multi-center studies are required to more accurately assess the effect of timing between preoperative radiotherapy/chemotherapy and surgery on the rate of postoperative SSIs, PJIs and WCs.

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# QUESTION 5: What strategies should be implemented to minimize the risk of surgical site infection/periprosthetic joint infection (SSI/PJI) in patients who have received chemotherapy or radiation therapy and are undergoing endoprosthetic reconstruction?

**RECOMMENDATION:** We believe patients who have received either chemotherapy or radiotherapy prior to endoprosthetic reconstruction should undergo extensive medical optimization. Consideration may also be given to the use of antimicrobial coated implants, extended (>24 h) and augmented postoperative antibiotic prophylaxis consisting of a first-generation cephalosporin and an aminoglycoside and/or vancomycin, as well as use of enhanced soft tissue reconstruction techniques. Surgery should also be expeditious in these patients minimizing dissection of soft tissues with gentle handling.

**LEVEL OF EVIDENCE:** Limited

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

## RATIONALE

Patients with neoplasia undergoing endoprosthetic reconstruction are at an increased risk of SSI/PJI. The chemotherapy-induced immunosuppression, the poor soft-tissue conditions due to radiotherapy, the length and complexity of the tumor resection and megaprosthetic reconstruction and the difficulty of achieving soft tissue coverage are some of the reasons that explain the very high rate of infection in these patients compared to patients undergoing conventional arthroplasty [1–5].

As these patients are at high risk of SSI and/or PJI, any measure proven to be effective against infection should be implemented. Several organizations have proposed evidence-based guidelines for the prevention of surgical site infections. These strategies, together with additional measures, should be implemented in these patients. We provide examples of some of the measures that may be used to minimize the risk of SSI/PJI in patients undergoing oncologic endoprosthetic joint reconstruction, particularly in patients who have received chemotherapy and/or irradiation treatment. These measures include:

- Preoperative measures [6–9]: Correction of hyperglycemia, treatment of anemia, treatment of malnutrition, smoking cessation, decolonization of *Staphylococcus aureus* (including methicillin-resistant *S. aureus* (MRSA)), skin cleansing with chlorhexidine or other antiseptic agents prior to surgery and numerous other preoperative measures that are discussed elsewhere in the consensus document should be considered.

- Intraoperative measures [6–9]: Administration of weight-based antibiotics, including coverage against MRSA if present, re-dosing of the prophylactic antibiotic for cases that last longer than two hours or have increased blood loss, minimizing blood loss by administration of tranaxemic acid, minimizing operating room traffic, use of antibiotic-impregnated bone cement, wound irrigation with antiseptic agents such as sterile dilute betadine, careful and gentle soft tissue dissection and expeditious surgery are some of the proven strategies that may be implemented intraoperatively.
- Postoperative measures [6–9]: Wound management is a critical aspect of prevention of SSI/PJI in these patients. Consideration should be given to administration of less potent anticoagulation to minimize hematoma formation or reduce the chance for persistent wound drainage. The incision may be managed by application of negative pressure or occlusive dressing. Every effort should also be made to minimize blood loss and the need for allogeneic blood transfusion.

There are many other preventative measures that have been proposed or explored in oncologic patient population undergoing megaprosthetic reconstruction. In recent years the use of implants coated with antimicrobial agents such as silver and iodine has been explored. Silver-coated prostheses for limb reconstruction after tumor resection has been reported to have a favorable outcome and be effective in reduction of infection. Among the metals known to have antimicrobial activity, silver has attracted interest among many investigators due to its excellent level of antimicrobial activity and low toxicity. The silver coating can inhibit bacterial colonization of the prosthetic body and potentially prevent subsequent PJI [10–12]. A study involving patients with bone sarcoma over a five-year period demonstrated that the infection rate was substantially reduced from 17.6% in the uncoated titanium megaprosthesis (proximal femur, n = 33; proximal tibia, n = 41) to 5.9% in the silver-coated megaprosthesis group (proximal femur, n = 22; proximal tibia, n = 29). The titanium group data were retrospective and the data for the silver group were collected prospectively [13]. Another study evaluating the infection rate in 98 patients with sarcoma or giant-cell tumor in the proximal tibia demonstrated that infection at 16.7% in the group who underwent reconstruction using titanium megaprostheses (n = 42) was significantly higher than the infection rate at 8.9% in the silver-coated megaprostheses group, resulting in five-year prosthesis survival rates of 90% in the silver-coated and 84% in the titanium only cohort. Although not reaching statistical significance, further work may suggest that silver-coated tumor prostheses may reduce the PJI rate in the high-risk oncological patients submitted to tumor resection and limb reconstruction.

Another study retrospectively investigated 68 oncology patients, 30 of whom received a titanium proximal femoral replacement and 38 patients who received a silver-coated proximal femur replacement. There was a lower rate of early infections (within the first 6 months) in the silver-coated group (2.6%) in comparison with 10% in the titanium group. However, the difference was not statistically significant. Regarding late-onset infections (later than 6 months), the difference between groups was not clear (5.3% in the silver group and 6.6% in the titanium group) [14]. The reports available on the use of silver-impregnated implants are all retrospective with their inherent limitations. The role of silver coating of megaprostheses in prevention of infection needs to be explored in a prospective manner.

Currently, there are no appropriate guidelines or recommendations in place for prophylactic antibiotics in patients with neoplasm undergoing endoprosthetic reconstruction. Although the beneficial role of perioperative antibiotic prophylaxis is proven, it is not known whether continuation of antibiotics beyond the traditional 24 hours is beneficial. Further, there is no consensus among the experts on the type of antibiotic prophylaxis that may be needed in tumor surgery patients with great variation between centers. Although most surgeons provide gram-positive coverage, others also provide gram-negative coverage. In addition, the length of administration of postoperative antibiotics has varied vastly [2,15]. A cross-sectional international survey of practicing orthopaedic oncology surgeons found that 73% (95% confidence interval (CI) 61, 82%) of respondents prescribe a first-generation cephalosporin, 25% favor additional coverage with an aminoglycoside (gentamycin) and/or vancomycin or teicoplanin. Of those who prescribe a cephalosporin, 33% prescribe a dosage of one gram for all patients and the remainder prescribe up to 2 grams based on the body weight. One in three surgeons (95% CI: 25, 48%) believe antibiotics could be discontinued after 24 hours, but 40% of surgeons (95% CI: 30, 53%) continue antibiotics until the suction drain is removed.

In higher-risk cases of tumor patients who have received chemotherapy and/or irradiation, no guidelines exist to direct antibiotic management. It is a common practice to continue the antibiotics beyond 24 hours in these patients. There is no prospective study that has examined the efficacy of different antibiotic regimens in preventing infection in long-bone prosthetic reconstruction [15].

Studies comparing single-dose prophylaxis and multiple-dose prophylaxis in a general surgery setting have not shown any benefit to extended course of antibiotics [16]. A systematic review involving 48 studies on a total of 4,838 patients (level IV retrospective studies) suggests that long-term (greater than 24 hours) postoperative antibiotic prophylaxis is more effective at minimizing infection risk in patients with lower extremity long-bone tumors that require surgery and endoprosthetic reconstruction. However, the data should be interpreted with caution owing to the retrospective nature of the included studies. The overall pooled weighted infection rate for lower-extremity limb salvage surgery with endoprosthetic reconstruction was approximately 10% (95% CI: 8%–11%), with the most common causative organism reported to be gram-positive bacteria in the majority of cases. Twenty studies reported postoperative antibiotic regimens, so they were further subdivided into short-term regimens (0 to 24 hours of postoperative antibiotics) and long-term regimens (greater than 24 hours of postoperative antibiotics) and compared. The pooled infection rate following short-term postoperative antibiotic prophylaxis was 13% (95% CI: 9% to 17%; $p < 0.001$), which is slightly higher than the overall pooled infection rate. The pooled infection rate for the long-term postoperative antibiotic prophylaxis was 8% (95% CI: 6% to 12%; $p < 0.05$), which is slightly lower than the overall pooled infection rate. This difference in the pooled infection rates following short-term and long-term postoperative antibiotics was statistically significant ($p < 0.05$) [2].

There is no dispute to suggest that tumor patients undergoing endoprosthetic reconstruction are at higher risk of infection than those undergoing conventional joint arthroplasty. The risk of infection is further increased in patients who have received chemotherapy or irradiation treatment. Thus, any measure to minimize the risk of infection in this patient population needs to be implemented. We have proposed some preventative measures above but there is a desperate need for further studies to examine further measures.

* These authors answered a different question that was very similar to this one. The consensus voted to remove that question from publication due to its similarity with the current question. Though the question was removed, we want to acknowledge these authors for their work.

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## 1.3. PREVENTION: RESEARCH CAVEATS

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## QUESTION 1: What are the significant risk factors for surgical site infection/periprosthetic joint infection (SSI/PJI) of an oncologic endoprosthesis following resection of a malignant bone tumor?

**RECOMMENDATION:** Patient-related risk factors for SSI/PJI of an oncologic endoprosthesis include increased patients' body mass index, overall presence of comorbidities, coexistence of superficial SSI or skin necrosis and lower preoperative hemoglobin or albumin levels. Disease-related risk factors for SSI/PJI of an oncologic endoprosthesis include lesion localization in proximal tibia, pelvis and lesion extending to pelvis from proximal femur. In addition, procedure related risk factors for SSI/PJI include preoperative hospitalization longer than 48 hours, resection of greater than 37% of the proximal tibia, resection of 3 or 4 heads of the quadriceps muscle in distal femoral lesions compared to 1 or 2 heads, increasing surgical time (longer than 2.5 h), use of cemented oncologic endoprosthesis, need for postoperative admission to the intensive care unit, increased postoperative blood transfusion requirement (2 or more units of allogeneic packed cells), presence of postoperative hematoma and the need for additional surgical procedures after the megaprosthesis implantation.

**LEVEL OF EVIDENCE:** Moderate

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

### RATIONALE

Periprosthetic joint infection represents one of the most challenging complications following any joint replacement and may result in devastating consequences. According to a recent systematic review, the mean rate of periprosthetic infection of a megaprosthesis (PMI) is 10% after primary procedure and 43% after revision procedures of infected cases [1,2].

Despite the lack of multiple randomized clinical trials, several retrospective studies (Level IV) showed significant risk factors for SSI/PJI of an oncologic endoprosthesis following resection of a malignant bone tumor. In a systematic review of the literature, De Gori et al. examined risk factors for PMI [3]. A total of 8 articles, all retrospective, including 2,136 patients, met the inclusion criteria and were analyzed [4–11]. The overall PMI rate was 14.2%. Patient-related factors associated with a significantly higher risk of PMI included increasing patients' body mass index and overall presence of comorbidities (but not the American Society of Anesthesiolgists (ASA) score or diabetes mellitus specifically) and coexistence of superficial surgical site infection or skin necrosis. Disease-related factors associated with increased risk for PMI included lesion localization in proximal tibia, pelvis and lesion extending to pelvis from proximal femur. In contrast, lesions localized in the distal femur appear to be protective for PMI occurrence. There was no association between primary tumor histological features or metastatic spread and PMI. In addition, there was no significant effect of chemotherapy and radiotherapy for the development of PMI, which is in contrast to several studies [12–15] which report increased incidence of infection rate associated with chemotherapy and radiotherapy. Controversy also still exists regarding whether primary or metastatic lesions have higher risk for PMI [3,12]. In this systematic review, procedure-related factors associated with higher risk of PMI included preoperative hospitalization longer than 48 hours, resection of greater than 37% of the proximal tibia, resection of 3 or 4 heads of the quadriceps muscle in distal femoral lesions compared to 1 or 2 heads, increasing surgical time (longer than 2.5 h), need for postoperative admission to the intensive care unit, increased postoperative blood transfusion requirement (2 or more units of allogenic packed cells), presence of postoperative hematoma and the need for additional surgical procedures after the megaprosthesis