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Infection in orthopaedic oncology: crucial problem in modern reconstructive techniques

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Abstract. – OBJECTIVE: Infection after orthopaedic oncology surgery is a relatively frequent complication. Infection rate ranges in the literature between 3.7% and 19.9%, increasing up to 47% after pelvic resection and reconstruction. It represents a challenging topic when occurring in oncologic patients because of the delay of systemic and local treatments, influencing prognosis. Infection is a major concern in terms of both prevention and treatment. The aim of our review was to analyze data reported in the literature about strategies and new materials for infection prevention in musculoskeletal oncology surgery.

MATERIALS AND METHODS: We reviewed the literature focusing on the use of new materials that can reduce the risk of infection, avoiding biofilm formation on the implant surface.

RESULTS AND DISCUSSION: New materials are available to try to reduce the risk of infection. Iodine-coating, DAC-coating or silver-coating, are the more promising technologies available at today. Initial results with DAC-coating in non-oncological patients are interesting; however, studies about its efficacy in preventing infection in orthopaedic oncology are not present in literature. On the other side, iodine-coating implants or silver-coating prostheses demonstrated efficacy against early infections, associated with lower risk of implant removal and amputation as final surgery.

CONCLUSIONS: Post-operative infections in orthopaedic oncology surgery are still frequent, and their diagnosis and treatment are demanding. According to the literature, silver-coated prostheses should be considered as the best option in case of revision surgery due to infection. However, there is no evidence that these new materials are effective to decrease the risk of infection drastically. Further studies with numerous series and long-term follow up are required.

Key Words
Infection, Tumour, Prosthesis, Musculoskeletal, Orthopaedic.

Introduction

Infection after total hip arthroplasties (THA) or total knee arthroplasties (TKA) is a public health issue as it may cause 5-12% revision arthroplasties with a mortality rate of 0.15%[1-4]. In non-oncological patients, the infection rate after arthroplasty ranges in the literature between 0.2% and 3.5% after primary THA[5-11], and between 0.39% and 1.22% after primary TKA[12-14].

Infection after prosthetic reconstruction in patients with bone tumors is a major concern. The higher infection rate after limb salvage procedures is due to extensive soft-tissue dissection, prolonged surgical times, postoperative hematoma and chemotherapy immunosuppression[15-22]. Infection is a relatively frequent complication, ranging in the literature between 3.7% and 19.9%[15-23], and it usually occurs in the first two years after primary surgery[22-36]. Consequently, it is easily understandable how post-operative infection may influence the oncologic outcome of patients delaying adjuvant chemotherapy and radiotherapy, necessary for local and systemic control of the disease. Recently, a large review article[37] reported the effectiveness of antimicrobial sutures in decreasing the risk for surgical site infection. However, when infection occurs, many options are feasible. Treatment of patients with deep infection requires an appropriate multidisciplinary approach based on early diagnosis, accurate identification of responsible pathogens, and the correct strategy of treatment with adequate antibiotic regimen[25].

Diagnosis of infection is still tricky and widely accepted guidelines are absent[25,38]. Typical clinical signs of inflammation, such as fresh joint pain, fever, erythema, and blood exams alteration (i.e., high white blood cell count, increased C-reactive protein and erythrocyte sedimentation velocity), associated with bone reabsorption or prosthetic loosening, remain the basis of suspicion of in-

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fection. Procalcitonin levels could be also useful in the evaluation of bloodstream infection for both Gram-positive and Gram-negative bacteria[39]. However, diagnosis of certainty is possible only in case of microorganism isolation. The microorganism can be identified analyzing synovial fluid, periprosthetic tissue samples or cultures after sonication[40-41]. The difficulties in diagnosis of infection often cause a delayed treatment. Treatment of deep infection is often challenging, with a high number of reoperations requiring prosthesis removal and a considerable risk of secondary amputation[22-36].

Nowadays, many efforts are ongoing to reduce the risk of infection[42-48]. The aim of our review was to analyze data reported in the literature about new materials able to prevent infections in orthopaedic oncology surgery.

Materials and methods

A review of the literature has been done in order to identify studies on the use of materials that can reduce the risk of infection, avoiding biofilm formation on the implant surface. The search of the literature of the past 17 years (from 2000 to 2017) has been performed in PubMed using the "MeSH" infection with and without the terms "bone tumour", "prosthesis", "DAC-coating", "iodine-coating", "silver-coating", and in ISI Web of Knowledge database searching "infection prosthesis" as topic. We excluded from the review analysis: 1) non-English language papers; 2) papers, whose exclusively abstract was available; 3) papers focused on infection in the non-orthopaedic field. We were able to find about 2500 papers that have been analysed independently by the Authors. We focused our attention on articles investigating specific materials for treatment and prevention of infection in orthopaedic surgery. The data resulting from the research were grouped in 4 categories: 1) antibiotic prophylaxis; 2) Iodine-coated implant, produced by the Chiba Institute of Technology (Narashino, Japan); 3) DAC©-coated device, marketed by (Novagenit Srl, Mezzolombardo, Italy); 4) Silver-coated prosthesis.

Results and discussion

Complications of modular prostheses in limb salvage surgery for sarcomas were analysed in a large multicentric study[21]. The incidence of infection reported by the Authors was 7% (385 cases of infection on 5133 patients) in the literature and 8.4% in the experience of 5 referred Centers, collecting the data of 2174 patients. The infection rate remains still high in extensive bone resections (such as total humerus, total femur or extra-articular knee resection) due to large soft tissue dissection and prolonged operative time[21,36,49], or in case of proximal tibia replacement due to inadequate soft tissue coverage[21,22,26,36,50,51]. However, it has been reported that the incidence of deep infection after proximal tibia replacement could be decreased using a medial gastrocnemius flap[20,22,49,51,52], while the use of synthetic ligaments and materials is controversial[11-13,51]. On the other hand, proximal humerus and proximal femur replacement have a lower infection rate, probably thanks to copiousness of soft tissue and vascular supply around these joints[21,31-36,49-56]. Infection is even more frequent after pelvic surgery for sarcoma, reaching 47 % in some series of patients treated with pelvic resection and reconstruction, due to even more long surgery times and proximity to abdominal viscera, in which bacteria normally live[57,58].

Conservative management, which consists in an aggressive surgical debridement without removal of prosthetic components associated with a long intravenous injection of antibiotics, could be successfully be performed only in case of early infections caused by susceptible pathogens without prosthetic loosening[59]. It must be avoided in case of late or persisting infection, where the percentage of success is poor[22,24,32,36]. A one-stage revision should be considered within 3-4 weeks from onset of infection, with a reported healing of about 42%[26-28]. This treatment is indicated in case of early or low-grade infection caused by antibiotic-sensitive pathogens or in case of general poor condition of patient[22,36]. The best chances of recovery from infection have been reported with a two-stage revision (success rate from 72% and 91% of cases[31-34]). This treatment is absolutely recommended in case of persistent infections, caused by antibiotic-resistant pathogens or in case of failed one-stage procedures[22,36]. Despite timely treatment, the risk of secondary amputation remains high, between 23.5% and 87%, and in some cases, only amputation (successful between 98% and 100% of cases) can cure the infection[35,36,53].

Nowadays, the major concern is how to reduce the risk of infection[42-48]. There is a still-open question regarding the antibiotic prophylaxis, which varies from Center to Center depending on surgeons' preferences and habits. To solve this problem, a multicenter prospective study involving some hospitals in USA and Canada was started in 2012[60]. The purpose of this trial was to compare the efficacy of a 24-hour or a 5-day pro-

phylaxis, in terms of lower incidence of postoperative deep infection. The results of a pilot study were published in 2015, confirming the feasibility of the multicenter recruitment of patients, but no data are available regarding the results of the two types of antibiotic prophylaxis, yet[61].

Some recent studies have focused on new materials that can reduce the risk of infection avoiding biofilm formation on implant surface; however, today a few options are available, such as iodine-coating, DAC-coating or silver-coating (Table I).

Since Oduwole et al[62] demonstrated that povidone-iodine was able to inhibit the biofilm formation by Staphylococci, it was used as a prosthetic coating agent. According to Hashimoto technique[63], the surface of the titanium implant was modified in order to obtain a porous coating thick between 5 and 10 μm able to contain 10-12 l g/cm^2 iodine. Some case series[64-66] reported a lower risk of infection using the iodine-coated implant. Tsuchiya et al[64] reported the primary results on a large series of 222 patients (including 95 oncologic cases) treated with titanium implants with iodine coating. These implants were used in 158 patients as primary implants and in 64 patients with infection as revision surgery. At a mean follow-up of 18.4 months, there were 3 (1.9%) infections in the first group (all treated with intravenous antibiotics, without implant removal). In the second group, in which prostheses were implanted as one-stage or two-stage revision, no additional surgery was needed. Shirai et al[65] reported their experience with 47 titanium iodine-coated megaprostheses in patients with bone sarcoma (29 cases), infected total knee arthroplasty (11 cases), chronic osteomyelitis (6 cases), and loosening of total knee arthroplasty (1 case). These prostheses were used to prevent infection in 21 cases and to treat active infection in 26 cases. At a mean follow-up of 30.1 months, there was only one case of infection in the prevention group (4.7%) that was cured by intravenous antibiotics without prosthesis removal; patients in treatment group were cured without additional surgery. Kabata et al[66] used 30 titanium iodine-coated total hip prostheses in 28 patients, to prevent infection in 16 cases (patients with immune system alterations) and treat infection in 14 cases. At a mean follow-up of 33 months, there were no cases of infection in prevention group, while in treatment group all patients with active infection were cured with one-stage or two-stage revision, with the exception of one patient with pelvic tumour replacement, in which C-reactive protein level increased again 24 months later. No side effects were observed in all the studies[64-66].

Another option is the Disposable Antibacterial Coating (DAC) hydrogel that could be combined with various antibacterial agents. It is a biocompatible hydrogel that could be positioned to cover the prosthesis before implantation, in order to avoid biofilm formation and subsequent bacterial colonization. This represents a physical barrier capable to release antibacterial agents, which undergoes complete degradation in the first hours after surgery. Its properties have been evaluated both *in vitro*[67] and *in vivo* studies[68]. Drago [67] studied this device in preclinical settings combining DAC with some antibiotics (i.e., gentamicin, vancomycin, tobramycin, sodium salicylate, N-acetylcysteine, and amikacin), and testing the ability to release antibacterial agents with spectrophotometry and microbiologic assay. They found that antibacterial release was completed 96 hours after implantation, with a peak of concentration between 2 and 4 hours, that is the period in which the biofilm begins to form[67,69,70]. Moreover, DAC combined with vancomycin, gentamicin, and N-acetylcysteine was able to greatly reduce MICs of these antibiotics[67]. Further studies confirmed efficacy and safety *in vivo*[68]: DAC® coating was capable to decrease bacterial count after contamination of an intra-medullary nail by high local MRSA, in rabbits, without side effects, and good long-term histocompatibility with bone tissue. Based on these encouraging results, DAC-coating was used in human patients to prevent deep infection after orthopaedic surgery[42,43]. Malizos et al[42] evaluated DAC-coating in 253 patients treated with open reduction and internal fixation for closed bone fractures. At a mean follow-up of 18.1 months, the use of DAC-coating was associated with a significantly (p=0.03) reduction of deep surgical site infection (0% in treated group *vs.* 4.7% in control group). It was also associated with a reduction, although no significant, of delayed wound healing (3.9% in treated group and 5.5% in control group) and delayed union (1.6% in treated group *vs.* 3.9% in control group). Romanò et al[43] enrolled 373 patients (189 treated and 184 controls) ready to knee or hip replacements, as primary or revision surgery. In treated group, the prosthesis was covered before implantation by DAC-coating, combined with antibiotics agents. At a mean follow-up of 14.5 months, DAC-coating was able to reduce post-operative deep infection both after primary surgery (0.7% in treated group *vs.* 3% in control group) and after revision surgery (0% in treated group *vs.* 13.4% in control group), without adverse effects.

Table I. Summarizing of study present in literature about new materials to prevent infection in orthopaedic surgery

Authors	Material	N. Patients (Case/control)	Follow-up	Risk of Infection	Treatment of infection
Hardes 2010	Silver prosthesis	125 (51/74)		5.9% in silver group 17.6% in titanium group	Silver group: antibiotic treatment (66.7%), one stage (33.3%) Titanium group: two-stage revision (53.8%), amputation (38.5%), prosthesis removal (7.7%)
Tsuchiya 2012	Iodine-coated implant	222	18.4 months	1.3%	Intravenous antibiotics, without implants removal
Shirai 2014	Iodine-coated prosthesis	47	30.1 months	2.1%	Intravenous antibiotics, without implants removal
Kabata 2015	Iodine-coated prosthesis	30	33 months	3.3%	–
Romanò 2016	DAC-coating prosthesis	373 (189/184)	14.5 months	0.7% in treated group 16.4% in control group	
Donati 2016	Silver prosthesis	68 (38/30)	46.5 months	7.9% in silver group 6.7% in titanium group	–
Scoccianti 2016	Silver prosthesis	33	25.9 months	9%	One-stage revision (66%), conservative treatment (34%)
Malizos 2017	DAC-coating implant	253 (126/127)	18.1 months	0% in treated group 4.7% in control group	
Wafa 2015	Silver prosthesis	170 (85/85)		11.8% in silver group 22.4% in titanium group	Silver group: Conservative debridement + antibiotic (70%) Titanium group: Conservative debridement + antibiotic (31.6%)
Hardes 2017	Silver prosthesis	98 (56/42)		12.5% in silver group 19% in titanium group	Silver group: antibiotics alone (14.3%), one-stage (28.6%), two stage (42.8%), amputation (14.3%) Titanium group: amputation (37.5%) and two-stage (62.5%)
Schmolders 2017	Silver prosthesis	30		3.3%	Two-stage
Schmolders 2017	Silver prosthesis	100		10%	Debridement alone (10%), one-stage (40%) two-stage (20%), prosthesis removal (30%)

Although there are no published studies about the efficacy of DAC-coating in preventing infection after orthopaedic oncology surgery, these previous results are encouraging and could justify the use of DAC-coating also in oncologic patients.

More data are available about the experience with silver-coated prostheses[54,46-48,69,72-75]. Three different types of silver-prosthesis are available: MUTARS® prosthesis (Implantcast, Buxtehude, Germany) is a titanium prosthesis covered by layer thick 10-15 mm containing 0.33-2.89 g of silver 99.7% pure and another gold layer thick 0.2 mm, which favours the release of ions. Stanmore prosthesis® (Stanmore Implants Worldwide Ltd, Elstree, United Kingdom) is covered by a layer thick 5 mm containing 0.006 g of Agluna® silver (Accentus Medical Ltd, Oxfordshire, United Kingdom). Link prosthesis® is covered by a deep layer thick 1 mm containing silver, and by external layer thick 0.1 mm containing TiAg20N. The efficacy of silver in animal model[48] and its safety have been reported[46,47,71], even if the results about silver-coating prosthesis in preventing infection remain controversial. The use of silver-coating in MUTARS® prosthesis seems to reduce the infection rate in the short-medium term; nevertheless, a significant statistical difference has not been reported. Hardes et al[46] compared a series of 51 patients treated with silver prosthesis (22 proximal femur and 29 proximal tibia) and 74 patients with titanium prosthesis (33 proximal femur and 41 proximal tibia) reporting a lower incidence of infection in silver group (5.9% *vs.* 17.6%), even if without significant difference (p=0.062). Considering proximal femur replacement, infection occurred in 18.6% and in 4.5% of patients in titanium group and in silver group, respectively (p=0.222). In proximal tibia replacement, it was 17.1% in titanium group and 6.9% in silver group. In 2017, same Authors[72] revised all cases of proximal tibia resection and reconstruction in their Institution and reported their series of 98 patients (42 titanium prosthesis and 56 silver-coated prosthesis), confirming better results with silver-coating. Schmolders et al[73] reported an infection rate of 3% (1/30) in a series of 30 patients treated with proximal humerus resection and reconstruction with silver-coated prosthesis. Another study[74] from the same Institute reported the outcome in 100 patients treated with silver prosthesis for lower limb reconstruction (52 proximal femur, 30 distal femur, 14 total femur, 1 proximal tibia and 3 Xpand® custom replacements). Infection occurred in 10 patients (10%): 8 cases in proximal femur (15.4%) and 2 cases in distal femur (6.6%). Six of these patients (60%) had acute infection within 4 weeks after surgery; one patient (10%) with pelvic tumour treated with LUMIC® and proximal femur replacement had early infection 2 months after surgery, and 3 patients (30%) had late infection (between 4 months and 2 years after surgery). Donati et al[71] reported a lower incidence of infection in silver group (7.9% *vs.* 16.7%) in a series of 68 patients treated with proximal femur resection and reconstruction at a mean follow-up of 46.5 months. Moreover, the Authors reported a lower incidence of early infection in silver group (2.6% *vs.* 10%), while there were no differences in late infections between the two groups (5.3% *vs.* 6.6%). This result was confirmed by heavy silver layer degradation found in the prostheses after removal. These studies also demonstrate that a less aggressive treatment of infection was possible, using silver-coated prosthesis[46,71-74]. Hardes et al[46] observed that infection was successfully treated by antibiotic treatment (66.7%) or by one stage revision (33.3%) in silver group, while an aggressive treatment, as two-stage revision (53.8%), amputation (38.5%) or definitive prosthesis removal (7.7%) was more frequently necessary in titanium group. In proximal tibia replacement, a lower need of amputation (14.3% *vs.* 37.5%) and two-stage procedure (42.8% *vs.* 62.5%) was observed in silver compared to titanium prosthesis[72]. Schmolders et al[74] reported same results: all cases of acute infections were cured by one-stage revision (66.7%) or conservative debridement (16.6%), while two-stage revision was rarely needed (16.6%). Instead, early and late infections required definitive implant removal (75%) or two-stage revision (25%). Similar results were reported using different types of silver-coating prosthesis[54,75]. Scoccianti et al[75] published a series of 33 patients treated with Link® silver-coated prosthesis after lower limb resection and reconstruction (13 proximal femur, 1 total femur, 13 distal femur, and 6 knee arthrodeses). Twenty-one patients had a previous history of infection, while 12 patients had a higher risk of infection due to poor general conditions. At a mean follow-up of 25.9 months, infection never occurred in patients without a history of a previous infection, while it recurred in only 2 patients (9.5%) previously treated for infected conditions. In all cases, infection was cured with one-stage revision (66%) or conservative treatment (34%). Wafa et al[54] compared 85 Agluna® silver-coated prostheses with 85 titanium prosthesis in a series of patients treated as primary reconstructions (29.4%) and as one-stage (46.5%) or two-stage (24.1%) revisions for infection. Infection was significantly lower (p=0.033) (11.8% *vs.* 22.4%), more easily treated with conservative

debridement and antibiotic administration (70% *vs.* 31.6%), and with a lower risk of chronic infections (3.5% *vs.* 15.3%) in silver compared to titanium group. Moreover, when prosthesis was implanted after two-stage revision, infection was significantly (p=0.05) easier controlled (85% in silver group *vs.* 57.1% in titanium group). Summarizing, the use of silver prosthesis seems to be associated with a lower rate of early infection, and it is particularly useful in two-stage revisions[46,54,71-75].

Conclusions

Post-operative infection in musculoskeletal oncology is still frequent and represents a major concern that could influence patient survival. New materials are available with the aim of reducing the infection rate. Preliminary results with DAC-coating in non-oncologic patients are promising, but studies about its efficacy in preventing infection in tumour megaprostheses are not available. Iodine-coating implants and silver-coating prostheses were able to decrease early infections, and are associated with less aggressive treatment of infection and with lower risk of implant removal and amputation. According to the literature, these prostheses should be used in case of revision surgery due to infection. However, there is no evidence that these new materials are effective to decrease the risk of infection drastically. Further studies with numerous series and long-term follow up are required.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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