. Reconstr Rev. 2017;7. doi:10.15438/rr.7.3.186.

Authors: Riaz Khan, Vasili Karas, Jonathan Coward

QUESTION 13: Is preoperative anemia a risk factor for surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Based on available evidence, preoperative anemia, as defined by a hemoglobin of less than 13.0 g/dl in men and 12.0 g/dl in women, is an independent risk factor for postoperative SSI/PJI following total joint arthroplasty (TJA).

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 89%, Disagree: 8%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Anemia is a common condition that is estimated to manifest in 21 to 35% of patients who present for primary TJA [1,2]. Anemia often presents as part of a spectrum of comorbidities and is difficult to study in isolation. However, recent literature demonstrates a link between postoperative complications and preoperative anemia in several published studies [3–13]. The majority of the orthopaedic literature focuses on TJA with one study investigating preoperative anemia in relation to total ankle arthroplasty (TAA) [14].

One of the most devastating complications following TJA is that of PJI or SSI and as the number of arthroplasties performed annually continues to increase, prevention will be paramount. Although rare, this devastating complication represents an increase in morbidity and mortality as well as a important economic burden [4,13,15]. Several documented patient-related risk factors exist for increased incidence of PJI including rheumatological disease, diabetes and obesity [4,16]. In some instances, preoperative optimization of these chronic diagnoses can lead to favorable risk modification preoperatively [16]. Preoperative anemia, most commonly defined by the World Health Organization (WHO) by a hemoglobin value of less than 13.0 g/dL in men and 12.0 g/dL in women, is one such risk factor that has been evaluated and found to be an independent predictor of postoperative complications including PJI [2,4,5,10,11,17,18].

A compelling study to this end is a retrospectively collected, case-controlled study that demonstrates patients who have preoperative hemoglobin values of less than 13.0 g/dl in men and 12.0 g/dl in women had a higher overall rate of complications (odds ratio (OR): 2.11) than their matched counterparts [11]. The cohort consisted of 2,576 (19%) patients who had anemia matched to 10,987 patients with lab values within normal limits. After controlling for other significant comorbidities, the rate of overall complications for the anemic cohort was 33.2% as compared to 15.4% in the non-anemic cohort. Pertinent to the present discussion, the rate of infection was 4.5% in the anemic patients compared to 1.12% in the non-anemic patients (OR: 2.83, 95% confidence interval (CI) 1.78 to 4.51; $p < 0.0001$) [11].

A pair of level II studies by Bozic et al., based on administrative data within a Medicare population, revealed an Adjusted Hazard Ratio for anemia in TJA to be 1.36 and 1.26 respectively ($p = 0.0347$ and $p = 0.0014$) [17,18]. In a level III study specifically investigating the relationship between preoperative anemia and PJI, Greenky et al. reported that anemia was independently associated with an adjusted odds ratio of 1.95 (1.38 to 2.56) for the risk of PJI postoperatively [5].

Swenson et al. reviewed an institutional series of patients with confirmed PJI and demonstrated that preoperative anemia in this setting leads to decreased success of open debridement and polyethylene exchange [10]. They demonstrated an odds ratio of 6.7 (CI 2.2 to 22.4, $p = 0.0013$) of failure in patients with preoperative anemia. Failure, they found, was exacerbated by a combination of infection with *Staphylococcus* species and preoperative anemia as patients that underwent irrigation and debridement absent these two factors had a 97.1% success rate as defined by maintenance of a well-fixed implant without the need for additional surgery or lifelong oral antibiotics [10].

The present data suggests with moderate certainty that patients with preoperative anemia are more likely to suffer from a periprosthetic joint infection postoperatively than those who undergo surgery and are not anemic. Although studies that draw this conclusion are few, they independently corroborate this conclusion in both large cohort administrative-based data and institutional registries. Although adjusted odds ratios from these studies vary (1.26 to 2.11), all demonstrate that a hemoglobin value below 13.0 g/dl in men and 12.0 g/dl in women is an independent risk factor for PJI [5,10,11,15,17,18].

It also remains unclear if the presence of preoperative anemia itself, regardless of management, is a risk factor or indeed if it is the treatment for anemia with allogeneic blood transfusion which conveys a risk. Preoperative anemia is also the greatest predictor of the need for blood transfusion even in the setting of routine tranexamic acid use [19–21] and allogeneic blood transfusion has been independently correlated to SSI/PJI [7,22,23]. Further research is needed into this area, preferably with robust, large scale, multi-centered trials.

REFERENCES

[1] Bierbaum BE, Callaghan JJ, Galante JO, Rubash HE, Tooms RE, Welch RB. An analysis of blood management in patients having a total hip or knee arthroplasty. J Bone Joint Surg Am. 1999;81:2–10.
[2] Goodnough LT, Vizmeg K, Sobecks R, Schwarz A, Soegiarso W. Prevalence and classification of anemia in elective orthopedic surgery patients: implications for blood conservation programs. Vox Sang. 1992;63:90–95.
[3] Cuenca J, Garcia–Erce JA, Martinez F, Cardona R, Perez–Serrano L, Munoz M. Preoperative haematinics and transfusion protocol reduce the need for transfusion after total knee replacement. Int J Surg. 2007;5:89–94.
[4] Eka A, Chen AF. Patient–related medical risk factors for periprosthetic joint infection of the hip and knee. Ann Transl Med. 2015;3:233.
[5] Greenky M, Gandhi K, Pulido L, Restrepo C, Parvizi J. Preoperative anemia in total joint arthroplasty: is it associated with periprosthetic joint infection? Clin Orthop Relat Res. 2012;470:2695–2701.
[6] Guinn NR, Guercio JR, Hopkins TJ, Grimsley A, Kurian DJ, Jimenez MI, et al. How do we develop and implement a preoperative anemia clinic designed to improve perioperative outcomes and reduce cost? Transfusion. 2016;56:297–303.
[7] Hart A, Khalil JA, Carli A, Huk O, Zukor D, Antoniou J. Blood transfusion in primary total hip and knee arthroplasty. Incidence, risk factors, and thirty–day complication rates. J Bone Joint Surg Am. 2014;96:1945–1951.
[8] Lu M, Sing DC, Kuo AC, Hansen EN. Preoperative anemia independently predicts 30–day complications after aseptic and septic revision total joint arthroplasty. J Arthroplasty. 2017;32:S197–S201.
[9] Munoz M, Acheson AG, Auerbach M, Besser M, Habler O, Kehlet H, et al. International consensus statement on the peri–operative management of anaemia and iron deficiency. Anaesthesia. 2017;72:233–247.
[10] Swenson RD, Butterfield JA, Irwin TJ, Zurlo JJ, Davis CM 3rd. preoperative anemia is associated with failure of open debridement polyethylene exchange in acute and acute hematogenous prosthetic joint infection. J Arthroplasty. 2018;33:1855–1860.
[11] Viola J, Gomez MM, Restrepo C, Maltenfort MG, Parvizi J. Preoperative anemia increases postoperative complications and mortality following total joint arthroplasty. J Arthroplasty. 2015;30:846–848.
[12] Zhang S, Huang Q, Xu B, Ma J, Cao G, Pei F. Effectiveness and safety of an optimized blood management program in total hip and knee arthroplasty: a large, single–center, retrospective study. Medicine (Baltimore). 2018;97:e9429.
[13] Zmistowski B, Karam JA, Durinka JB, Casper DS, Parvizi J. Periprosthetic joint infection increases the risk of one–year mortality. J Bone Joint Surg Am. 2013;95:2177–2184.
[14] Althoff A, Cancienne JM, Cooper MT, Werner BC. Patient–related risk factors for periprosthetic ankle joint infection: an analysis of 6977 total ankle arthroplasties. J Foot Ankle Surg. 2018;57:269–272.
[15] Kurtz SM, Lau E, Watson H, Schmier JK, Parvizi J. Economic burden of periprosthetic joint infection in the United States. J Arthroplasty. 2012;27:61–65.e1.
[16] Baek SH. Identification and preoperative optimization of risk factors to prevent periprosthetic joint infection. World J Orthop. 2014;5:362–367.
[17] Bozic KJ, Lau E, Kurtz S, Ong K, Berry DJ. Patient–related risk factors for postoperative mortality and periprosthetic joint infection in medicare patients undergoing TKA. Clin Orthop Relat Res. 2012;470:130–137.
[18] Bozic KJ, Lau E, Kurtz S, Ong K, Rubash H, Vail TP, et al. Patient–related risk factors for periprosthetic joint infection and postoperative mortality following total hip arthroplasty in Medicare patients. J Bone Joint Surg Am. 2012;94:794–800.
[19] Klement MR, Peres–Da–Silva A, Nickel BT, Green CL, Wellman SS, Attarian DE, et al. What should define preoperative anemia in primary THA? Clin Orthop Relat Res. 2017;475:2683–2691.
[20] Maempel JF, Wickramasinghe NR, Clement ND, Brenkel IJ, Walmsley PJ. The pre–operative levels of haemoglobin in the blood can be used to predict the risk of allogenic blood transfusion after total knee arthroplasty. Bone Joint J. 2016;98–b:490–497.
[21] Yeh JZ, Chen JY, Bin Abd Razak HR, Loh BH, Hao Y, Yew AK, et al. Preoperative haemoglobin cut–off values for the prediction of post–operative transfusion in total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc. 2016;24:3293–3298.
[22] Browne JA, Adib F, Brown TE, Novicoff WM. Transfusion rates are increasing following total hip arthroplasty: risk factors and outcomes. J Arthroplasty. 2013;28:34–37.
[23] Everhart JS, Sojka JH, Mayerson JL, Glassman AH, Scharschmidt TJ. Perioperative allogeneic red blood–cell transfusion associated with surgical site infection after total hip and knee arthroplasty. J Bone Joint Surg Am. 2018;100:288–294.

Authors: Riaz Khan, Vasili Karas, Jonathan Coward

QUESTION 14: What preoperative optimization for anemia can be done to increase the hemoglobin concentration?

RECOMMENDATION: Literature suggests that the administration of iron and/or erythropoietin (EPO) increases preoperative hemoglobin concentration and decreases the need for postoperative allogeneic blood transfusion. However, iron may only be effective for patients with pre-existing iron deficiencies and is associated with many side effects. Given the high costs of EPO, it's preoperative administration to avoid transfusion alone has not been found to be cost effective. Further research is required to assess the risks and benefits of preoperative allogeneic blood transfusion.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 3%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

The current literature presents several strategies to increase preoperative hemoglobin including iron supplementation, human recombinant (EPO) injection and preoperative blood transfusion.

Recommended initial management is correction of any deficiencies (such as iron, folate, ferritin, B12, etc.). If patients are noted to be iron deficient, the hemoglobin level can be raised with iron alone, either intravenous (IV) or oral [1]. Oral iron is cheap but takes two to three months to work [2]. Oral iron formulations are also associated with a high gastrointestinal (GI) side effect profile. A 2015 systematic review and meta-analysis examined 43 randomized controlled trials (RCTs) comparing oral iron vs. IV formulations or placebos and found more GI side effects with oral vs. IV formulations (odds ratio (OR): 3.05), and oral vs. placebo (OR: 2.32). This increase in GI side effects in turn reduces compliance with treatment [3]. Intravenous iron is more expensive but may increase hemoglobin levels in two to four weeks depending on the pre-treatment hemoglobin level and the degree of iron deficiency.

Side effects are few and generally mild, but rare cases of anaphylaxis are seen as documented by a systematic review which noted 8 cases out of 2,186 infusions [4].

The use of preoperative iron supplementation to raise preoperative hemoglobin for all patients, regardless of iron status, is a more controversial intervention. This is due to conflicting literature, side effects of treatment and ambiguity as to the length of treatment needed to achieve a demonstrable perioperative hemoglobin improvement. Cuenca et al. demonstrated that the use of preoperative iron supplementation, vitamin C and folate for 30 to 45 days before surgery resulted in lower transfusion rate in primary total knee arthroplasty (TKA) patients (5.8 vs. 32%) without existing hematological deficiencies [5]. A further study by Cuenca et al. from 2004 investigated the use of IV iron given on admission and prior to surgery for patients with femoral neck fractures, again without hematological deficiencies, vs. a control group. They concluded that IV iron resulted in a lower transfusion rate postoperatively [6]. However, a study by Lachance et al. refutes this point and showed no difference in the postoperative transfusion rates of total joint arthroplasty (TJA) patients who participated in iron supplementation for three weeks prior to surgery [7]. In addition, iron supplementation was again associated with high levels of side effects including constipation (33%), heartburn (13.8%) and abdominal pain (12.6%) [7]. One limitation of these studies is that none mention improvements of preoperative hemoglobin levels.

The preoperative administration of EPO has universally demonstrated an increase in preoperative hemoglobin and a decreased need for postoperative allogeneic blood transfusion, but with limitations. In a systematic review [8], eight studies (five RCTs and three cohort studies) were included in investigating the effects of preoperative EPO in conjunction with oral or IV iron in patients undergoing major orthopaedic surgery vs. various control groups [8]. After treatment, the mean preoperative hemoglobin was 14.3 ± 0.3 g/dl in the EPO cohort compared to the control (12.4 ± 0.4) [8]. EPO has also been shown in several studies, including randomized controlled trials, to decrease the postoperative rate of allogeneic transfusion [9] .

These studies demonstrate a significant decrease in allogeneic transfusion with EPO as compared to routine care [10–12]. Furthermore, in a meta-analysis spanning 26 trials and 3,560 participants, Alsaleh et al. showed that the preoperative use of erythropoiesis stimulating agents reduced allogeneic blood transfusion in patients undergoing hip and knee surgery (rate ratio (RR): 0.48, 95% confidence interval (CI) 0.38 to 0.60, $p < 0.001$) without an increased risk in the development of thromboembolism [13]. Additionally, the largest prohibitive factor for the use of EPO remains cost [14]. Bedair et al. performed a cost-analysis on preoperative use of EPO in TJA patients to avoid transfusion [14]. They demonstrated that the EPO strategy was more costly compared to no EPO (USD 2,632.00 versus USD 2,284.00) and its cost would need to be less than USD 225/dose for this to change. Similarly, in their RCT, So-Osman et al. reported that the cost per avoided blood transfusion in TJA when using EPO preoperatively was 7,300 euros or approximately 9,000 USD, with the authors concluding that this made EPO prohibitively expensive [9].

The combination of iron supplementation, EPO and tranexamic acid (TXA) has also been studied. Zhang et al. investigated the safety and effectiveness of optimized blood management for patients undergoing elective hip and knee arthroplasty by retrospectively comparing the use of TXA with and without the addition of iron supplementation and recombinant human erythropoietin [15]. This study demonstrated that the use of TXA, iron and EPO decreased total blood loss, the need for transfusion and hemoglobin drop without increasing the incidence of venous thromboembolism or mortality [15].

Another method described to increase preoperative hemoglobin is preoperative blood transfusion. A 2010 systematic review assessed four cohort studies, each with 100 patients or more, that compared preoperative autologous transfusion against usual care [8]. The results suggested that preoperative transfusions reduced the need for postoperative transfusions. However, there was no specific mention regarding the improvements in preoperative hemoglobin concentration, nor investigation into other clinical outcomes or adverse events that may be associated with blood transfusions [8].

In conclusion, there is limited evidence to suggest that routine administration of iron and preoperative transfusions increase preoperative hemoglobin and moderate evidence to suggest that EPO increases preoperative hemoglobin. Oral iron is useful in the setting of iron deficiency, but, when used routinely, it is not particularly effective and has a high rate of side effects, particularly gastrointestinal. EPO has routinely been shown to be more effective at increasing preoperative hemoglobin, but has a high monetary cost.

REFERENCES

[1] Spahn DR, Goodnough LT. Alternatives to blood transfusion. Lancet (London, England). 2013;381:1855–1865.

[2] Nørgaard A. International Society for Blood Transfusion – Pre–operative optimisation of haemoglobin. http://wwwisbtweborg/working–parties/clinical–transfusion/3–pre–operative–optimisation–of–haemoglobin. Accessed May 13, 2018.

[3] Tolkien Z, Stecher L, Mander AP, Pereira DI, Powell JJ. Ferrous sulfate supplementation causes significant gastrointestinal side–effects in adults: a systematic review and meta–analysis. PloS One. 2015;10:e0117383.

[4] Litton E, Xiao J, Ho KM. Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta–analysis of randomised clinical trials. BMJ. 2013;347:f4822.

[5] Cuenca J, Garcia–Erce JA, Martinez F, Cardona R, Perez–Serrano L, Munoz M. Preoperative haematinics and transfusion protocol reduce the need for transfusion after total knee replacement. Int J Surg. 2007;5:89–94.

[6] Cuenca J, Garcia–Erce JA, Munoz M, Izuel M, Martinez AA, Herrera A. Patients with pertrochanteric hip fracture may benefit from preoperative intravenous iron therapy: a pilot study. Transfusion. 2004;44:1447–1452.

[7] Lachance K, Savoie M, Bernard M, Rochon S, Fafard J, Robitaille R, et al. Oral ferrous sulfate does not increase preoperative hemoglobin in patients scheduled for hip or knee arthroplasty. Ann Pharmacother. 2011;45:764–770.

[8] Spahn DR. Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. Anesthesiology. 2010;113:482–495.

[9] So–Osman C, Nelissen RG, Koopman–van Gemert AW, Kluyver E, Poll RG, Onstenk R, et al. Patient blood management in elective total hip– and knee–replacement surgery (Part 1): a randomized controlled trial on erythropoietin and blood salvage as transfusion alternatives using a restrictive transfusion policy in erythropoietin–eligible patients. Anesthesiology. 2014;120:839–851.

[10] Deutsch A, Spaulding J, Marcus RE. Preoperative epoetin alfa vs.autologous blood donation in primary total knee arthroplastyJ Arthroplasty. 2006;21:628–635.

[11] Stowell CP, Chandler H, Jove M, Guilfoyle M, Wacholtz MC. An open–label, randomized study to compare the safety and efficacy of perioperative epoetin alfa with preoperative autologous blood donation in total joint arthroplasty. Orthopedics. 1999;22: s105–s112.

[12] Weber EW, Slappendel R, Hemon Y, Mahler S, Dalen T, Rouwet E, et al. Effects of epoetin alfa on blood transfusions and postoperative recovery in orthopaedic surgery: the European Epoetin Alfa Surgery Trial (EEST). Eur J Anaesthesiol. 2005;22:249–257.

[13] Alsaleh K, Alotaibi GS, Almodaimegh HS, Aleem AA, Kouroukis CT. The use of preoperative erythropoiesis–stimulating agents (ESAs) in patients who underwent knee or hip arthroplasty: a meta–analysis of randomized clinical trials. J Arthroplasty. 2013;28:1463–1472.

[14] Bedair H, Yang J, Dwyer MK, McCarthy JC. Preoperative erythropoietin alpha reduces postoperative transfusions in THA and TKA but may not be cost–effective. Clin Orthop Relat Res. 2015;473:590–596.

[15] Zhang S, Huang Q, Xu B, Ma J, Cao G, Pei F. Effectiveness and safety of an optimized blood management program in total hip and knee arthroplasty: a large, single–center, retrospective study. Medicine. 2018;97:e9429.

Authors: Riaz Khan, Vasili Karas, Jonathan Coward

QUESTION 15: Does an effort to increase preoperative hemoglobin concentration influence the rate of postoperative surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: Despite the absence of evidence demonstrating a reduction in SSIs/PJIs with optimization of preoperative hemoglobin, we recommend that all efforts be made to address and optimize anemia preoperatively.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 90%, Disagree: 4%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

With moderate evidence to suggest that preoperative anemia is associated with an increase in SSIs/PJIs and modalities exist to increase preoperative hemoglobin, the next logical step is to determine whether modification of this preoperative variable reduces the risk of SSIs/PJIs. However, no studies have investigated whether increasing preoperative hemoglobin decreases postoperative SSIs/PJIs. Studies have demonstrated that treatment of preoperative hemoglobin reduces postoperative transfusions [1], which have also been associated with PJIs [2–4], but the direct link between increased preoperative hemoglobin and decreased PJI/SSI reduction has not been established. This information would be important as it would help balance the potential benefits of preoperative iron treatments against the known risks and costs. Until evidence exists to suggest the administration of erythropoietin (EPO) and or iron supplementation safely decreases SSIs/PJIs, we cannot recommend their routine use in total joint arthroplasty for this purpose alone.

REFERENCES

[1] Guinn NR, Guercio JR, Hopkins TJ, Grimsley A, Kurian DJ, Jimenez MI, et al. How do we develop and implement a preoperative anemia clinic designed to improve perioperative outcomes and reduce cost? Transfusion. 2016;56:297–303.
[2] Hart A, Khalil JA, Carli A, Huk O, Zukor D, Antoniou J. Blood transfusion in primary total hip and knee arthroplasty. Incidence, risk factors, and thirty–day complication rates. J Bone Joint Surg Am. 2014;96:1945–1951.
[3] Browne JA, Adib F, Brown TE, Novicoff WM. Transfusion rates are increasing following total hip arthroplasty: risk factors and outcomes. J Arthroplasty. 2013;28:34–37.
[4] Everhart JS, Sojka JH, Mayerson JL, Glassman AH, Scharschmidt TJ. Perioperative allogeneic red blood–cell transfusion associated with surgical site infection after total hip and knee arthroplasty. J Bone Joint Surg Am. 2018;100:288–294.