RATIONALE

Rates of infectious complications following knee and hip arthroplasty are generally less than 2% [1]. However, rates of infectious complications following lower-extremity limb salvage therapy with endoprostheses are approximately 10% [2]. The reason for this difference remains unclear, possibly due to systemic factors not directly related to the presence of localized malignancy [3].

Preoperative parenteral antibiotics have been demonstrated to reduce wound infections following TJA [4]. In a meta-analysis of antibiotic prophylaxis in TJA, which included 7 studies with 3,065 participants, the relative risk of infection was reduced by 81% compared to placebo [4]. None of the studies included in the meta-analysis or accompanying systematic review specifically addressed prophylaxis in patients undergoing orthopaedic endoprosthetic reconstruction.

Based on the preponderance of evidence, clinical guidelines recommend the use of perioperative parenteral antibiotics before TJA and other orthopaedic surgeries with foreign body placement [5,6]. No data exist regarding the tailoring of prophylaxis in oncologic patients with endoprosthetic reconstruction. Therefore, antibiotics should be given in accordance with accepted regimens.

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1.2. PREVENTION: CHEMOTHERAPY

Authors: R. Lor Randall, Brian M. Smith, Karan Goswami, John S. Groundland, Antonios I. Papadopoulos, Panayiotis J. Papagelopoulos

QUESTION 1: Do we need to evaluate the gut and skin microbiome of patients after chemotherapy to assess the risk for potential infection after endoprosthetic reconstruction?

RECOMMENDATION: Unknown. There is no evidence in the literature to suggest that evaluation of the gut and/or skin microbiome following chemotherapy aids with risk stratification for potential infection in patients undergoing endoprosthetic limb salvage surgery.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

In the orthopaedic oncology literature, infection rates following metallic endoprosthesis limb salvage surgery are high and vary from 2.2–34% [1–4]. In a systematic review of the literature, Henderson et al. found the overall rate of infection-related failure of endoprostheses to be 7.8% and infection as the most common mode of failure in their current investigation of primary endoprostheses. Proximal tibia replacements and total femur replacements were noted to be at particular risk, requiring infection-related revision surgery in 19.7% and 17.5% of cases, respectively [1].

While not fully understood or rigorously investigated, the causes of these high rates of infection are likely multi-factorial, including extensive surgical dissection and resection, increased operation time, substantial loss of blood, inadequate soft tissue coverage, implantation of large constructs with foreign material and, often in the case of oncology patients, a poor nutritional and compromised immune status [5].

Perioperative chemotherapy has been shown to increase the total revision rates of endoprosthetic reconstruction to 40% from 10% due to its reduction of osseointegration [6]. The impact of chemotherapy on the rates of infection following endoprosthetic reconstruction remains unclear. There are conflicting reports on whether immunological deficiency following chemotherapy is a risk for postoperative infection of endoprostheses. In a review, Kapoor and Thiyam documented that a compromised immune status after neoadjuvant chemotherapy may result in postsurgical infection having an increased infection rate of 20% [5]. While in a multicenter retrospective review, Morii et al. showed chemotherapy did not affect infection risk and suggested no drawbacks related to chemotherapy in regards to postoperative infection control of endoprostheses [2]. It was shown that some patients who developed infection during postoperative chemotherapy were controlled by amelioration of myelosuppression alone, while others required revision and antibiotic therapy [7].

Any measure that leads to decreased infection rates of metallic endoprosthesis reconstruction would be desirable. Given the prevalence of the problem and the severity of the consequences of deep infection, even weak evidence supporting a decrease in postoperative infection rates would be worth considering. While a few interven-

tions have been noted to be beneficial, as reported in retrospective case series, no rigorous, prospective studies have been completed in this population. In regard to the question above, there is no evidence (level I, II, III or IV) to support or reject evaluation of the skin or gut microbiome after neoadjuvant or adjuvant chemotherapy.

Conceptually, chemotherapy is known to alter the gut microbiome, which likely influences the development and manifestations of chemotherapy-associated mucositis [8–10]. When undergoing induction chemotherapy for acute myeloid leukemia, patients who developed infection after treatment were shown to have significantly lower baseline stool bacteria diversity and the therapy itself was shown to decrease microbiome diversity [11]. Taxonomic shifts in the gut biome have been demonstrated in lymphoma patients following chemotherapy, with decreases in Firmicutes (species including *Staphylococcus, Streptococcus, Enterococcus*) and Actinobacteria (*Streptomyces, Proprionibacteria*) and increases in Proteobacteria (*Escherichia, Salmonella, Vibrio, Helicobacter, Yersinia, Legionellales*) [8]. In a pediatric study of acute lymphoblastic leukemia (ALL), the abundance of Proteobacteria in the gut microbiome before chemotherapy was predictive of the infection risk and domination of the gut by *Enterococcaceae* or *Streptococcaceae* during current and subsequent phases of chemotherapy [12]. Decreased diversity in the taxa of the gut microbiome has been used as a predictive tool for chemotherapy-related bloodstream infection risk [13]. Chemotherapy alters the skin microbiome in that fungal infections are common during and following chemotherapy [14].

Despite these documented changes in the microbiome of the gut and on the skin and their relation to infection risk, there is no proven association or theoretical link with postoperative endoprosthetic infection. This is illustrated in two ways. First, the causative organisms of endoprosthetic infection are those typically found in postoperative periprosthetic joint infections (e.g., *Staphylococcus, Streptrococcus, Enterococcus,* Pseudomonas species) [2,7,15], which are not species noted to increase following chemotherapy (e.g., *Proteobacteria* and Fungi) [8]. Second, the average time to infection-related surgical revision of endoprostheses is 47 months following index endoprosthesis placement [1]. This timeline is long after chemotherapy has been completed and more than enough time for chemotherapy-induced changes in the diversity of the gut and skin microbiome to return to normal.

There is still a need for further research to clarify whether skin and gut microbiome testing would prove useful in risk stratification for infection following endoprosthetic reconstruction.

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Authors: Andreas F. Mavrogenis, Takeshi Morii, Jorge Manrique

QUESTION 2: Should an absolute neutrophil count of >1000/mm³ be the minimum for patients undergoing limb salvage surgery after receiving chemotherapy?

RECOMMENDATION: Yes. An absolute neutrophil count of >1000/mm³ should be the minimum for patients undergoing limb salvage surgery after receiving chemotherapy.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

Neutropenia has been defined as an absolute neutrophil count (ANC) of 1500/mm³ or lower [1]. Historically, this cutoff value has been considered as a risk factor for developing infections and complications. Bodey et al. [2] initially described this association. They observed that the infection rate in patients with ANC below 1000/mm³ was 14% and below 100/mm³ up to 60% [2]. Furthermore, lower ANC levels have been identified as an independent risk factor for infections [3]. This latter publication also demonstrated that the