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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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

risk gradually increases as ANC decreases. In a more recent study, Lima et al. [4] evaluated patients with ANC levels less than or equal to 500 cells/mm³ further support this relationship.

Different chemotherapeutic agents are used in the treatment of bone and soft tissue sarcomas. Some have shown to be myelosuppressive and thus reduce the ANC [5]. This is also one of the most critical criteria to administering chemotherapeutic regimens as it has been directly associated with an increased risk of complications [3,6]. The combination of wide resection and neo-adjuvant/adjuvant chemotherapy is a standard treatment modality for bone sarcomas [7]. The combination of methotrexate (MTX), doxorubicin (ADR), cisplatin (CDDP) and ifosfamide (I) are agents used for conventional osteosarcoma [7–11]. For small round cell sarcoma including Ewing's sarcoma, multi-agent chemotherapy with vincristine-doxorubicin-cyclophosphamide, ifosfamide-etoposide (VDC-IE) is used [12,13]. Chemotherapy for high-grade non-round cell, soft tissue sarcoma is controversial, but the effectiveness of chemotherapy for such sarcomas has been shown in several studies [14–20]. The conventional key drugs for such condition include ADR and I [14,15,17]. In addition, dacarbazine (DTIC), gemcitabine (G) and docetaxel (D) became the options for soft tissue sarcomas [20–24]. Recent innovation in this area provided additional reagents including pazopanib, trabectedin and eribulin, which are mainly used as second line treatment for advanced soft tissue sarcomas [25–31].

When evaluating patients with low ANC undergoing surgical interventions, these patients also exhibit an increased risk of surgical site infection compared to patients with normal counts. Natour et al. [32] evaluated patients undergoing abdominal surgery in the setting of neutropenia. They categorized patients with ANC < 500/mm³, between 500/mm³ and 1000/mm³, and between 1000/mm³ and 1500/mm³. Patients with lower ANC also exhibited higher postoperative infection rates, hospital stay and mortality. A relatively recent study evaluated the risk for infection of implantable port devices in pediatric oncology patients [33]. Again, patients with low ANCs had higher infection rates compared to those with normal ANC.

No study was identified that directly associates infection risk in patients undergoing limb salvage and low ANC. Given that limb salvage surgery is a complex procedure, all efforts to avoid infection should be undertaken. Based on the available literature, we consider that patients with an ANC below 1000/mm³, either from the chemotherapy or the solid tumor itself, should not undergo limb salvage surgery until ANC is above 1000/mm³ and possibly above 1500/mm³.

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QUESTION 3: Should the serum white blood cell (WBC) count be taken into account prior to endoprosthetic reconstruction in patients who have undergone recent chemotherapy?

RECOMMENDATION: The association between chemotherapy and infection following endoprosthetic reconstruction remains controversial. However, in a multifactorial decision making process, there may be some benefit in accounting for the serum WBC count prior to endoprosthetic reconstruction.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Infection continues to be one of the most serious complications after the reconstruction of an extremity using a tumor endoprosthesis. Past reports showed that the infection rate of a tumor endoprosthesis ranged from 4–36% [1–5]. The myelosuppressive properties of many chemotherapeutic drugs remain a theoretical risk for developing infection in these patients receiving a tumor endoprosthesis for an extremity tumor or metastatic lesions. However, this theoretical risk remains controversial. A handful of studies demonstrate a significant relationship between chemotherapy and periprosthetic infection in patients receiving an endoprosthetic device for an extremity tumor [3,6–9].

On the contrary, there are numerous studies that provide data supporting the idea that chemotherapy is not a significant risk factor for the development of periprosthetic joint infection (PJI) and surgical site infection (SSI) in these patients. Peel et al. [10] were able to demonstrate that chemotherapy, febrile neutropenia and bacteremia were not associated with the development of PJI. Jeys et al. [11] showed that there was no significant relationship between chemotherapy and the risk of infection. Biau et al. [12] reported that there was no significant difference in the rate of infection between patients who had received adjuvant treatment (including irradiation and chemotherapy) and those who had not received such treatment ($p = 0.13$). Finally, Meijer et al. [13] found no association between chemoradiation and increased rates of endoprosthetic infection.

Despite the conflicting evidence surrounding chemotherapy and the risk of endoprosthetic infection, there may be some benefit in taking into account the patient's serum WBC count prior to endoprosthetic reconstruction. It is widely known that lymphocytes play an essential role in combatting invading pathogens and facilitating wound healing after surgery [14]. In addition, Gulack et al. [15] reported that preoperative leukopenia prior to emergent abdominal surgery was a predictor for significant postoperative morbidity and mortality. However, they were not able to demonstrate a significant difference in the incidence of deep wound infection in patients with leukopenia vs. patients with a normal WBC count preoperatively ($p = 0.462$). These findings contrast with the work by Natour et al. [16], who noted that patients undergoing abdominal surgery with a preoperative absolute neutrophil count (ANC) less than 500 had significantly higher postoperative infection rates compared to patients who had a preoperative ANC between 500 and 1500. However, one must be cautious with the results from these studies, as they may not be generalizable to the particular patient cohort of focus.

Due to the fact that the literature doesn't show any significant differences between the infection rates between patients who are undergoing chemotherapy and those who are not receiving it, it makes sense to determine the WBC number as an additional diagnostic tool.

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