

## 1.4. PREVENTION: HOST RISK MITIGATION, GENERAL FACTORS

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### QUESTION 1: Can immunotherapy and immunoprophylaxis be used to prevent biofilm formation and implant-associated infections?

**RECOMMENDATION:** Yes. Although no vaccine or passive immunization has been approved by the Food and Drug Administration (FDA) for an orthopaedic indication, a four-antigen vaccine (SA4Ag) with established safety and immunogenicity in healthy volunteers is currently being tested for efficacy in a phase II clinical trial of spine fusion patients. This is also supported by evidence from the literature regarding cochlear implants for children showing a decreased incidence of pneumococcal meningitis. However, there are no high-level studies supporting this trend with evidence and further study needed.

**LEVEL OF EVIDENCE:** Moderate

**DELEGATE VOTE:** Agree: 62%, Disagree: 18%, Abstain: 20% (Super Majority, Weak Consensus)

### RATIONALE

It has been well-established that foreign body implants are a nidus for infection by biofilm-forming bacteria [1–3]. Thus, increasing host immunity against the most common pathogens associated with a particular implantation procedure is a rational approach to reduce postoperative infections [4,5]. Additionally, immunotherapy and immunoprophylaxis have been used in various surgical disciplines to prevent surgical site infections (SSI) with varying success rates [6,7]. This has also been evaluated in orthopaedics, primarily with vaccines and passive immunizations against *Staphylococcus aureus*, as this is the most prevalent bacteria associated with these infections [8]. Various *S. aureus* antigens have been incorporated into vaccines with varying levels of success [9,10]. A few investigators have also investigated antigen vaccines against *Staphylococcus epidermidis* [11,12].

To identify the clinical and basic science evidence to support this intervention, a systematic review was completed on the peer-reviewed literature identified by a PubMed search performed on February 8, 2018 using the key words “immunoprophylaxis or immunotherapy or vaccine or vaccination + implant + infection or biofilm.” This literature search identified 136 references from 1974 to 2018. After eliminating 56 that did not contain information directly addressing the question, the remaining 80 were divided into three categories: Primary Clinical Research (n = 5, four positive, one negative), Primary Pre-clinical Research (n = 47, all positive), and Reviews (n = 27, 25 positive, two negative).

In the specific case of cochlear implants for children, vaccination with seven-valent pneumococcal conjugate vaccine (PCV7) (Prevnar<sup>®</sup>), 23-valent pneumococcal polysaccharide vaccine (PPV23) (Pneumovax<sup>®</sup>) or both, according to the Advisory Committee on Immunization Practices (ACIP) schedules for persons at high risk, immunoprophylaxis has been indicated to reduce the incidence of pneumococcal meningitis, primarily from *Streptococcus pneumoniae* implant-associated infections. As summarized in a systematic review by Wei et al. [13], scientific data supports the FDA recommendation of pneumococcal vaccination for the prevention of meningitis in cochlear implant recipients. While randomized control trials have not been performed to formally establish immunoprophylaxis efficacy, the incidence of pneumococcal meningitis in children receiving cochlear implants has been reduced from that of the pre-vaccine era. Importantly, this conclusion is also supported by strong pre-clinical data demonstrating that the PPV23 vaccine protects rats from implant-associated infections following *S. pneumoniae* challenge via hematogenous and middle-ear routes [14].

A review of the pre-clinical literature revealed 14 primary research articles that demonstrated the efficacy of immunotherapy and immunoprophylaxis to prevent biofilm formation and implant-associated infections. The pathogens studied were *S. aureus* [9,15–21], *Streptococcus epidermidis* [11,12], *Enterococcus faecalis* [21,22], *Aggregatibacter actinomycetemcomitans* [23], and *S. pneumoniae* [14]. However, translating this research to human subjects remains a challenge as evidenced by the results of several anti-*S. aureus* vaccines and passive immunizations that have been investigated in clinical trials [6,24]. Tefibazumab was shown to be safe in phase II trials against *S. aureus* bacteremia [25], but its efficacy is yet to be proven. Veronate, an intravenous immune globulin, failed to prevent staphylococcal sepsis in infants [26]. A vaccine against *S. aureus* lsdB failed to prevent sepsis in cardiothoracic patients and was associated with increased mortality [27]. A vaccine against types 5 and 8 capsular polysaccharides failed to show any efficacy in preventing infection in end-stage renal disease patients undergoing hemodialysis [28]. On the positive side, a vaccine against four *S. aureus* antigens has been shown to be safe and immunogenic in humans in phase I trials [29]. Most recently, another four-antigen vaccine has also demonstrated safety and efficacy beyond one year post-immunization in healthy volunteers [30]. This vaccine is currently being tested for efficacy in spine fusion patients and the study is expected to be completed in late 2018.

Given that (1) the acknowledged efficacy of the FDA-approved pneumococcal vaccines to reduce the incidence of meningitis in children receiving cochlear implants, (2) the experimental evidence demonstrating plausible mechanisms and in vivo proof of concept with various pathogens and animal models and (3) the ongoing clinical trials based on promising efficacy data, we conclude that immunotherapy and immunoprophylaxis can be used to prevent biofilm formation and implant-associated infections in some situations.

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## QUESTION 2: Does routine screening for diabetes and glycemic control reduce the risk of surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: The routine screening for diabetes and glycemic control has the potential to reduce the incidence of SSI and/or PJI following total joint arthroplasty (TJA).

LEVEL OF EVIDENCE: Consensus

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

### RATIONALE

The burden of diabetes is rising, and it is projected that in the next 20 years the number of diabetics in the United States will reach 44 million, about two times the present prevalence [1,2]. Patients with diabetes, especially those with inadequate glycemic control, are at increased risk for both joint-related and systemic adverse outcomes following TJA [3–6], of which PJI has been the most studied. Multiple professional organizations have published screening recommendations for diabetes [7–10]. While there are slight differences between them, they all agree that patients with an increased risk for diabetes should be screened. It has been found that a large proportion of patients undergoing TJA have undiagnosed diabetes; hence, it is reasonable to provide screening recommendations for this patient population [11].

Diabetes is an established risk factor for severe osteoarthritis [12], and a higher prevalence has been reported in patients undergoing TJA [13,14]. In a recent study, the prevalence of diabetes in patients undergoing TJA was 20.7%, which is almost two times the rate within the general population [15,16]. Interestingly, 40.9% (8.4% of the total cohort) were undiagnosed. Moreover, 38.4% of the total cohort were pre-diabetic, resulting in a total of 59.1% dysglycemic patients. This could explain why numerous studies show that perioperative hyperglycemia, elevated glycated hemoglobin (HbA1c) and high glucose variability are associated with PJI even without a diagnosis of diabetes, as these patients are simply unaware of their dysglycemic status [17–19].

The fact that individuals approaching TJA undergo preadmission testing provides an ideal screening setting, for both patient and physician. Screening TJA patients for diabetes could allow early detection and rapid treatment, which may reduce the burden of diabetes and both its surgical and non-surgical complications. Furthermore, patients with inadequate glycemic control and undiagnosed diabetes may be treated and appropriately optimized in the preoperative setting which could improve their outcomes. Furthermore, lifestyle changes and pharmacologic interventions may reduce progression and delay development in undiagnosed diabetics and pre-diabetics [7,20,21].

Although no studies exist to show that tight glycemic control could reduce the rate of PJI following TJA, it is well-established that inadequately-controlled diabetes is associated with higher rates of PJI. Based on the potential link between strict glycemic control in the perioperative period and reduction in PJI rates, and due to the extremely high rate of unknown diabetics and prediabetics in patients undergoing TJA, we extrapolate that screening all patients prior to surgery could assist in reducing the incidence of SSI and PJI.

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### QUESTION 3: What is the most accurate marker for assessing glycemic control that best predicts surgical site infection/periprosthetic joint infection (SSI/PJI)?

**RECOMMENDATION:** While there is evidence showing an association between elevated glycated haemoglobin (HbA1c) and fasting blood glucose and increased risk for subsequent SSI/PJI, this association is not strong. Recent findings suggest that fructosamine in the preoperative period and glucose variability in the immediate postoperative period may provide greater prediction of SSI or PJI.

**LEVEL OF EVIDENCE:** Moderate

## RATIONALE

Diabetes mellitus (DM) patients are predisposed to a host of complications following total joint arthroplasty (TJA) [1–3], with SSI and PJI being perhaps the most dreaded [4]. Glycemic control throughout the perioperative period has been a focus of many recent studies, since it could serve as a modifiable risk factor and targeting it holds the potential to reduce SSI/PJI rates following TJA [5–9]. However, the proper marker for assessing glycemic control in the perioperative period remains unknown. Studies into the subject have produced conflicting results due to diversity in the marker used for assessment, timing of assessment and different cutoff values used for stratifying patients.

Traditional markers for assessing glycemic control can crudely be divided into long-term (HbA1c) and short-term (glucose levels) in the preoperative and postoperative period. A recent meta-analysis of ten studies suggested that elevated HbA1c levels were not significantly associated with a higher risk of SSI/PJI after TJA (pooled odds ratio (OR): 1.49, 95% confidence interval (CI): 0.94 to 2.37,  $p = 0.09$ ). However, this was most likely due to the low threshold (7%) chosen to define inadequate control in the majority of the studies, with accumulating evidence to support the utility of preoperative HbA1c levels above 7.5 to 8.0% as a predictor for PJI. Similar to HbA1c, the prognostic value of perioperative hyperglycemia remains unclear [10,11]. Studies supporting the association between perioperative hyperglycemia and PJI were underpowered and did not take into account other confounders [9,12]. In those studies that did include important confounders, the association was markedly attenuated [5–9,12–14].

We conducted a systematic review and found ten studies examining the association between glycemic control and PJI. Of those, six examined HbA1c solely [10,11,15–18], one looked at perioperative control alone [12] and three assessed both [5,6,8]. Similar to the meta-analysis mentioned above, the results of our review suggest that higher HbA1c levels are not clearly associated with higher PJI rates, possibly due to inaccurate cutoffs to define inadequate glycemic control. We also found that hyperglycemia in the perioperative period appears to have some association with PJI; however, this relationship is complex and is not well-characterized by the studies reviewed given their varied design.

The uncertainty of the independent role perioperative HbA1c or hyperglycemia have on PJI raises the question of whether these are the most appropriate markers for assessing glycemic control. The focus on fluctuation of glucose around the mean has gained popularity in recent years and has been studied extensively [19–21]. Both *in vivo* and *in vitro* studies attribute the negative effects of these fluctuations to the activation of pro-inflammatory proteins and excessive oxidative stress [22]. Short-term fluctuations in glucose levels may have a larger effect on inflammatory cytokine levels than continuous hyperglycemia that may impair host defense from infection [23,24]. Lately, fructosamine (in the preoperative period) and glucose variability (in the postoperative period), which are medium and short term markers for glycemic control, respectively, were shown to correlate strongly with the risk for PJI in both diabetics and unknown-diabetics who seemed to be adequately-controlled based on traditional markers [25].

Fructosamine measures the level of glycated serum proteins and reflects the average glucose levels over a 14- to 21-day time period [26]. It better detects fluctuation and rapid variations of glucose and may detect short term hyperglycemic events better than HbA1c. In a recent study, fructosamine above 292 mmol/L had a better association with SSI and PJI compared to HbA1c when 7% was used as a threshold for inadequate control. One of the immense advantages of fructosamine, compared to HbA1c, is the shorter half-life of the glycated proteins that may reflect the effect of treatment within a week or 2 as opposed to glycated hemoglobin that could take up to 120 days.

In conclusion, our systematic review of the literature on the subject could not detect the most accurate marker for assessing perioperative glycemic control and further research in this area, with consistent study design, is required to answer this question. Based on recent findings, we conclude that fructosamine can serve as an alternative to HbA1c in the setting of preoperative glycemic assessment. Further research to solidify its utility and specify and exact threshold level indicative of inadequate glycemic control should be conducted. With improvement in technology, non-invasive continuous glucose monitoring devices could become more readily available. Future studies should evaluate the role of continuous glucose monitoring in the perioperative period to reduce glucose variability.

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## QUESTION 4: What is the threshold for glycated haemoglobin (HbA1c) that is predictive of subsequent surgical site infection/periprosthetic joint infection (SSI/PJI) in patients undergoing orthopaedic procedures?

RECOMMENDATION: The upper threshold for HbA1c that may be predictive of subsequent SSI/PJI is most likely to be within the range of 7.5 to 8%.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 88%, Disagree: 3%, Abstain: 9% (Super Majority, Strong Consensus)

### RATIONALE

A wide range of complications have been reported among patients with diabetes undergoing orthopaedic procedures, namely SSIs. Therefore, it is thought that maintaining appropriate glycemic control during the perioperative period is crucial for potentially decreasing the risk of such complications [1–3]. Serum HbA1c is a surrogate for patient glycemic status over a two- to three-month period and is widely used as a marker for perioperative glycemic control [4].

The American Diabetes Association (ADA) guidelines recommend a maintenance of an HbA1c level of less than 7% for patients with diabetes in order to minimize potential complications [5]. However, the orthopaedic literature is less conclusive regarding a specific threshold that would reduce the risk of complications. Several studies were not able to reach significance between a specific HbA1c threshold and postoperative infection [1,3,6–10], while others reported a significant association between infections and HbA1c level, but with no clear consensus on one predictive value among the studies [2,5,11–21]. It is worth noting that many of these studies adopted the ADA recommended HbA1c value of 7% as a cutoff level in their design phase to stratify their cohorts (diabetic vs. non-diabetic) and attempted to validate this previously-established threshold rather than examining HbA1c as a continuous variable [1,3].

With regards to total joint arthroplasty (TJA), Han et al. found an HbA1c level of more than 8% to be significantly associated with a higher risk of postoperative wound complications for patients undergoing total knee arthroplasty (TKA) [15]. Similarly, Hwang et al. found that a HbA1c greater than 8% is associated with superficial SSIs following TKA in patients with diabetes, while the HbA1c level of 7% was not detected as a significant cutoff value for higher likelihood of infection or wound complications, in contradiction to the guidelines of the ADA [17].

Cancienne et al. found that patients having a HbA1c level equal to or more than 8% were more likely to have an infection within one year of performing TKA compared to those having HbA1c levels less than 8% (adjusted odds ratio (OR): 1.7, 95% confidence interval (CI) 1.2 to 2.4,  $p = 0.004$ ). However, it was indicated that this threshold of 8% is of limited clinical utility when taken as an independent predictor for postoperative infection due to its poor sensitivity and intermediate specificity [2]. In another parallel study of total hip arthroplasties [14], Cancienne et al. also identified that a perioperative HbA1c of more than 7.5% is a significant risk factor for the development of postoperative PJI, yet, is of poor clinical utility as a stand-alone predictor for PJI [5]. Stryker et al. reported that patients with a preoperative HbA1c level of more than 6.7% have nine times the odds of having increased risk of wound complication following primary TJA compared to those having a HbA1c less than 6.7% (95% CI 1.14 to 71.20,  $p = 0.03$ ) [19]. Jansen et al. identified a threshold of HbA1c of 6.5% above which the rates of PJI were significantly higher [18]. On the other hand, a recent study by Tarabichi et al. presented receiver operating characteristic (ROC) curves and used Youden index to estimate the optimal cutoff value of HbA1c predictive of complications to find the threshold of 7.7% to be predictive of PJI in TJA (95% CI 6.25 to 8.05, Youden index 0.38, cutpoint 0.019) [20]. A systematic review and meta-analysis by Yang et al. indicated that the cutoff HbA1c value of 7% as predictive of PJI remains controversial [21]. Similarly, a recently released systematic review and meta-analysis by Shohat et al. indicated that the orthopaedic literature has failed to agree on the optimal HbA1c value predictive of SSI in TJA [22].

Cancienne et al. reported an HbA1c level of 7.5% to be a significant threshold predictive of infection [12] in spinal and cervical surgery. Hikata et al., on the other hand, found that preoperative HbA1c values were significantly higher in patients with diabetes who developed postoperative SSIs and recommended that HbA1c levels should be maintained below 7% to prevent SSIs [16].

In one of the very few studies addressing foot and ankle surgeries and HbA1c threshold, Domek et al. reported a significant association between greater HbA1c values and infections, yet they were not able to identify an HbA1c value that could potentially predict a greater risk of infection [13].

Among the minimal number of studies on arthroscopy, Cancienne et al. recently reported that a perioperative HbA1c of 8% could serve as a threshold, yet they found limited clinical applicability due to low sensitivity [11].

Generally, Dronge et al. reported findings from a cohort of 490 diabetic patients who underwent non-cardiac surgery, of which 63 underwent orthopaedic surgeries, and detected that HbA1c levels less than 7% were associated with a significantly lower risk of postoperative infections [14].

In conclusion, studies on different types of orthopaedic procedures reported a broad range of HbA1c threshold levels that may be predictive of postoperative infections. No consensus was reached, neither within studies addressing the same orthopaedic procedures nor across studies targeting different orthopaedic surgeries. The ultimate HbA1c threshold remains controversial; however, the literature indicates that this threshold is most likely in the range of 7.5 to 8%. Larger studies examining the optimal threshold for HbA1c as well as studies examining alternative markers of glycemic control are necessary [10].

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## QUESTION 5: Is thrombocytosis associated with an increased risk of surgical site infections/periprosthetic joint infections (SSIs/PJIs) in patients undergoing orthopaedic procedures?

RECOMMENDATION: It is unlikely that thrombocytosis is associated with an increased risk of postsurgical SSIs/PJIs. However, patients with severe thrombocytosis should undergo evaluation prior to orthopaedic procedures.

LEVEL OF EVIDENCE: Limited

## RATIONALE

The upper limit of the platelet count differs among various sources and laboratories, but is generally accepted to be in the range of 350,000 to 450,000/mL (350 to 450 x 10<sup>9</sup>/L) [1,2]. Newly recognized thrombocytosis may be a marker for the presence of a clonal (neoplastic, autonomous) hematologic disorder or a reactive phenomenon (secondary) [1].

Reactive thrombocytosis refers to thrombocytosis in the absence of a chronic hematologic disorder and is due to any inflammatory process such as bacterial infection, neoplasia, sepsis, multiple trauma or a recent surgery. Reactive thrombocytosis associated with underlying inflammation or infection constitutes the vast majority of cases encountered in practice [1-3].

Elevated levels of interleukins (IL) and C-reactive protein (CRP) are associated with infections. Any condition that elevates serum IL levels (especially IL-6) subsequently triggers an increase in circulating platelet count [4,5]. Although the exact mechanism is unknown, more than 81% of patients with reactive thrombocytosis have elevated serum levels of IL-6 or C-reactive protein [6,7]. Reactive thrombocytosis is usually associated with modest elevations in platelet count (up to 700,000/ $\mu$ L), normal platelet structure and function and a normal bone marrow. However, the concentration of IL-6 in the serum does not predict the observed platelet counts [7].

In reactive thrombocytosis, the structure and function of platelets are believed to remain normal, thus bleeding during or after surgical procedure is thought to be unlikely. In the absence of abnormal bleeding and hematoma formation, the association between thrombocytosis and subsequent SSI/PJI remains undefined. In non-orthopaedic literature, one study utilizing an administrative database suggested a link between thrombocytosis and increased infection in neurosurgical procedures [8]. The latter study, however, suffered from all the issues related to databases and lack of granular data to prove such an association.

Therefore, an association between reactive thrombocytosis and an increased risk for infection remains unproven. However, based on the fact that reactive thrombocytosis could be a sign of an ongoing neoplasm, infection or other important pathologies, the condition should be investigated prior to elective orthopaedic procedures.

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