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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.

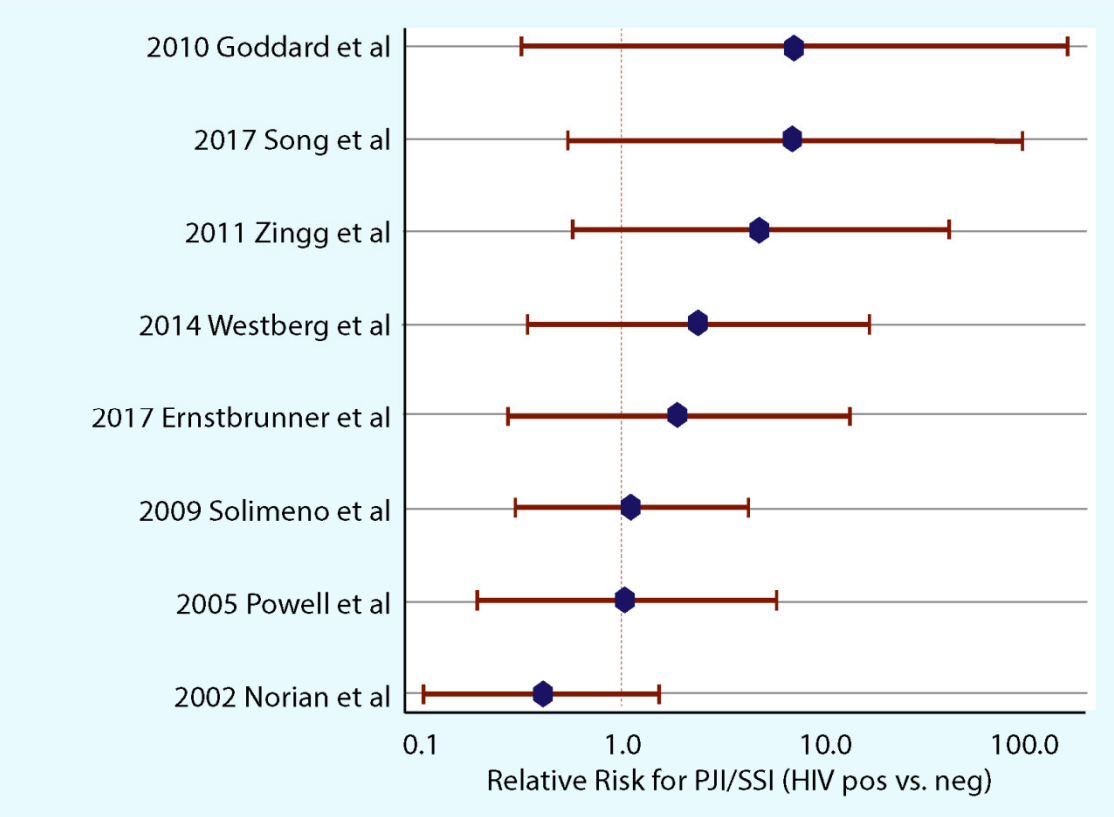

FIGURE 1. Forest plot of relative risk of PJI/SSI in HIV-infected hemophiliacs vs. HIV-negative hemophiliacs.

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.

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