Management of Postoperative Infection After Limb Salvage Surgery in Osteosarcoma Patients

12

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Abstract

Postoperative infection is one of the most severe complications associated with limb salvage surgery in osteosarcoma patients. The incidence of infection is approximately ten times higher than that of conventional orthopedic surgery, and the impact of infection on limb survival and functional loss is significant. Due to the paucity of the surrounding soft tissue, the local conditions of limb salvage surgery for osteosarcoma patients and the pathophysiological mechanisms of infection are specific. Accordingly, preventative strategies should be based both on general guidelines on surgical site infection and on the specific properties of infection associated with orthopedic oncological surgery. Various treatment modalities and their success rates have been reported, and it has been found that the selection of management strategy should be based on both soft tissue conditions and infection conditions, with particular focus on the intensity, establishment period, and extension area of an infection.

Keywords

Limb salvage • Surgical site infection • Osteosarcoma

12.1 Introduction

Osteosarcoma patients are subject to a number of risk factors for postoperative infection, such as a lack of soft tissue, an immunocompromised host condition, and the use of endoprosthetics in reconstruction. Postoperative infection can result in

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T. Ueda, A. Kawai (eds.), *Osteosarcoma*, DOI 10.1007/978-4-431-55696-1_12

long-term hospitalization, a requirement for multistep operations for recovery, a reduced quality of life, and in some cases failure of limb salvage [1].

In this chapter the etiology, management practices for prevention and treatment, and perspectives on postoperative infection are reviewed. The evidence presented here comes from studies of osteosarcoma patients and from studies of cohorts with other malignant bone tumors due to the rarity of studies focusing only on osteosarcoma. However, it should be recognized that the fundamental properties of osteosarcoma patients differ from those with other primary or metastatic malignant bone tumors in terms of age, tumor site, reconstruction modalities, and chemotherapy regimens.

12.2 Defining Surgical Site Infection

The importance of defining surgical site infection (SSI) in surveying, interpreting, forming consensus on, or comparing infection characteristics is emphasized in the Guideline for Prevention of Surgical Site Infection from the US Centers for Disease Control and Prevention (CDC), and failure to use objective criteria has been shown to substantially affect reported SSI rates [2]. In this guideline, SSI is classified into three types: superficial incisional, deep incisional, and organ/space. Deep incisional infection involves deep soft tissues (e.g., facial tissue and muscle layers), whereas organ/space infection occurs in a part of the anatomy other than the incision site or any area that was manipulated during surgery. For all categories, SSI is defined as an infection that occurs within 30 days of surgery without implants or within 1 year with implants (these are now processing of revision at 2013 June [3]). However, these definitions cannot be clearly applied to the field of orthopedic oncology, where infections are often reported over a year post-surgery [1, 4]. As infections associated with limb salvage operations for osteosarcoma have different properties to ordinary SSIs, including those with prosthesis placement for joint reconstruction in degenerative diseases, infection after a prolonged period post-surgery could be accepted as a treatment-related infection if the specific case of osteosarcoma was clearly defined in the reports.

Clinical curing of infections is also difficult to define as recurrence is sometimes seen. Hardes et al. defined a clinical cure of infection as “no clinical signs of inflammation and negative C-reactive protein assessed by the treating clinician at the date of the last available follow-up” [5]. In previous reports, we have applied the same definition [1, 6].

12.3 Etiology

12.3.1 Incidence

The infection rate associated with surgery for malignant bone tumor resection is approximately ten times higher than that for conventional orthopedic surgery, including osteosynthesis, spine surgery, and arthroplasty [1, 7, 8].

For endoprosthesis placement, a recent systematic review of 48 studies, including a total of 4838 patients, concluded that the overall pooled weighted infection rate for lower-extremity limb salvage surgery with endoprosthetic reconstruction was approximately 10 % (95 % CI, 8–11 %) [9]. In addition, several recent studies on reconstruction following resection of a malignant bone tumor, using both biological materials and prostheses, have shown similar values for the incidence of infection at approximately 10 % (Fig. 12.1) [1, 4, 5, 10–33].

12.3.2 Time to Infection Presentation

Hardes et al. have reported that time to infection after insertion of a prosthesis can range from 1 to 70 months (mean, 16 months) [5]. I, along with my colleagues, have previously reported on 57 cases of infection following tumor-related endoprosthetic placement surgery, where time to infection from initial surgery ranged from 1 to

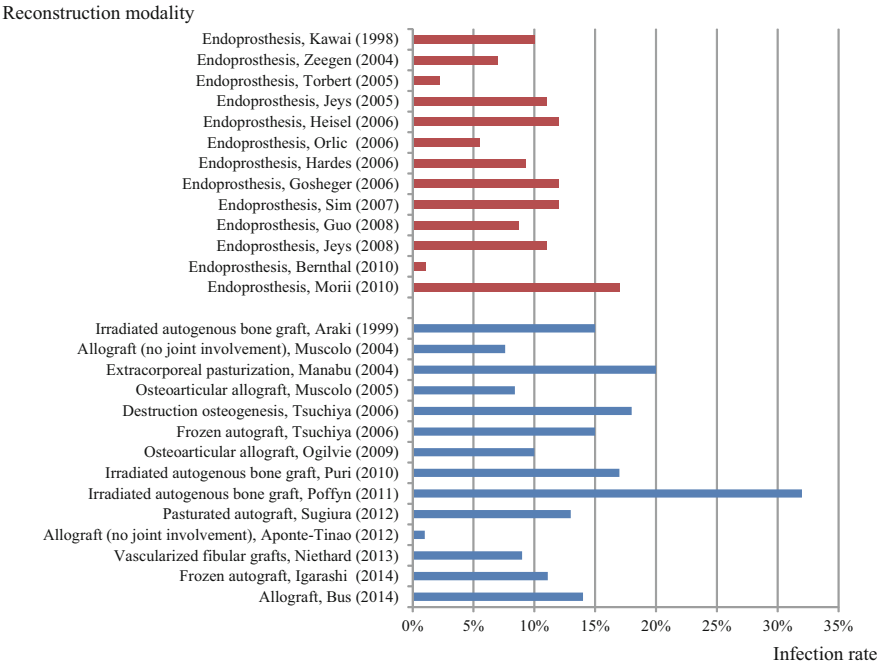

Fig. 12.1 Incidence of surgical site infection by reconstruction modality [1, 4, 5, 10–33]

85 months. In this study, the mean period and median period to infection were 12.8 and 4 months, respectively, and of the total infections 26.3 % occurred more than 12 months after initial surgery [6].

In a study of 76 patients with allografts, six contracted infection. Of these infections, four developed during the early postoperative period, while the other two developed later and were considered to be chemotherapy-related [19]. Meanwhile, in another study of 108 patients undergoing biological reconstruction using irradiated autogenous bone grafts, there were 17 cases of early and 18 cases of late infection [15], suggesting a considerably higher rate of late infection compared with prosthetic reconstruction.

12.3.3 Risk Factors

The incidence of infection seems to be regulated by factors such as tumor site and adjuvant therapy, including neoadjuvant chemotherapy and perioperative radiotherapy. Theoretically, immunological changes due to malignancy or chemotherapy, lack of soft tissue as a result of wide resection, prolonged surgery duration, a large volume of blood loss, a large amount of avascular material in reconstruction, and radiotherapy are all risks for infection in patients with osteosarcoma. Many studies have suggested that tumor site is an obvious risk factor for infection. Figure 12.2

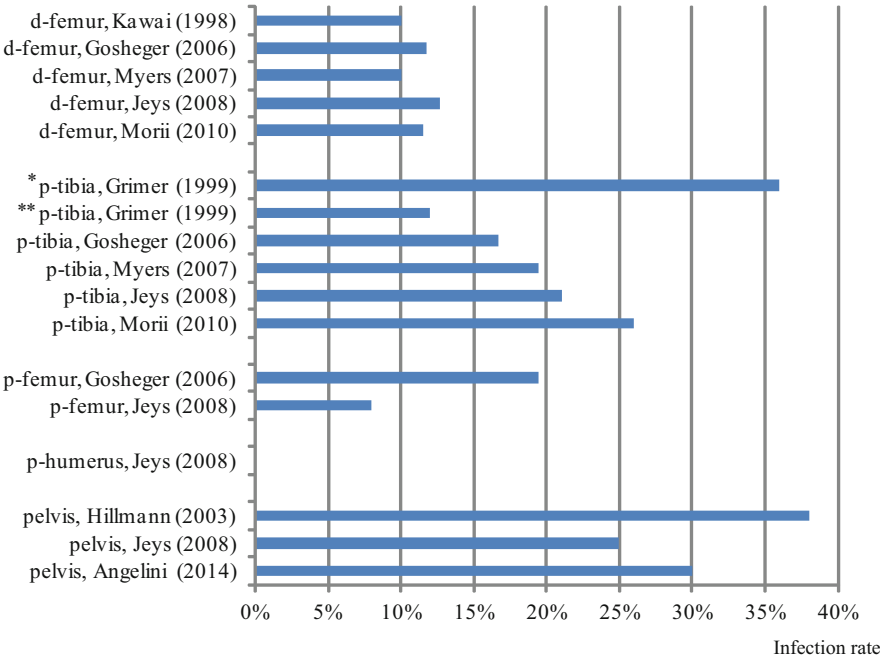

Fig. 12.2 Association between infection rate and the site of endoprosthetic reconstruction. The infection rate with tumor-associated endoprosthetic placement in the proximal tibia is higher in cases without a flap of the medial gastrocnemius* than with** [1, 24, 27, 32–37]

Table 12.1 Risk factors for infection in orthopedic oncological surgery

Significant risks	References
Proximal tibia tumor	[4, 27]
Pelvic tumor	[4, 34]
Proximal femur tumor	[27]
Chemotherapy	[37]
Radiotherapy	[4, 38]
Subsequent patellar resurfacing	[4]
Use of extendable prosthesis	[4]
Subsequent surgery to replace bushing	[4]
Extra-articular resection	[27]
Composite allograft reconstruction (vs. allograft without prosthesis)	[10]
Not using a gastrocnemius flap (for proximal tibia tumors)	[32]
Skin necrosis	[1]
Prior skin infection	[1, 39]
Antibiotic administration <24 h (vs. >24 h)	[9]
Pseudarthrosis in irradiated autograft	[5]
Nonsignificant factors	
Age	[1, 4, 32]
Sex	[1, 4]
Tumor type	[1, 4, 32]
Chemotherapy	[1, 4, 15, 32, 38]
Bone resection length	[1, 32]
Local recurrence	[4]

shows the infection rate with endoprosthesis placement in relation to tumor site [1, 24, 27, 32–37]. Here there is an obviously higher incidence of infection for the pelvis and proximal tibia. In previous reports of infection with malignant bone tumor resection, several significant risk factors for infection have been identified, although some remain controversial (Table 12.1) [1, 4, 9, 10, 15, 27, 32, 34, 37–39]. Some of these factors, such as extra-articular resection and not using a gastrocnemius flap, suggest a close relationship between SSI and a lack of soft tissue, while other factors such as skin necrosis and radiotherapy suggest that the condition of soft tissue is significant in SSI establishment.

12.3.4 Clinical Characteristics

12.3.4.1 Symptoms

Common clinical symptoms of deep infection include pain, local heat, discharge/pus, local redness, and an elevation of body temperature [2]. In my previously described study, discharge/pus around the prosthesis and loosening of the endoprosthesis were detected in 56.1 % and 8.7 % of cases, respectively, and

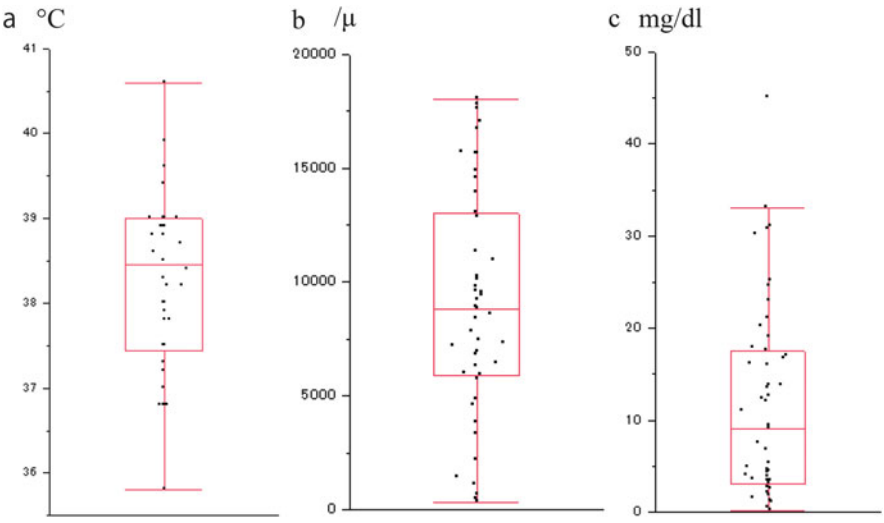

Fig. 12.3 Clinical parameters at the establishment of infection in tumor-associated endoprosthetic placement ([6] and unpublished data from T. Morii), showing (**a**) body temperature, (**b**) white blood cell count, and (**c**) C-reactive protein

body temperature at the time of presentation ranged from 35.8 to 40.6 °C (mean, 38.3 °C; median, 38.5 °C, Fig. 12.3a) [6].

With tumor-related endoprosthetic placement, clinical symptoms are sometimes representative of patient condition. For example, infection has been shown to occur significantly earlier in those with discharge/pus as opposed to those without and significantly later in cases with loosening of the endoprosthesis than in those without. Additionally, discharge/pus was significantly more likely among cases with extra-articular resection [6].

12.3.4.2 Laboratory Data

As for other infections, blood tests including erythrocyte sedimentation rate, C-reactive protein level, and white blood cell counts are used in the diagnosis of SSIs [40]. Grimer et al. reported an elevated erythrocyte sedimentation rate ranging from 31 to 140 mm/h (normal rate <15 mm/h) for patients with endoprosthesis-associated infections [40]. In my previous study, white blood cell counts (per mm^3) ranged from 300 to 18,000 (mean, 9,023; median, 8,800) (Fig. 12.3b) [6]. However, for some immunocompromised patients undergoing systemic chemotherapy, the white blood cell number was below the normal range. In their study, Grimer et al. suggested that white blood cell count was not actually helpful, as it was above 11,000 (per mm^3) for only 12 of the 34 patients [40]. C-reactive protein levels in our study ranged from 0.2 to 45.1 mg/dL (mean, 11.4 mg/dL; median, 9.0 mg/dL, Fig. 12.3c) [6]. In endoprosthesis-associated infection, analysis of synovial fluid, such as synovial fluid white blood cell counts and the calculation

of neutrophil percentage, could be useful for diagnosis [41]. However, technetium bone scans, gallium scans, or white blood cell scans were reported not to be useful [40].

12.3.4.3 Pathogens

In endoprosthesis-associated infection, the infecting organism is isolated in approximately 75.4–93 % of cases [4–6], with coagulase-negative staphylococcus, *Staphylococcus aureus*, and *Staphylococcus epidermidis* infections being common [5, 6, 32, 38, 40]. *Enterococci*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Proteus mirabilis*, and *Streptococcus pyogenes* are found to a lesser extent [5]. In my study, 37 % of *S. aureus* cases were methicillin resistant, and we noted that methicillin-resistant *S. aureus* infection is significantly associated with extra-articular resection and prolonged surgery [6].

In allograft studies, *S. epidermidis*, *S. aureus*, alpha-hemolytic streptococcus, *Pseudomonas* species, *Enterococci*, and *Enterobacter* species have been reported as of the most common postoperative pathogens [19].

12.3.5 Impact of Infection on Patient Outcomes

12.3.5.1 Oncological Outcomes

In general, once infection occurs during the treatment of osteosarcoma, adjuvant chemotherapy is interrupted because of its immunosuppressive effects. Thus, postoperative infection might worsen oncological outcome, especially overall survival. However, others and I have seen no association between infection and oncological outcome [1]. Interestingly, a paper by Jeys et al. reported increased survival after deep postoperative infection in osteosarcoma patients [38]. They speculated that the underlying mechanisms might include stimulation of tumor necrosis factor alpha (TNFα), tumor suppression through cell-mediated cytotoxicity, and prevention of tumor neovascularization due to infection conditions.

12.3.5.2 Limb Survival

Infections associated with endoprosthesis placement following limb salvage surgery for malignant bone tumors have been reported as a risk factor for amputation. Grimer et al. reported a risk of amputation due to infection following tumor-associated endoprosthesis placement in the proximal tibia [32]. Likewise, I have found that in addition to extracapsular resection, infection leads to an increased risk of amputation with prosthetics around the knee, although this was not found to be an independent risk factor in multivariate analysis [42].

12.3.5.3 Prosthesis Survival

Infection following endoprosthesis placement has been reported to impact prosthesis survival. Zeegen et al. reported that, along with prosthesis location, infection was an independent risk factor for prosthesis loss [31]. In my research, I have also found infection to be a significant risk for prosthesis loss [1]. In this series, resection

of extended part of the quadriceps muscle, i.e., loss of soft tissue, was reported to be a risk for deep infection of the proximal femur tumor endoprosthesis. Interestingly, Hardes et al. have emphasized the importance of soft tissue condition in salvaging an infected limb along with prosthesis reconstruction, suggesting a protective role of soft tissue around the prosthesis against infection [5].

12.3.5.4 Limb Function

Zeegen et al. [31] reported that prosthesis infection was an independent risk for functional loss. I have found that functional score can be significantly different between the infected limb and the limb without infection. However, there is no clinical difference in the average scores, at 19.3 and 21.6, respectively, for patients with and without infection [42] using the Musculoskeletal Tumor Society scoring system. These findings suggest that once amputation is avoided through effective treatment of infection, there is no clinical difference in functionality.

12.4 Management

12.4.1 Prevention

12.4.1.1 General Approaches to the Prevention of Surgical Site Infection

Recently there have been many studies on the prevention of SSIs. These include studies on the administration of preoperative antimicrobial agents timed such that serum and tissue concentrations are established at the start of surgery, the implementation of glycemic control in diabetic patients to ensure perioperative blood glucose levels are $<$200 mg/dL [2], the maintenance of perioperative normothermia [43], and the administration of a higher fraction of inspired oxygen (FiO2) both intraoperatively and in the immediate postoperative period [44]. The findings of these studies have been incorporated into guidelines on the prevention of SSIs by the CDC and others. In general, I believe that most of these findings are relevant to infections in osteosarcoma patients. However, in some aspects, there must be differences in the pathophysiological conditions of SSI establishment between conventional orthopedic surgery and surgery for orthopedic malignancy. This is discussed in the next section.

12.4.1.2 Properties of Infections in Orthopedic Oncology

The most obvious risk for infection in osteosarcoma patients is the lack of soft tissue resulting from the wide margin used in tumor resection, and there is a large amount of evidence directly or indirectly suggesting the significance of soft tissue preservation in the management of infection. A study by Grimer et al. in 1999 on the management of proximal tibia osteosarcoma showed an infection rate of 12 % and 36 %, respectively, in cases with and without a gastrocnemius flap [32]. In a study of SSI following proximal tibia reconstruction with prosthesis due to malignancy, patients with gastrocnemius muscle flap coverage at initial surgery needed

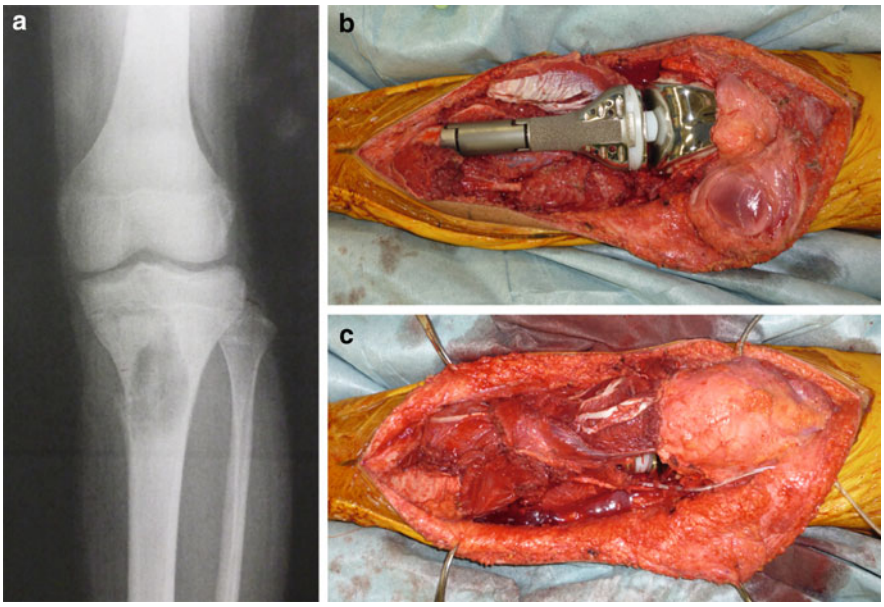

Fig. 12.4 Application of a gastrocnemius flap in the reconstruction of the proximal tibia in osteosarcoma. (**a**) Radiographs at presentation, (**b**) a wide resection of the proximal tibia followed by endoprosthetic reconstruction in a 16-year-old boy with osteosarcoma, and **c** gastrocnemius flap application with blood flow from the posterior tibia vessels

significantly fewer surgical procedures to control subsequent infection than those without a flap [6]. Thus, the routine application of a muscle flap, both with prosthetic and biological reconstruction, is currently recommended for infection control (Fig. 12.4) [10]. Likewise, in a previous study, I have shown that extended resection of the quadriceps in distal femur cases increased the risk for deep infection following prosthetic reconstruction [1]. Patients with extracompartmental resection tend to lose more soft tissue, as a larger margin is resected with the tumor. In infected patients, the final infection control rate is better for intracompartmental rather than extracompartmental resection [6]. Moreover, the risk of amputation is elevated with extracompartmental resection [6]. Although the preservation of soft tissue is practically dependent on the tumor extension, I would refer to the routine use of gastrocnemius muscle flap coverage in proximal tibia cases. In addition, if extended resection of soft tissue is required and a severe lack of soft tissue is expected due to surgery at another site, plastic surgery should be considered at the initial surgery for soft tissue coverage.

These findings highlight the differences in surgical conditions between oncological resection for osteosarcoma and conventional orthopedic surgery. A recent study on SSI in orthopedic surgery recommends a shorter period of single antimicrobial prophylaxis to prevent the emergence of antibiotic-resistant bacterial infection [45]. So far, there have been few studies of antimicrobial prophylaxis

modality in orthopedic oncology. In 2013, Racano et al. conducted a systematic review of articles published in English between 1980 and July 2011 on clinical studies of infection rates in adults with primary bony malignancies of the lower extremities that were treated with surgery and endoprosthetic reconstruction. The pooled weighted infection rate was 13 % after short-term (<24 h) postoperative antibiotic administration and 8 % after long-term (>24 h) postoperative antibiotic administration [9], suggesting that long-term antibiotic prophylaxis reduces the risk of deep infection. Likewise, a considerably lower rate of postoperative infection with long-term antibiotic administration has been recently reported [46]. In addition, others and I have found that the use of one instead of two antibiotics during orthopedic oncological resection and endoprosthetic reconstruction surgery conferred a significant risk of amputation [6]. This shows that the prevention of SSI during conventional procedures is not always applicable to SSI in osteosarcoma surgery. Although the low case number and heterogeneity in terms of tumor location, surgery duration, tumor size, and reconstruction modality, in addition to immunological suppression in patients would make it difficult, concrete guidelines on the prevention of SSI in orthopedic oncology should be established.

12.4.2 Treatment Strategy

Surgical modalities in the control of SSIs involve the preservation of reconstruction materials, or either temporary or permanent removal of reconstruction material. As shown in Fig. 12.5, there is a large variation in the invasiveness of each modality. In general, a higher level of infection control is achieved with more invasive procedures; however, these require more time, surgical procedures, and cost and sometimes incur more functional loss than less invasive procedures. Currently,

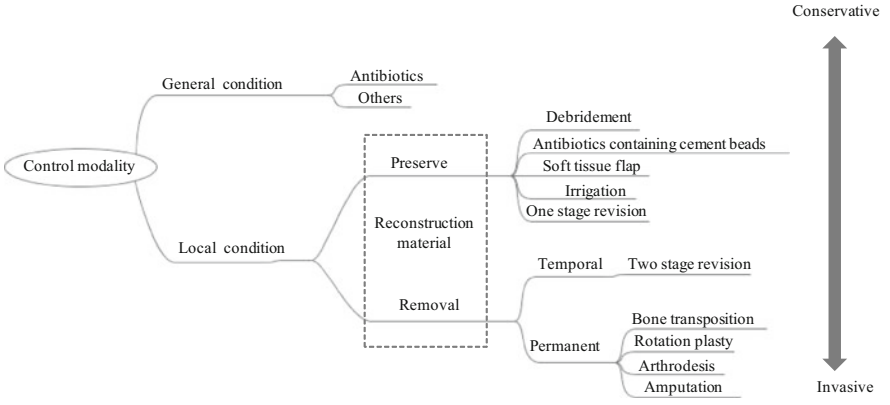

Fig. 12.5 Management modalities for surgical site infection. Surgical modalities involve either the preservation or removal of reconstruction materials. As indicated in the figure, surgery with material removal is more invasive

there are few principles on which to base selection of an appropriate modality. Both patients and surgeons tend to select those in which reconstruction materials such as endoprosthetics are preserved. Recent evidence shows that infection control is more effective with surgical procedures than conservative therapy, and that surgical procedures in which reconstruction material is removed are more effective than those in which it is preserved. For example, in the management of postoperative infection following limb salvage surgery with prosthetic reconstruction, prosthesis removal resulted in better infection control than conservative or prosthesis preserving therapy [4–6].

12.4.2.1 Conservative Therapy

Antibiotic administration is easy to perform and less invasive and is used in the management of most SSIs in the early stages of disease. As mentioned above, infection control with antibiotics alone occurs for <10 % cases with both endoprosthetic [4] and biological reconstruction (Table 12.2) [10, 12–14, 19, 47–49]; however, for both patients and surgeons, this is the best option. Thus, I analyzed the properties of cases from a previous study with tumor-associated endoprosthetic reconstruction around the knee, in which conservative therapy was effective in SSI control, and found that conservative therapy was significantly more successful in cases with prostheses in the tibia than the femur and more successful in cases without discharge/pus at infection presentation [6]. In addition, Hardes et al. reviewed 30 such patients and found that only one patient with a late, low-grade infection could be treated successfully with intravenous antibiotics [5]. In biological reconstruction, surface infection is more successfully controlled by conservative therapy [14, 47].

Table 12.2 Successful modalities for the control of surgical site infection following biological reconstruction

Lead author	Reconstruction modality	Infection control/case number	References
Bus	Allograft	Antibiotics 3	[10]
Aponte-Tinao	Allograft	Two-stage (allograft) 2	[13]
Muscolo	Allograft	Arthrodesis 4	[19]
		Two-stage (composite) 1	
		Two-stage (endoprosthesis) 1	
Niethard	Vascularized fibular grafts	Two-stage (autograft) 2	[12]
Puri	Irradiated autograft	Cement spacer 2	[49]
		Rotationplasty 1	
		Amputation 1	
Sugiura	Pasteurized autograft	Debridement 2	[14]
		Graft removal 2	
Tsuchiya	Distraction osteogenesis	Antibiotics 1	[47]
		Two-stage (bone transport) 1	

12.4.2.2 Surgery Without Reconstruction Material Removal

Infection control modalities that do not involve the removal of reconstruction material include debridement, the use of antibiotic containing cement beads, soft tissue flap, and wound irrigation, either alone or in combination. The principle of these is to alter conditions so that they are less favorable for bacterial growth and more favorable for local immunity, without removing reconstruction materials. It has been shown that soft tissue is critical in the prevention of infection following malignant bone tumor resection [1, 32]; this would suggest that soft tissue reconstruction, such as flap application, should be used as part of the treatment regimen for infection following limb salvage surgery. Obviously, a large amount of good quality soft tissue with a blood supply would improve defenses against bacterial growth. However, in many cases this modality is not sufficient to control infection if conditions around the reconstruction materials are bad, such as an infected bone graft or biofilm formation on an endoprosthesis. Theoretically, once an infection has extended into the medullary area of the bone, these modalities would not be effective in its control because of the weakness of bone against infection. Thus, they should only be used in the early stages of infection. Indeed, the infection control rates associated with these modalities are unacceptable. In my previous study on endoprosthetic infection, infection control rates with soft tissue flap application, irrigation, debridement, and antibiotic containing beads were 43 %, 29 %, 21 %, and 20 %, respectively [6].

Compared with two-stage revision, one-stage revision has advantages such as the avoidance of temporary gross instability, less suffering for the patient, a shorter period of hospitalization, and lower costs [50]. In fact, this type of procedure is successful under limited conditions [4, 5, 50, 51], and, in general, can be used for short-term infections or patients with extreme comorbidities. Hardes et al. reported that debridement with prosthesis retention and one-stage reimplantation without changing stems can be successful in early infections (one superinfected seroma patient); however, they did not recommend one-stage revision in the case of late, high-grade infection [5]. Holzer et al. analyzed their one-stage revision cases and concluded that the procedure should be conducted when infection is localized within the scar tube and does not invade the medullary canal [50]. If anchorage components are well fixed to the bone and the infection does not involve the medullary bone, one-stage revision seems to be more successful. On the other hand, the procedure is not recommended if there is a lack of sufficient soft tissue or in patients with antibiotic-resistant infections. Likewise, for infection control with biological reconstruction, a limited number of cases with one-stage revision have been reported to date (Table 12.2).

12.4.2.3 Two-Stage Revision

The concept of two-stage revision is based on the hypothesis that once an infection becomes chronic and the medullary bone is involved, the removal of bacterial growth cannot be achieved without total resection of the infected material. Taking into consideration the pathophysiological mechanisms of chronic osteomyelitis, this hypothesis seems to be reasonable. Once these conditions are established,

improving the surrounding conditions alone would not sufficiently control infection.

Two-stage revision has been reported to successfully control SSIs around tumor-associated endoprosthetic implants [40]. The process, as described by Grimer et al. [40], includes complete removal of the prosthesis, debridement, and insertion of a sufficiently sized spacer made of cement with gentamicin or vancomycin; this is followed by waiting period (minimum 6 weeks, usually ranging from 10 to 34 weeks) before insertion of the new endoprosthesis. In 24 out of 34 patients, infections were completely controlled using this method [40]. In contrast, Hardes et al. [5] reported that one-stage revision was successful in only one out of three cases, and only in acute, early infections, and they emphasized the importance of the removal of the old stems. In their study, 24 patients underwent two-stage revision and 15 of these underwent reimplantation 3 weeks to 10 months after the initial removal procedure [5]. They emphasized the importance of soft tissue conditions in limb salvage with this process. Likewise for biological reconstruction materials, total removal of infected bone seems to be required. Thus, based on the literature, this modality is frequently successful in infection control, especially for deep and chronic infections (Table 12.2) [12, 13, 19, 47], although the reconstruction modality used for revision surgery shows wide variation including allografts, composites of grafts and prosthetics, endoprosthetics, or bone transposition. Thus, for infection control following limb salvage procedures, two-stage revision is the most reliable method, despite the prolonged treatment period and high costs.

12.4.2.4 Amputation and Other Modalities with Permanent Removal of Reconstruction Materials

Amputation is the final solution in the process of SSI control. Although the functional loss and psychological impact is significant, infection is totally eradicated [6]. For other modalities involving the permanent removal of reconstruction materials, success rates are quite high as the most profound source of infection for late-occurring infections is completely removed. Both for tumor-associated endoprosthesis placement and biological reconstruction, rotationplasty and arthrodesis are limb salvage options in infection control [5, 19, 49].

The decision to amputate is difficult for both patients and surgeons. Thus, amputation at an early stage of the infection control process is unlikely unless there is a specific condition, such as a limited prognosis, in which early hospital discharge is desired. I, together with my colleagues, analyzed the risk factors for amputation in controlling infections following tumor-associated endoprosthesis placement and found that, in the case of metastatic bone tumors, extra-articular resection at initial surgery, the use of a single antibiotic post-surgery, and the presence of discharge/pus at the diagnosis of infection were significant risks [6, 42].

12.5 Perspectives

SSI is a universal complication in surgery. In this chapter, I have emphasized the significance of soft tissue conditions in the establishment of SSIs following orthopedic osteosarcoma resection based on the previous findings. Thus, the most important factors in SSI control seem to be the reconstruction materials used and the soft tissue surrounding them. Here I discuss perspectives in SSI control focusing on these two factors.

12.5.1 Reconstruction Modality

The surface of reconstruction materials is a critical factor in infection as they lack blood supply. The eradication of biofilm-producing bacteria from prosthetic surfaces is difficult, and in these cases, the removal of the medical device seems to be the only way to resolve infection [52, 53]. Thus, the pretreatment of prosthesis surface with antibacterial materials such as silver or iodine has been conducted. Currently, endoprosthetics coated with antibacterial materials are being used in practice [52, 54, 55].

Hardes et al. compared silver-coated endoprosthetics to conventional titanium prosthetics and found a reduction in infection rate from 17.6 % to 5.9 % for the titanium and silver groups, respectively. Moreover, 38.5 % of patients in the titanium group ultimately had to undergo amputation following the development of periprosthetic infection. However, these mutilating surgical procedures were not necessary in the silver group [55].

Tsuchiya and his group at Kanazawa University (Kanazawa, Japan) developed an antimicrobial coating system using titanium implants coated with iodine (Fig. 12.6) and used them in clinical practice [54]. Among the high-risk 158 cases, such as those with cancer, with diabetes mellitus, or undergoing steroid treatment or chemotherapy, postoperative infection occurred in only 3 cases, most of which were cured conservatively. This implies that one of the main factors in preventing SSI in oncological reconstruction is the surface of the prosthesis.

12.5.2 Oncological Management: Preservation of Soft Tissue by Narrowing the Surgical Margin

There is a lot of evidence to show that preservation of soft tissue is critical in the prevention and management of postoperative infection for osteosarcoma [1, 5, 53]. Obviously, a decrease in the wide resection margins is challenging due to the fear of recurrence. Thus, enhancing the effects of adjuvant therapy might decrease the frequency of infection in these patients. Since 1987, Tsuchiya et al. have published reports on the possibility of marginal excision for osteosarcoma in conjunction with caffeine-assisted chemotherapy [56]. Caffeine can enhance the cytocidal effects of anticancer drugs safely through its inhibitory effects on DNA

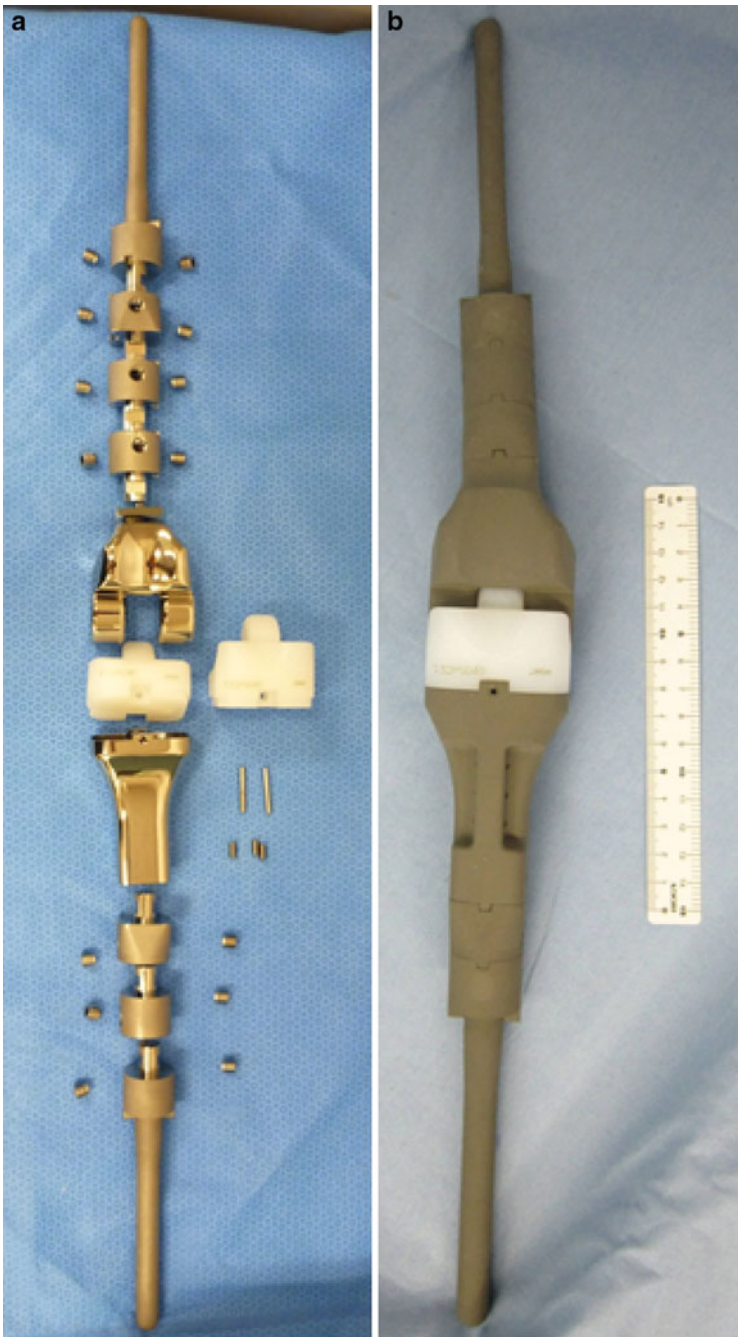

Fig. 12.6 Surface anodization of titanium implants. Povidone-iodine was used as an electrolyte to form an adhesive, porous anodic oxide with the antiseptic properties of iodine. (**a**) Before and (**b**) after modification (Figure kindly provided by Prof. Hiroyuki Tsuchiya, Department of Orthopaedic Surgery, Graduate School of Medical Science, Kanazawa University, Kanazawa Japan)

repair and as a result, the wide resection margins for osteosarcoma can be decreased practically and safely. They reported an infection rate in the treatment of osteosarcoma of 9.5 %. Another candidate for decreasing margins is photodynamic therapy using acridine orange with/without low-dose radiation as proposed by Kusuzaki et al. [57, 58]. Acridine orange has a strong cytocidal effect after it is illuminated with blue light or treated with low-dose X-ray radiation and with local administration has been reported to be equal to conventional wide resection in controlling high-grade sarcoma [59]. In terms of infection control, limited data has been reported on these modalities; however, at least theoretically, their widespread use could reduce infection rates following osteosarcoma surgery.

12.6 Summary

Considering its high incidence compared to conventional orthopedic surgery, the risk of SSI in limb salvage surgery for osteosarcoma should be recognized throughout the treatment period. Although general guidelines on SSI should be understood and reviewed by surgeons, the specific properties of infection in orthopedic oncological patients should be recognized, as the pathophysiological mechanisms of infection are different. Both the reconstruction material used and the surrounding soft tissue are significant in the establishment of infection, in addition to the general condition of patients, and should be well considered in the prevention, treatment, and development of management strategies for postoperative infection after limb salvage surgery in osteosarcoma patients.

This study was supported in part by the Health and Labour Sciences Research Expenses for Commission, Applied Research for Innovative Treatment of Cancer from the Ministry of Health, Labour and Welfare (H26-084).

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