Infected Tumor Prostheses

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educational objectives

As a result of reading this article, physicians should be able to:

1. Understand the epidemiology of megaprosthesis infections.
2. Classify the infections.
3. Know the clinical, histological, and microbiological criteria for the diagnosis of infection.
4. Identify the risk factors for infection and recognize the methods and third-generation metals used to prevent the infections.
5. Provide a rationale for treatment.

ABSTRACT

Infection of tumor prostheses has been a major concern because of the extensive soft tissue dissection, long operating times, and patients’ immunosuppression by cancer and adjuvant treatments. Infections most often present within 2 years postoperatively, with approximately 70% of postoperative deep infections presenting within 12 months after surgery. They are typically low organism burden infections, the pathogenesis of which is related to bacteria growing in biofilms. Staphylococci are the most common pathogens involved in prosthetic joint infections, accounting for approximately 50% of infections overall, followed by streptococci, enterococci, Enterobacteriaceae species, and...
**Pseudomonas aeruginosa**, and **anaerobe** species. Multiple pathogens may be isolated in approximately 25% of cases, with the most common combination being coagulase-negative *Staphylococcus* and group-D *Streptococcus*. Early diagnosis and appropriate treatment are necessary. However, diagnosis may be challenging because clinical symptoms are highly variable and numerous preoperative and intraoperative diagnostic laboratory tests are nonspecific. In most cases, a 1- or 2-stage revision surgery is necessary for eradicating the megaprosthetic infection. Prevention of infection is important. The future will see technical advances for infections of tumor prostheses in areas such as microbiological diagnostics and biofilm-resistant prostheses.

The long-term survival of patients with malignant bone tumors has increased due to better imaging modalities, improved understanding of tumor biology, and advances in chemotherapy and radiation therapy. Although patients with bone tumors usually require limb amputation in the past, current limb salvage surgery and megaprosthetic or allograft reconstruction can be performed in 80% to 85% of cases. The advantages of megaprosthetic reconstruction include early stability, rapid restoration of function, good long-term functional outcomes, and patients' high acceptance and emotional satisfaction. However, the reported complication rate of tumor prostheses remains 5 to 10 times higher than the respective rates seen in routine total joint arthroplasties. These include mechanical failures, such as breakage or fracture of the implant and instability due to wear, and biologic failures, such as infection, aseptic loosening, and wound or soft tissue breakdowns. These events require additional treatment and revision of the prostheses beyond those needed for the original limb salvage.

Infection of tumor prostheses has been a major concern because of the extensive soft tissue dissection, long operating times, and patients' immunosuppression by cancer and adjuvant treatments. The infection rate after primary limb salvage surgery has been between 8% and 15%. Following revision surgery, an infection rate as high as 43% has been reported. The infection rate of tumor prostheses has been comparable with that associated with other methods of reconstruction following limb salvage surgery, such as autograft or allograft reconstruction.

Infection of the megaprostheses exposes the patient to the risks of repeated surgical procedures, long rehabilitation, pain, a possibly poor functional outcome, and amputation. The risk of amputation due to infected tumor prostheses for oncological reconstructions has been reported to be between 23.5% and 87%. One study of 547 patients who underwent megaprosthetic reconstruction after resection of osteosarcoma reported a survival advantage in patients with infected megaprostheses, suggesting a potential immunologic antineoplastic advantage induced by infection that can potentially be isolated and used in sarcoma treatment.

**Epidemiology**

Megaprosthetic infections are typically low organism burden infections, the pathogenesis of which is related to bacteria growing in biofilms. Bacterial biofilm is defined as a sessile microbial community characterized by cells that attach to a substratum or to each other (embedded in a matrix of extracellular polymeric substances that they have produced) and exhibit an altered phenotype with respect to growth rate and gene expression. Biofilm-associated bacteria exhibit dramatically increased antimicrobial resistance compared with bacteria studied in suspension cultures.

The presence of organisms in biofilms and the associated low organism burden may also explain the poor sensitivity of Gram stain and culture of synovial fluid and periprosthetic tissue. The prostheses may be colonized by the bacteria at the time of implantation, either through direct inoculation or airborne contamination of the wound or later through hematogenous seeding or direct contiguous spread.

*Staphylococci* are the most common pathogens involved in prosthetic joint infections, accounting for approximately 50% of infections overall, followed by *Streptococci, enterococci, Enterobacteriaceae species, Pseudomonas aeruginosa,* and *anaerobe* species. Multiple pathogens may be isolated in approximately 25% of cases, with the most common combination being coagulase-negative *Staphylococcus* and group-D *Streptococcus*. However, the presence of multiple pathogens has not been associated with poorer results of treatment of the infection or acceptable functional results of the surgery.

**Classification**

Infection most often presents within 2 years postoperatively, with approximately 70% of postoperative deep infections presenting within 12 months after surgery. Prosthetic joint infections have been classified as class I (or early infections occurring within 4 weeks postoperatively), class II (occurring between 4 weeks to 2 years postoperatively), and class III (late infections occurring thereafter).

Class II infections are usually hematogenous in origin. Early postoperative and hematogenous prosthetic joint infections are typically caused by relatively virulent pathogens, such as *S aureus,* and are often characterized by acute onset of symptoms and signs of infection including a persistently leaking wound or acute onset of fever, pain, swelling, effusion, and erythema at the implant site. Untreated infections may lead to chronic sinusoses formation, bacteremia, and sepsis.

Late postoperative prosthetic joint infections are generally chronic (low grade) and more commonly associated with relatively less virulent pathogens, such as...
coagulase-negative Staphylococci. Late infections are characterized by more subtle signs of inflammation and chronic persistent postoperative pain. Radiographic evidence of early loosening of the implant may be present; however, in the absence of a sinus, it can be difficult to distinguish septic and aseptic loosening. In general, loosening occurring relatively soon within the projected lifespan of a prosthetic joint should be suggestive of infection.

**Risk Factors**

Complex arthroplasty and reconstruction procedures, large implant sizes, greater surgical exposure, soft tissue dissection or resection, lack of soft tissue cover, malignant tumors, previous surgery, long operating times, radiation therapy, and immunosuppression are the major factors associated with higher infection rates of tumor prostheses compared with conventional arthroplasties performed for uncomplicated primary arthritis.

In a series of patients with limb salvage surgery and megaprosthetic replacement, the infection rate in the group who did not have radiation therapy was 9.8%, compared with 20.7% in those who had preoperative radiation and 35.3% in those who had postoperative radiation therapy.

Other reported risk factors for megaprosthetic infections were malnutrition, anemia, chemotherapy, advanced age, diabetes mellitus, previous native joint infection, obesity, skin disease, and preexisting joint disease. In a series of patients with limb salvage surgery and megaprosthetic replacement, the infection rate in the group who did not have radiation therapy was 9.8%, compared with 20.7% in those who had preoperative radiation and 35.3% in those who had postoperative radiation therapy.

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**Diagnosis**

Early diagnosis of infection and appropriate treatment are necessary. However, diagnosis may be challenging because clinical symptoms are highly variable, and numerous preoperative and intraoperative diagnostic laboratory tests are nonspecific (Table). The diagnosis of infection should be made by a combination of clinical, histological, or microbiological criteria. Patients are considered to have a deep infection if they had clinical evidence of infection with a positive micro-
biological culture or periprosthetic pus and histology compatible with infection at operation. When possible, antibiotics should be withheld until all diagnostic microbiological tests have been completed. Preoperative administration of antibiotics is accepted in patients in which sepsis or deteriorating local disease demands immediate antibiotic therapy.

Routine blood tests that show a raised C-reactive protein or white blood cell count may suggest a diagnosis of infection. However, these are not helpful in the early postoperative period because they will be increased for approximately 14 days postoperatively regardless. However, persistent elevated values increase the possibility of infection.

Radiographs are not useful in early infections but may help exclude other causes of joint symptoms and signs. In chronic infections, radiographs may show bone loss and evidence of loosening around an implant, but these findings are not specific for infection. Ultrasonography may show joint effusion or synovial hypertrophy, and if the joint is amenable to aspiration or biopsy this should be attempted and samples should be sent for histology and microbiology. Magnetic resonance imaging is not generally of value due to artefacts from the prosthesis. The use of combined labeled leukocyte imaging and complementary bone marrow imaging with technetium 99m sulfur colloid is logical and reliable because both radiotracers accumulate in marrow regardless of its location, whereas only labeled leukocytes accumulate in infection but sulfur colloid does not. The combined labeled leukocytes-technetium 99m sulfur colloid marrow imaging is positive for infection when there is activity on the labeled leukocyte image without corresponding activity on the marrow image. When any other pattern is present, the study is negative for infection.

Exactly why hematopoietically active marrow develops around joint prostheses is uncertain. This phenomenon may be due, in part, to displacement of the marrow during the implantation process. Perhaps the intramedullary component of the prosthesis stimulates the conversion of fatty marrow into hematopoietically active marrow. Aseptic loosening is frequently accompanied by an intense inflammatory reaction, which may also stimulate the conversion of fatty marrow into hematopoietically active marrow. Regardless of the explanation, insertion of a joint prosthesis can produce alterations in the normal distribution of the bone marrow. The combined labeled leukocytes-technetium 99m sulfur colloid marrow imaging allows this problem to be overcome and permits the accurate assessment of whether infection is present.

Synovial aspiration is associated with a small risk of introduction of infection and is not always possible or may be difficult. Microbiological examination of synovial fluid is generally helpful when a pathogen is detected. However, a negative result does not exclude a megaprosthetic infection; cultures of synovial fluid may be negative because of prior antimicrobial exposure, a low number of pathogens because of adherence to the prosthesis surface, inappropriate culture media (such as in the case of anaerobes), and fastidious or atypical organisms such as mycobacteria. Sinus tract cultures should be avoid-
ed because they may represent colonization with normal skin organisms.26

Fluoroscopy-guided biopsy and multiple arthroscopic-assisted synovial biopsies may increase the chances of sampling the area with the highest density of organisms in chronic infections.31 The development of nucleic amplification techniques is promising for the detection of new and fastidious pathogens.31 The realization that bacterial 16S ribosomal DNA (rDNA) can be rapidly detected directly in clinical specimens and that the source bacterium can be accurately identified by studying the sequence of the rDNA has introduced a new era in diagnosing prosthetic joint infections.26

**TREATMENT**

The treatment of patients with infected tumor prostheses is often challenging and time consuming, with a high number of reoperations required.14 Early diagnosis, selection of an appropriate treatment strategy, accurate identification of the responsible pathogens, and construction of an appropriate antibiotic regimen are essential elements of any management strategy.31

Several strategies to reduce the frequency or severity of infections related to oncological reconstructions have been introduced. These include perioperative antibiotic prophylaxis, the use of antibiotic impregnated allografts and cement, sterilization of prostheses or grafts by microwave or autoclaving, and the evolution of noninvasive expandable prostheses.52-54 The results of these strategies vary depending on the susceptibility of the infecting pathogen, the type and duration of postoperative antibiotics, the timing of reimplantation of a new prosthesis, and the use of allograft bone and cemented or cementless implants in the subsequent reconstruction.33,37

In general, the options for management include no surgery (with or without antibiotic suppression), amputation, joint fusion (Figure 1) or removal, prosthesis retention with debridement, lavage, irrigation and antibiotics, and 1- or 2-stage joint revision (Figure 2).31,37

Conservative surgical management involves debridement of a joint with exchange of modular components but retaining the prosthesis itself, combined with prolonged antibiotic therapy.31 Some reported that arthroscopic debridement is as effective as open debridement in prosthetic knee joints that are well fixed with little cement.32 Conservative treatments may be effective in early infections, patients with a short duration of symptoms, a well-fixed and functional implant, and ideally with well-characterized microbiology demonstrating a highly susceptible pathogen.56

Late prosthetic infections have been associated with poor results when treated by lavage, debridement, and prolonged antibiotics administration.57 Eradication of late infections with local treatment alone has been successful in only 6% of patients.35 In addition, the long-term use of oral antibiotics should be avoided in patients with persisting infection because of the possibility of a resistant strain and loosening due to progressive bone loss.38 In these cases, removal of the infected prosthesis should be performed as either a 1- or 2-stage procedure or an amputation.5,6,11,18,36 These treatments successfully eradicated the infection in 98% to 100% (amputation), 72% to 91% (2-stage revision), and 42% (1-stage revision) of cases.18

One-stage revision involves removal of all modular components and polyethylene parts, with the exception of the anchorage components, in addition to thorough debridement of all infected surrounding soft tissues and the periprosthetic scar tissue sleeve.37 One-stage revision of infected tumor prostheses has been recommended for patients with early or low-grade infection and antibiotic-sensitive pathogens, poor general condition of the patient, and long delay of chemotherapy.36,38,58 Patients treated with revision surgery within 2 weeks of diagnosis achieved statistically higher rates of implant retention than those treated after 2 weeks.38 The advantages of 1-stage revision procedures are the avoidance of removal of the prosthesis and creation of a large bone defect, the need for only 1 operation, less anxiety for the patient, a shorter period of hospitalization, and lower cost. In addition, it
offers the comfort of continuously preserving the patient’s function and mobility.37 However, in most cases, a 2-stage revision surgery is necessary for eradicating the megaprosthetic infection.2,31,59 Two-stage revision of infected tumor prostheses involves a complete exchange of all prosthetic components and use of systemic antibiotics and antibiotic-loaded bone cement.37 Two-stage revision is recommended for patients with persistent and higher grade infections, antibiotic-resistant pathogens, or a failed 1-stage procedure.36 An attempt at isolating the infecting organism by joint aspiration prior to the 1-stage procedure is of particular importance with this strategy.60 Results suggest that infection in the setting of a well-fixed cementless modular tumor prosthesis can be managed with retention of the anchorage stems as part of a 2-stage revision of an infected tumor prosthesis.21,57 A cement spacer is essential for the knee and hip joint. Commercially available antibiotic-loaded bone cements can be used, and a range of other antibiotics can also be added to the cement provided they are heat-stable.61 Most surgeons administer systemic antibiotics for up to 6 weeks postoperatively, followed by the second stage of reimplantation of a new prosthesis 2 or more months later.62 Reimplantation should be delayed after completion of chemotherapy.36 The disadvantages of 2-stage revision were a long hospitalization, increased bone loss and disuse osteoporosis, difficulty of revision operation, and shortening of the affected limb.63,64

**Prevention of Infection and Third-Generation Metals**

The severe consequences of infection heighten the importance of prevention and emphasize that prevention of infection is of utmost importance after implantation of a prosthesis, especially in patients with tumors. For this reason, several methods have been devised to decrease the risk of contamination and colonization of the implant. These include hygienic precautions, the development of hydrophilic materials to minimize bacterial adhesion, and impregnation with antiseptics and antibiotics. Removing bacteria in a biofilm is impossible, and the local or systemic antibiotic treatment is not effective. In addition, the bacteria are protected by the biofilm from the host’s defense system,65 resulting in local infection and sepsis deriving from switching from sessile bacteria in the biofilm to planctonic forms in the surrounding bone and tissue.66 In most cases, removal or amputation in cases of persistent infection or poor soft tissue conditions are the only solutions.21,36 Therefore, the inhibition of bacterial adhesion is regarded as the most critical step to prevent implant-associated infection.57

In the past, several hypotheses attempted to explain the lower infection rates associated with titanium in comparison with cobalt-chrome alloy. The latter produces reduced biocompatibility because the ions lead to a deficiency of the local monocyte-macrophage system.68,69 Others stated that cobalt-chrome alloy is less readily colonized by host cells and is consequently colonized more easily by bacteria (“race for the surface”).70,71

In a study on the influence of the alloy of megaprostheses on infection rate, cobalt-chrome alloy prostheses were associated with a significantly higher infection rate compared with titanium alloy megaprostheses (31.2% versus 14.2%).72 Third-generation metals, such as silver-coated titanium megaprostheses, may further reduce infections.73 Among metals with antimicrobial activity, silver (in particular free silver ions) has broad-spectrum antimicrobial activity and lower toxicity to cells.73,77 In experimental studies, silver-coated megaprostheses proved their effectiveness in reducing infection rates after artificial colonization.73 Silver compounds are poorly water-soluble, resulting in the release of low concentrations of silver ions into the surrounding medium and blood. However, local or systemic side effects were not observed.74,78 In light of silver’s potential for toxicity, regardless of how limited it may appear to be, extensive research is still essential.74 The future will no doubt see technical advances for infections of tumor prostheses in areas such as microbiological diagnostics and biofilm-resistant prostheses.

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