2.4. TREATMENT: TWO-STAGE EXCHANGE

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QUESTION 1: What factors may improve the outcome of a two-stage exchange arthroplasty in patients with an infected oncologic endoprosthesis?

RECOMMENDATION: There are numerous factors that improve the outcome of two-stage exchange arthroplasty in general, and after oncologic reconstruction in particular. These include host-related factors (such as host optimization by treating anaemia, malnutrition, hyperglycemia, immunosuppressive state and so on), organism-related factors (such as administration of appropriate systemic and local antibiotics) and surgery-related factors (such as aggressive debridement of soft tissue and bone, optimal soft tissue management and prevention of postoperative complications).

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Surgical reconstruction using a mega-endoprosthesis after tumor resection can be frequently associated with deep surgical site infection that leads to prosthetic joint infection (PJI). The prevalence of PJI associated with oncologic endoprosthesis is 7-28% compared to only 1-2% in primary joint replacements. Cancer patients are at a higher risk for developing PJI after receiving an endoprosthesis due to numerous risk factors, which lead to local and systemic immunodeficiency. These risk factors include chemotherapy, radiotherapy, prolonged surgical time, increased bleeding, larger implant surface area and compromised soft tissue envelope.

In case of an infected oncologic endoprosthesis, debridement, antibiotics and implant retention (DAIR) can be performed, especially in early acute infections (< 3 months). If DAIR fails to eradicate the infection, a two-stage revision is necessary. In literature, two-stage revision is generally reported as a good surgical approach for infection control with a reported success rate of 63-100% [1–6]. Eradication of infection is generally worse after a single-stage revision and, of course, better after an amputation [4,7–9].

Although various studies assessed infection after oncologic endoprostheses, only a few have specifically evaluated the efficacy of DAIR or two-stage revision [2,3]. The factors associated with infection control in oncologic endoprostheses have been individually discussed. After review of the literature, 41 articles were included in our literature analysis. The most important study characteristics are described in the evidence table.

Antibiotics

Little is known about the use of antibiotics in two-stage revision for an infected oncologic endoprostheses. In all studies, antibiotic regimens differed per patient according to culture results and local protocol without specific details being provided. In general, antibiotics should be administered for three months, and the type of antibiotics is decided based on culture results, as well as the consultation with an infectious disease specialist. There are no studies stating that administering antibiotics longer than three months is necessary. Regarding antibiotic prophylaxis, it is recommended to administer prophylactic antibiotics for more than 24 hours, since a systematic review of Racano et al. showed that this reduces the infection rate from 13% to 8% [10]. Regarding the timing for reimplantation after PJI treatment, there is no evidence for the optimal timing other than waiting for completion of chemotherapy before reimplantation [11].

Chemotherapy

The influence of chemotherapy can be expected since it down regulates the host defence mechanisms. However, this is not uniformly reported in the assessed studies. Several studies found an increased risk of developing an infection after implantation of an oncologic endoprostheses in patients undergoing chemotherapy [5,11,12]. However, other studies did not confirm this notion [8,13,14]. Because of the immunocompromised status of patients receiving chemotherapy, it is advised to delay reimplantation until after completion of chemotherapy [15].

Radiotherapy

Application of radiotherapy increases the risk of infection after oncologic endoprosthesis [7,16]. Grimer et al. and Flint et al. found a higher failure rate in patients who underwent radiotherapy [2,3]. Regarding timing of radiotherapy, postoperative radiation has a bigger influence on the infection rate than preoperative radiotherapy [16]. The success rate of DAIR procedures in which postoperative radiotherapy had been applied was lower. Radiation influences the quality of soft tissue and hampers local defence mechanisms.

Microorganisms

The most common microorganisms causing infection of oncological endoprostheses are *Staphylococcus aureus* and coagulase negative staphylococci that account for > 50% of PJI. Many of the documented infections were also polymicrobial infection accounting 21-45% of cases [1,4,7,8,17]. There was no difference between monomicrobial and polymicrobial infections regarding cure rate [4]. A study by Peel et al. demonstrated that the majority of infections were caused by multi-resistant microorganisms [9]. Cure rates for DAIR as well as for two-stage revision after PJI did not show any correlation between the infecting organism and the success of eradicating the infection [2]. It is important to note that the aforementioned results are based on a small number of patients. Therefore, it is difficult to draw firm conclusions that can be generalized to all cases of infection associated with oncologic endoprostheses.

Silver-coated Arthroplasty

Few studies have reported on the benefits of using silver-coated endoprostheses to decrease the risk of developing PJI in patients

treated for primary and metastatic bone cancer. Silver cations possess bactericidal properties by disrupting cellular membrane and DNA formation. Donati et al. and Wafa et al. reported a 50% less incidence of PJI in patients treated with silver-coated megaprosthesis compared to uncoated ones [12,18]. In addition, Wafa et al. showed that the success rate of using DAIR as well as two-stage revision to treat infected silver-coated megaprosthesis was significantly higher than when used to treat infected uncoated implants [12]. Zajonz et al. reported that reinfection rate after healed reinfection in the silver group was slightly better than the non-silver group (40 vs. 57%) [19].

Hardes et al. showed that silver levels in the serum were detected up to 24 months post implantation of sliver-coated prostheses [20]. Also, there were no reports of toxicity or adverse local tissue reaction in patients treated with silver-coated implants. Despite these promising results, there are only a handful of studies that reported on outcomes after using these coated implants.

DAIR

The DAIR procedure is one of the treatment approaches described for PJI of endoprostheses in cancer patients. However, treatment outcomes after DAIR are highly variable and unpredictable in an oncology setting. Success rates vary between 39-70% [1,9,12,17,21]. Reported factors that are associated with better outcomes after DAIR include superficial early infection, short duration of symptoms, well-fixed implants and well-characterized microbiology demonstrating a highly susceptible pathogen [13,15,22]. Unfortunately, the studies that reported on DAIR outcomes have a highly variable period of clinical follow-up (34 months–10 years).

REFERENCES

[1] Dhanoa A, Ajit Singh V, Elbahri H. Deep infections after endoprosthetic replacement operations in orthopedic oncology patients. Surg Infect (Larchmt). 2015;16:323–332. doi:10.1089/sur.2014.049.

[2] Flint M, Griffin A, Bell R, Wunder J, Ferguson P. Two-stage revision of infected uncemented lower extremity tumor endoprostheses. J Arthroplasty. 2007;22:859–865. doi:10.1016/j.arth.2006.11.003.

[3] Grimer R, Belthur M, Chandrasekar C, Carter S, Tillman R. Two-stage revision for infected endoprostheses used in tumor surgery. Clin Orthop Relat Res. 2002;395:193–203.

[4] Jeys L, Grimer R, Carter S, Tillman R. Periprosthetic infection in patients treated for an orthopaedic oncological condition. Journal of Bone and Joint Surgery - Series A 2005;87:842–9. doi:10.2106/JBJS.C.01222.

[5] Lee S, Oh J, Lee K, Yoo K, Kim H. Infection after prosthetic reconstruction in limb salvage surgery. Int Orthop. 2002;26:179–184. doi:10.1007/s00264-001-0328-y.

[6] Morii T, Morioka H, Ueda T, Araki N, Hashimoto N, Kawai A, et al. Deep infection in tumor endoprosthesis around the knee: a multi-institutional study by the Japanese Musculoskeletal Oncology Group. BMC Musculoskeletal Disord. 2013;14:1. doi:10.1186/1471-2474-14-51.

[7] Funovics P, Hipfl C, Hofstaetter J, Puchner S, Kotz R, Dominkus M. Management of septic complications following modular endoprosthetic reconstruction of the proximal femur. Int Orthop 2011;35:1437–1444. doi:10.1007/s00264-010-1054-0.

[8] Hardes J, Gebert C, Schwappach A, Ahrens H, Streitburger A, Winkelmann W, et al. Characteristics and outcome of infections associated with tumor endoprostheses. Arch Orthop Trauma Surg. 2006;126:289–296. doi:10.1007/s00402-005-0009-1.

[9] Peel T, May D, Buising K, Thursky K, Slavin M, Choong P. Infective complications following tumour endoprosthesis surgery for bone and soft tissue tumours. Eur J Surg Oncol. 2014;40:1087–1094. doi:10.1016/j.ejso.2014.02.241.

[10] Racano A, Pazionis T, Farrokhyar F, Deheshi B, Ghert M. High infection rate outcomes in long-bone tumor surgery with endoprosthetic reconstruction in adults: a systematic review. Clin Orthop Relat Res. 2013;471:2017–2027. doi:10.1007/s11999-013-2842-9.

[11] McDonald D, Capanna R, Gherlinzoni F, Bacci G, Ferruzzi A, Casadei R, et al. Influence of chemotherapy on perioperative complications in limb salvage surgery for bone tumors. Cancer. 1990;65:1509–1516. doi:10.1002/1097-0142(19900401)65:7<1509::AID-CNCR2820650710>3.0.CO;2-I.

[12] Wafa H, Grimer R, Reddy K, Jeys L, Abudu A, Carter S, et al. Retrospective evaluation of the incidence of early periprosthetic infection with silver-treated endoprostheses in high-risk patients: case-control study. Bone Joint J. 2015;97-B:252–257. doi:10.1302/0301-620X.97B2.34554.

[13] Mavrogenis A, Pala E, Angelini A, Calabro T, Romagnoli C, Romantini M, et al. Infected prostheses after lower-extremity bone tumor resection: clinical outcomes of 100 patients. Surg Infect. 2015;16:267–275. doi:10.1089/sur.2014.085.

[14] Morii T, Yabe H, Morioka H, Beppu Y, Chuman H, Kawai A, et al. Postoperative deep infection in tumor endoprosthesis reconstruction around the knee. J Orthop Sci. 2010;15:331–339. doi:10.1007/s00776-010-1467-z.

[15] Mavrogenis AF, Papagelopoulos PJ, Coll-Mesa L, Pala E, Guerra G, Ruggieri P. Infected tumor prostheses. Orthopedics. 2011;34:991–998. doi:10.3928/01477447-20111021-24.

[16] Jeys L, Luscombe J, Grimer R, Abudu A, Tillman R, Carter S. The risks and benefits of radiotherapy with massive endoprosthetic replacement. J Bone Joint Surg Br. 2007;89-B:1352–1355. doi:10.1302/0301-620X.89B10.19233.

[17] Manoso M, Boland P, Healey J, Cordeiro P. Limb salvage of infected knee reconstructions for cancer with staged revision and free tissue transfer. Ann Plast Surg. 2006;56:532–535. doi:10.1097/01.sap.0000203990.08414.ad.

[18] Donati F, Di Giacomo G, D'Adamio S, Ziranu A, Careri S, Rosa M, et al. Silver-coated hip megaprosthesis in oncological limb salvage surgery. BioMed Res Int. 2016;2016:1–6. doi:10.1155/2016/9079041.

[19] Zajonz D, Zieme A, Prietzel T, Moche M, Tiepoldt S, Roth A, et al. Periprosthetic joint infections in modular endoprostheses of the lower extremities: a retrospective observational study in 101 patients. Patient Saf Surg. 2016;10:1–9. doi:10.1186/s13037-016-0095-8.

[20] Hardes J, Ahrens H, Gebert C, Streitbuerger A, Buerger H, Erren M, et al. Lack of toxicological side-effects in silver-coated megaprostheses in humans. Biomaterials. 2007;28:2869–2875. doi:10.1016/j.biomaterials.2007.02.033.

[21] Bus M, Szafranski A, Sellevold S, Goryn T, Jutte P, Bramer J, et al. LUMiC endoprosthetic reconstruction after periacetabular tumor resection: short-term results. Clin Orthop Relat Res. 2017;475:686–695. doi:10.1007/s11999-016-4805-4.

[22] Li X, Moretti V, Ashana A, Lackman R. Perioperative infection rate in patients with osteosarcomas treated with resection and prosthetic reconstruction. Clin Orthop Relat Res. 2011;469:2889–2894. doi:10.1007/s11999-011-1877-z.

[23] Chambers C, Proctor C, Kabler P. Bactericidal effect of low concentrations of silver. J Ame Water Works Assoc. 1962;54:208–216.

[24] Felden A, Vaz G, Kreps S, Anract P, Hamadouche M, Biau D. A cemented acetabular component with a reinforcement cross provides excellent medium-term fixation in total hip arthroplasty after pelvic irradiation. Bone Joint J. 2015;97-B:177–184. doi:10.1302/0301-620X.97B2.34545.

[25] Gitelis S, Yergler J, Sawlani N, Schiff A, Shott S. Short and long term failure of the modular oncology knee prosthesis. Orthopedics. 2008;31:362.

[26] Hardes J, von Eiff C, Streitbuerger A, Balke M, Budny T, Henrichs M, et al. Reduction of periprosthetic infection with silver-coated megaprostheses in patients with bone sarcoma. J Surg Oncol. 2010;101:389–395. doi:10.1002/jso.21498.

[27] Henderson E, Groundland J, Pala E, Dennis J, Wooten R, Cheong D, et al. Failure mode classification for tumor endoprostheses: retrospective review of five institutions and a literature review. J Bone Joint Surg Am. 2011;93:418–429. doi:10.2106/JBJS.J.00834.

[28] Hollinger M. Toxicological aspects of topical silver pharmaceuticals. Crit Rev Toxicol. 1996;26:255–260.

[29] Hsu R, Sim F, Chao E. Reoperation results after segmental prosthetic replacement of bone and joint for limb salvage. J Arthroplasty. 1999;14:519–526.

[30] Jacobs J, Kull L, Frey G, Gitelis S, Sheinkop M, Kramer T, et al. Early failure of acetabular components inserted without cement after previous pelvic irradiation. J Bone Joint Surg Am. 1995;77:1829–1835. doi:10.2106/00004623-199512000-00006.

[31] Jeys L, Grimer R, Carter S, Tillman R. Risk of amputation following limb salvage surgery with endoprosthetic replacement, in a consecutive series of 1261 patients. Int Orthop. 2003;27:160–163. doi:10.1007/s00264-003-0429-x.

[32] Jeys L, Grimer R, Carter S, Tillman R, Abudu A. Post operative infection and increased survival in osteosarcoma patients: are they associated? Ann Surg Oncol. 2007;14:2887–2895. doi:10.1245/s10434-007-9483-8.

[33] Jeys L, Grimer R. The long-term risks of infection and amputation with limb salvage surgery using endoprostheses. Recent Results Cancer Res. 2009;179:75–84.

[34] Kaminski P, Szmyd J, Ambrozy J, Jaworski J, Franczuk B. A comparison of outcomes of treatment with resection prosthesis of the hip in revision and oncological surgery. Ortop Traumatol Rehabil. 2017;19:145–156.

[35] Kim K. Uncemented total hip arthroplasty in patients with a history of pelvic irradiation for prostate cancer. J Bone Joint Surg Am. 2007;89:798–805. doi:10.2106/JBJS.F.00183.

[36] Lansdown A. A pharmacological and toxicological profile of silver as an antimicrobial agent in medical devices. Adv Pharmacol Sci. 2010;2010:1–16. doi:10.1155/2010/910686.

[37] Massin P, Duparc J. Total hip replacement in irradiated hips: a retrospective study of 71 cases. J Bone Joint Surg Br. 1995;77:847–852.

[38] Mittermayer F, Windhager R, Dominkus M, Krepler P, Schwameis E, Sluga M, et al. Revision of the Kotz type of tumour endoprosthesis for the lower limb. J Bone Joint Surg Br. 2002;84:401–406.

[39] Pilge H, Gradl G, von Eisenhart-Rothe R, Gollwitzer H. Incidence and outcome after infection of megaprostheses. Hip Int. 2012;22:83–90.

[40] Renard A, Veth R, Schreuder H, van Loon C, Koops H, van Horn J. Function and complications after ablative and limb-salvage therapy in lower extremity sarcoma of bone. J Surg Oncol. 2000;73:198–205. doi:10.1002/(SICI)1096-9098(200004)73:4<198::AID-JSO3>3.0.CO;2-X.

[41] Sherman S, Cunneen K, Walcott-Sapp S, Brause B, Westrich G. Custom total femur spacer and second-stage total femur arthroplasty as a novel approach to infection and periprosthetic fracture. J Arthroplasty. 2008;23:781–786. doi:10.1016/j.arth.2007.05.027.

TABLE 1. Evidence table

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Bus 2017 [21]	Retrospective cohort 2008–2014	N = 47 LUMIC reconstruction for pelvic tumor	* 69% DAIR * 31% implant removal	3.9 years	* 28% had infection. * 69% were successfully treated with DAIR (2). * 31% needed implant removal. Two had amputation, 1 rotationplasty and 1 LUMIC prosthesis. * More blood loss was associated with a higher risk of infection; other factors were not associated.
Chambers 1962 [23]	Narrative review	X	X	X	* Article on the bactericidal effects of silver (1f).
Dhanoa 2015 [1]	Retrospective cohort 2007–2011	N = 105 Endoprosthetic reconstruction for tumor	* 54% DAIR * 46% 2-SR	32 months	* 12.4% infection at 0-63 months. * Higher risk after additional procedures (13x), comorbidity, proximal tibia endoprostheses, pelvic endoprostheses and preoperative hospitalization >48 hour. Lower risk with distal femoral prostheses. * 80% of infections had operations >2.5h, compared to 16.3% in non-infections. * 38% *Staph aureus*, 31% CNS, 23% Klebsiella pneumoniae, 23% Pseudomonas aeruginosa. 38.5% had polymicrobial infection (1d). * 80% of 2-SR were successful; 1 patient had antibiotic suppression. * 43% of DAIR were successful; 2 patients had antibiotics; 2 patients had amputation (2).
Donati 2016 [18]	Retrospective case-control 2005–2016	N = 68 Megaprosthesis reconstruction for proximal femur tumors	X	47 months (12-114 months)	* Overall infection rate 11.8% at mean 25 months: silver 7.9%, control 16.7% (1f). * In late infection, explanted megaprostheses had important degradation of the coating surface (1f). * No differences in functional scores between silver and control (1f). * No local or general signs of toxicity (1f).
Felden 2015 [24]	Prospective cohort 1995–2011	N = 45 Pelvic irradiation before cemented THA	X	51 months (17-137 months)	* Patient survival was 71% at 2y, 52% at 5y and 41% at 10y. * The cumulative probability of revision was 2.2% at 1y, 2.2% at 2y, 8.1% at 5y and 20.2% at 10y. * 6% underwent revision for infection, 1 treated with 2-SR, 2 treated with 1-SR (all successful).
Flint 2007 [2]	Prospective cohort 1989–2004	N = 15 Infection after uncemented Kotz prostheses for bone sarcoma	2-SR	42 months (3-150 months)	* Prosthetic infection occurred at mean 28 months (1-132 months). * 75% CNS, 33% *Staph aureus*, 8% Pseudomonas aeruginosa, 8% E. coli, 8% Streptococcus viridans (1d). * 73% had second-stage revision: 27% had amputation, 73% with infection control after second-stage. * 60% success with retention of diaphyseal stems; 40% success with removal of anchorage pieces. * No relation between success and anatomical location or infecting organism (1d). * 66% of failures had previous radiation (1c). * In case of infection within 6 months 86% of 2-SR was successful, after 6 months only 25%.

TABLE 1. Evidence table (*Cont.*)

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Funovics 2011 [7]	Retrospective cohort 1982–2008	N = 166 Endoprosthetic reconstruction for tumor	* 83% 1-SR * 8% muscle flap * 8% deceased	47 months (0-365 months)	* Survival rate without infection was 95.9% at 1y, 89.2% at 5y, 89.2% at 10y and 77.8% at 20y. * 7.2% had infection at mean 39 months (0-167 months). * 30% CNS, 30% Staph epidermidis. Polymicrobial infection in 30.8% (1d). * Higher rate of infection in primary tumors, cemented prostheses, pelvic reconstruction, additional operations or radiotherapy (1c). * 63% infection control by 1-SR, 13% additional 1-SR, 25% additional 2-SR.
Gitelis 2008 [25]	No full text	X	X	X	X
Grimer 2002 [3]	Prospective cohort 1989–1998	N = 34 Infection after endoprostheses for sarcoma	2-SR	6-116 months	* Obvious causes of infection included lengthening or rebushing procedures, infected ingrown toenail, chest infection, infected burn blister, infected Hickman catheter and neutropenic septicaemia. * 53% CNS, 32% *Staph aureus*, 6% streptococci, 3% Enterobacter and 3% Corynebacterium (1d). * 70% had infection control after 2-SR. 6% needed amputation within 6 months. 6% needed additional 2-SR (1 successful, 1 not). 18% had late infections with various treatments. * Overall success rate for controlling infection was 94% at 6 months, 91% at 1 year, 74% at 5 years and 65% at 10 years. * Reinfection occurred in all 3 patients with previous radiotherapy (1c). * Functional outcome after successful infection control was mean 77% MSTS (47-100%).
Hardes 2006 [8]	Retrospective cohort 1992–2003	N = 30 Infection after MUTARS tumor endoprostheses for sarcoma	* 3.3% antibiotics * 10% 1-SR * 80% 2-SR	32 months (3-128 months)	* Infection occurred at mean time 16 months (1-70 months). * 62% CNS, 21% *Staph aureus*, 14% Enterococcus species. 21% had polymicrobial infections (1d). * 1-SR was successful in 33%, 2-SR in 63% * 33% of 2-SR failures needed amputation, 33% rotationarthroplasty, 11% arthrodesis, 22% retained the spacer (1 died after 4 months, 1 had satisfactory function). * 8.3% needed a change of spacer (1f). * The most important risk factor for failed limb salvage was poor soft tissue. * Chemotherapy, time of occurrence of infection, virulence and type of infection had no influence (1b). * A mean of 2.6 revision operations per patients, mean duration of hospital stay 68 days.
Hardes 2007 [20]	Prospective cohort 2002–2004	N = 20 Silver-coated MUTARS tumor endoprostheses for metastasis	X	19 months (2-32 months)	* No patients had signs of local or systemic argyrosis (1f). * The mean serum silver concentration was 0.37 ppb preoperatively, 2.80 ppb 2 week postoperatively. Between 2 and 24 months silver concentration varied from 1.93 – 12.98 ppb (1f). * 10 patients showed decreased glomerular filtration rates (1f). * The silver-coating was intact in all patients. Histologic examination showed no signs of chronic inflammation, granulomas or necrotic tissue (1f).

TABLE 1. Evidence table (*Cont.*)

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Hardes 2010 [26]	Prospective case-control 2005–2009	N = 51 (74 control) Silver-coated replacement for bone or soft-tissue tumors	Various	19 months (3-63 months)	* 5.9% with silver had infections compared to 17.6% with titanium prostheses, at mean 11 months (1f). * Patients with infection had longer operating time (305 vs. 228 minutes). * 38.5% with titanium prostheses had amputation or rotationplasty for infection, 0% in silver group (1f). * In the silver group 2 were treated with antibiotics alone, 1 had minor revision (one-stage without removal of the stem), all were successful (1f).
Henderson 2011 [27]	Retrospective cohort 1974–2008	N = 2,174 Limb preservation with metallic endoprostheses for tumor	X	X	* 24.5% were considered failures, of which 12% had soft tissue problems, 19% aseptic loosening, 17% fracture, 17% tumor progression, 34% infection. * Infection occurred more often in hinged prostheses than in polyaxial protheses ($p < 0.05$). * Failure incidence decreased over time. The mean time to failure was 47 months. * Literature review of 4359 patients with 29% failures.
Hollinger 1996 [28]	No full text	X	X	X	X
Hsu 1999 [29]	Prospective cohort 1975–1986	N = 38 Limb salvage for tumors needing revision surgery	* 50% revision * 32% amputation * 10% arthrodesis * 8% miscellaneous	51 months	* Indications for reoperation were aseptic loosening (34%), instability (13%), infection (13%), tumor recurrence (13%), fracture (11%) and miscellaneous (16%). * 16% died after revision at a mean of 40 months after revision. * After revision functional results were excellent (12.5%), good (81.3%) or fair (6.25%). * 63% had radiolucent zones immediately after revision. 25% of these developed progressive changes that had an effect on limb function. * Patients with revision had higher survival rates and longer disease-free intervals than patients with amputation ($p < 0.01$). * Overall 18.4% had complications: 5.3% aseptic loosening, 5.3% infection, 2.6% non-union, 2.6% local recurrence and 2.6% instability.
Jacobs 1995 [30]	Retrospective cohort 1983–1991	N = 9 Uncemented THA with previous pelvic irradiation	X	37 months (17-78 months)	* 4/9 radiographic and clinical migrations, 2/4 had revision, of which 1 needed Girdlestone after revision (1c).

TABLE 1. Evidence table (*Cont.*)

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Jeys 2003 [31]	Retrospective cohort 1966–2001	N = 1,261 Endoprostetic replacement	Amputation	5.2 years	* Overall patient survival was 60% at 5 years, 54% at 10 years and 40% at 20 years. * Overall limb survival without amputation was excellent with 91% at 20 years. * Overall risk of amputation was 8.9% of which the reasons were local recurrence (63%), infection (34%), mechanical failure (2%) and persistent pain (1%). * Risk of amputation after infection was 19% compared to 36% for local recurrence. * Time to amputation was a mean of 32 months for infection.
Jeys 2005 [4]	Retrospective cohort 1966–2001	N = 1,240 Prosthetic replacement for bone tumor	* 43% 2-SR * 32% amputation * 24% 1-SR * 2% Girdlestone	5.8 years (0.3-34 years)	* 11% had infection from 1996-2001 3.7%, 14% from 1966-1996. * 88% presented within 2 years after the last surgical procedure. * 48% had Staphylococcus epidermidis, 26% had polymicrobial infection (1d). * Polymicrobial infections did not reduce the rate of successful treatment of infection (1d). * Success rates: amputation 98%, 2-SR 72%, Girdlestone 50%, 1-SR 42%.
Jeys 2007 [32]	Retrospective cohort 1966–2001	N = 412 Endoprosthetic reconstruction for osteosarcoma	X	6.7 years (0-20 years)	* 10% had deep infection at mean time 4.6 months. * 52% had Staph epidermidis, 29% Staph aureus (1d). * There was better survival in patients infected with Staphylococcus (10y survival 92%, mixed organisms 79%, no infection 62.2%, Streptococcus 50%) (1d). * There was no evidence that patients with infections had more effective chemotherapy (1b). * There were more infections after radiotherapy (p=0.02) (1c).
Jeys 2007 [16]	Retrospective cohort 1966–2001	N = 1,254 63 radiotherapy Endoprosthetic replacement for bone tumor	X	5.8 years (0.3-33 years)	* Mean postoperative MSTS function score was lower after radiotherapy (64% vs. 81.3%) (1c). * Risk of infection without radiotherapy 9.8%, preoperative radiotherapy 20.7%, postoperative radiotherapy 35.3% (1c). * Risk of amputation without radiotherapy 7.8%, preoparative radiotherapy 17.2%, postoperative radiotherapy 14.7% (1c). * 10y survival was worse after radiotherapy (29%) than without radiotherapy (58%) (1c).
Jeys 2009 [33]	No full text (chapter book)	X	X	X	X
Kaminsky 2017 [34]	No full text	X	X	X	X

TABLE 1. Evidence table (*Cont.*)

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Kim 2007 [35]	Prospective cohort 1997–2003	N = 51 Uncemented THA with irradiation of the pelvis for adenocarcinoma of the prostate	X	4.8 years (2-7.5 years)	* 47% had radiation induced osteonecrosis of the femoral head (1c). * 6% had wound discharge, which healed without surgical treatment (1c). * 2% had deep infection, which required subsequent resection arthroplasty (successful) (1c).
Lansdown 2010 [36]	Narrative review	X	X	X	* Paper about the mechanisms of absorption and metabolism of silver in the human body, presumed mechanisms of argyria and the elimination of silver-protein complexes in the bile and urine (1f). * Argyria and argyrosis are the principle effects associated with heavy deposition of insoluble silver precipitates in the dermis and cornea/conjunctiva. Argyria is not associated with pathological damage (1f).
Lee 2002 [5]	Retrospective cohort 1985–1998	N = 145 18 infection Tumor prosthesis for bone and soft tissue tumors	* 78% DAIR * 11% 2-SR * 11% 1-SR	44 months (5-136 months)	* 12.4% had infection at mean 8 months (0.5-54 months). * 39% was successfully treated with DAIR or revision; 17% needed arthrodesis and 11% amputation (2). * 100% of 2-SR were successful, 0% of 1-SR were successful. * 33% with uncontrolled infection by DAIR and refused prosthesis removal had suppressive antibiotics. * The knee joint seemed to show poor outcome, but this was not statistically meaningful. * Infection control was poor in cases of cementless fixation ($p < 0.01$). * Chemotherapy gave a higher risk of infection (18.7% vs. 5.6%) (1b). * Soft tissue defects (sinus, pus discharge, wound dehiscence) correlated with poor prognosis ($p < 0.05$).
Li 2011 [22]	Retrospective cohort 1993–2008	N = 53 Endoprosthetic reconstruction for sarcoma	DAIR	10 years	* 1.9% had early infection, successfully treated with DAIR (2). * 5.7% had late infections, all treated with DAIR. One was successful, 2 needed revision (successful) (2). * 7.5% had wound complications requiring repeat surgery (debridement and closure) (2).
Manoso 2006 [17]	Retrospective cohort 1990–2001	N = 11 Infected knee reconstruction after limb-salvage surgery for cancer treated with staged protocol	Staged reconstruction protocol	X	* 82% had chronic infection, with a sinus tract in 45% at mean time 6 months (1-210 months). * 45% had failed DAIRs (2). * 55% had Staph aureus, 27% had Staph epidermidis. In 55%, a single organism caused the infection (1d). * 82% were immunocompromised with the administration of chemotherapy at the time of infection (1b). * All limbs were spared without amputation or flap loss. Overall cure rate was 91%. * Early complications were 2 peroneal palsies and 1 venous flap congestion requiring wound revision. * The mean functional outcome was 23/30 and mean knee range of motion 98 degrees.

TABLE 1. Evidence table (*Cont.*)

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Massin 1995 [37]	Excluded	X	X	X	X
Mavrogenis 2015 [13]	Retrospective cohort 1983–2010	N = 1,161 Megaprosthesis reconstruction after limb salvage surgery for sarcoma	* 83% 2-SR * 12% 1-SR * 5% amputation	Mean 9 years (3-20 years)	* 8.6% had infection at mean time 3.7y. * Most common isolates were Staph epidermidis (47%), *Staph aureus* (19%) and pseudomonas (6%) (1d). * Overall survival rate of megaprostheses was 88% at 10y and 84% at 20y. * Survival was higher for cementless reconstruction, not different for type of megaprosthesis, site of reconstruction or adjuvant therapy (1b).
Mavrogenis 2011 [15]	Narrative review	X	X	X	* DAIR may be effective in early infections, with short duration of symptoms, well-fixed implants and ideally with well-characterized microbiology demonstrating a highly susceptible pathogen (2). * Success in 2-SR 72-91%, 1-SR 42% and amputation 98-100%. * 2-SR is recommended for persistent infections, antibiotic-resistant pathogens or failed 1-SR. In well-fixed cementless modular prostheses anchorage stems can be retained. * Disadvantages of 2-SR are long hospitalization, increased bone loss, disuse osteoporosis, difficult revision operations and shortening of the affected limb. * Reimplantation should be delayed after completion of chemotherapy (1b). * An antibiotic-loaded cement spacer is essential in 2-SR; added antibiotics should be heatstable (1e). * Most surgeons administer systemic antibiotics 6 weeks, with reimplantation after > 2 months (1a).
McDonald 1990 [11]	Retrospective cohort 1970–1986	N = 304 271 malignant 33 benign Prosthesis or non-biological spacer in limb salvage surgery for primary bone tumors	X	2 years	* 11.8% had infection, 22% of these patients needed amputation. * Adjuvant and neo-adjuvant chemotherapy gave a higher risk of complications (32.8% and 55.4% vs. 25.2%). Reconstruction with uncemented prostheses had fewest complications (1b).
Mittermayer 2002 [38]	Excluded	X	X	X	X
Morii 2010 [14]	Retrospective cohort 2000–2008	N = 82 Endoprosthetic reconstruction for knee tumors	X	52 months (9-105 months)	* 17% had infection at mean time 10.9 months. * 50% had *Staph aureus*, 30% Staph epidermidis and 10% Pseudomonas (1d). * Age, sex, tumor origin, co-morbidities, operating time, blood loss, chemotherapy, clean air operating room, extracapsular resection, prosthesis type, number of postoperative antibiotics, posterior muscle flap were not risk factors for infection (1b). * Skin necrosis and surface infection were risk factors for infection.

TABLE 1. Evidence table (*Cont.*)

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Morii 2013 [6]	Retrospective cohort 1995–2009	N = 388 Endoprosthetic reconstruction for knee tumors	* 45% debridement * 14% 2-SR * 10% amputation * 9% 1-SR * 7% soft tissue flap	66 months (5-213 months)	* 14.6% had infection at mean time 13 months. * 47% Staph aureus and 17.5% Staph epidermidis (1d). * Infections were controlled in 84.2% the others had an accepted fistula or suppressive antibiotics. * Patients with diabetes, bone metastasis, lack of gastrocnemius flap coverage and pus required more surgical interventions for infection control. * The most successful therapy was 2-SR (80% success). Therapies with prosthesis removal were more successful than other therapies.
Peel 2014 [9]	Retrospective cohort 1996–2010	N = 121 Tumor endoprostheses surgery	* 53% DAIR * 24% 2-SR * 12% 1-SR * 6% resection * 6% amputation	34 months (17-80 months)	* 14% had infection at median time 18 months * Parenteral antibiotics median 9 days (0-58), 82% received oral combination antibiotic therapy with rifampicin (365 days) (1a). * Success rates: DAIR 75%, 1-SR 100%, 2-SR 50%, resection 0%, amputation 100% (2). * The majority of treatment failures occurred in patients with multi-resistant organisms (1d).
Pilge 2012 [39]	No full text	X	X	X	X
Racano 2013 [10]	Systematic review 1990–2011	N = 4,838 in 48 level IV studies	X	X	* Pooled infection rate was 10% (0-25%). * Most common organisms were Staph aureus and Staph epidermidis (1d). * There is considerable variation in antibiotic regimens. 0-24 hour antibiotic prophylaxis had 13% infection, >24 hour prophylaxis had 8% infection ($p < 0.05$) (1a).
Renard 2000 [40]	Prospective cohort 1975–1995	N = 77 Limb saving surgery (50) or ablative surgery (25) for sarcoma	X	97 months (28-271 months)	* 6% had deep infection, leading to amputation in 2/3 cases. * 4% had superficial infection successfully treated with DAIR and gentamicin beads (2).
Sherman 2008 [41]	Excluded	X	X	X	X
Shin 1999 [42]	Retrospective cohort 1970–1990	N = 52 41 malignant 11 benign Limb salvage surgery for musculoskeletal tumor	* 67% revision * 21% amputation * 8% arthrodesis * 2% fibular graft * 2% ORIF	12 years (37-296 months)	* 11.5% had infection. * Functional rating was 63%. Pain 69%, function 53%, emotional acceptance 72%, support 60%, walking ability 62%, gait 54%, hand positioning 66%, manual dexterity 94% and lifting ability 63%. * After revision 33% needed reoperation for complications: 58% aseptic loosening, 25% infection, 17% prosthetic failure and 8% patellar dislocation. * Survival after reoperation was 79% (5y) and 65% (10y).

TABLE 1. Evidence table (*Cont.*)

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Sim 2007 [43]	Retrospective cohort 1996 – 2005	N = 50 Endoprosthetic reconstruction for knee tumors (GRMS)	3 washouts	24.5 months (2-124 months)	* Patients with metastatic disease or pathological fractures did not have higher complication rates. * 12% had deep infection for which patients received multiple washouts and long-term antibiotics (2). * 1/6 had revision; 1/6 had amputation (2).
Wafa 2015 [12]	Prospective case-control 2006–2011	N = 170 Reconstruction with silver-enhanced endoprostheses for several indications	X	12 months	* 11.8% infection in silver group, 22.4% in control group (1f). * Higher incidence of Pseudomonas in the silver group (1d/1f). * 70% of infected prosthesis was successfully treated with DAIR, 31.6% in the control group (1f/2). * 15.3% required implant removal, amputation or antibiotic suppression, 3.5% in the silver group (1f). * 18.8% with adjuvant chemotherapy developed infection (1b). * 15% had relapse infection after 2-SR in the silver group, 42.9% in the control group (1f).
Wirganowicz 1999 [44]	Prospective cohort 1980–1995	N = 64 Failed endoprostheses for neoplastic disease	* 75% revision * 25% amputation	2 years	* 13% failed because of an infection. * 50% of infected prostheses had revision with the same prosthesis, 25% with a different prosthesis and 25% underwent amputation. * Patients receiving revision endoprostheses were not at increased risk for a subsequent revision or amputation compared to primary endoprostheses reconstruction.
Zajonz 2016 [19]	Retrospective cohort 1994–2014 Excluded	N = 34 Modular endoprostheses of the lower extremity for infection	X	72 months (6-267 months)	* Reinfection rate after healed reinfection in silver group was 40%, in the non-silver group 57% (1f).
Zajonz 2017 [45]	Retrospective cohort 1994–2011	N = 101 45 tumor Modular endoprostheses of the lower extremity	* 62% 2-SR * 11% resection * 11% arthrodesis * 8% DAIR * 8% amputation	27 months (5-179 months)	* 17.7% had infection (3 early infections, 16 late infections), reinfection rate 37%. * 36.6% CNS, 26.3% Staph epidermidis, 15.8% *Staph aureus* (1d). * Patients with infection had same age and sex, but higher BMI. * Prosthesis for tumors had fewer infections than other indications (8.9% vs. 21.7%).

[42] Shin D, Weber K, Chao E, An K, Sim F. Reoperation for failed prosthetic replacement used for limb salvage. Clin Orthop Relat Res. 1999;358:53–63.
[43] Sim I, Tse L, Ek E, Powell G, Choong P. Salvaging the limb salvage: management of complications following endoprosthetic reconstruction for tumours around the knee. Eur J Surg Oncol. 2007;33:796–802. doi:10.1016/j.ejso.2006.10.007.
[44] Wirganowicz P, Eckardt J, Dorey F, Eilber F, Kabo J. Etiology and results of tumor endoprosthesis revision surgery in 64 patients. Clin Orthop Relat Res. 1999;358:64–74.
[45] Zajonz D, Birke U, Ghanem M, Prietzel T, Josten C, Roth A, et al. Silver-coated modular megaendoprostheses in salvage revision arthroplasty after periimplant infection with extensive bone loss - a pilot study of 34 patients. BMC Musculoskelet Disord. 2017;18:1–7. doi:10.1186/s12891-017-1742-7.

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QUESTION 2: What is the best reconstruction technique for an infected allograft?

RECOMMENDATION: The best reconstruction technique for an infected allograft is resection of the infected allograft and reconstruction (preferable two-stage) with an endoprosthesis.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 93%, Disagree: 0%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Use of allograft in the reconstruction of a massive bone defect created by resection of a tumor is frequently successful. However, as with all tumor reconstruction methods, it is also plagued with complications, infection being one of them. A number of observational studies have been published on the subject. The largest case series by Mankin et al. described 121 allograft infections in 945 patients accounting to an infection rate of 12.8% [1]. The study did not, however, address management of the infected allograft. A more recent systematic review by Aponte et al. [2] reviewed the available literature and infection rates reported in previous studies [3–7]. The infection rate of allograft used after tumor resection ranged from 8.5% to 13.3%. The infection rate in their own series was 9% with 60 infections in 673 patients who received massive allografts after oncological resections. Only 18% (11/60) of the patients in that cohort were successfully treated by debridement and antibiotics with salvage of the original allograft. Of the 41 patients who underwent two-stage revision, 24 were revised with allograft and 17 with endoprostheses. Reinfection occurred in 14 patients of which 12 were in the allograft group and 2 were in the endoprostheses group. This demonstrated a lesser rate of reinfection when revision to endoprostheses was done as opposed to revision to another allograft.

Our search did not find any reports of revision to a vascularized fibular autograft or treatment with bone transport. Although these are both biological methods of reconstruction and their efficacy in the treatment of bone defects created by trauma and infection as well as for primary reconstruction following tumor resection is well established [8,9].

REFERENCES

[1] Mankin HJ, Hornicek FJ, Raskin KA. Infection in massive bone allografts. Clin Orthop Relat Res. 2005:210–216.
[2] Aponte-Tinao LA, Ayerza MA, Muscolo DL, Farfalli GL. What are the risk factors and nanagement options for infection after reconstruction with massive bone allografts? Clin Orthop Relat Res. 2016;474:669–673. doi:10.1007/s11999-015-4353-3.
[3] Hernigou P, Delepine G, Goutallier D. [Infections after massive bone allografts in surgery of bone tumors of the limbs. Incidence, contributing factors, therapeutic problems]. Rev Chir Orthop Reparatrice Appar Mot. 1991;77:6–13.
[4] Lord CF, Gebhardt MC, Tomford WW, Mankin HJ. Infection in bone allografts. Incidence, nature, and treatment. J Bone Joint Surg Am. 1988;70:369–376.
[5] Loty B, Tomeno B, Evrard J, Postel M. Infection in massive bone allografts sterilised by radiation. Int Orthop. 1994;18:164–171.
[6] Tan MH, Mankin HJ. Blood transfusion and bone allografts. Effect on infection and outcome. Clin Orthop Relat Res. 1997:207–214.
[7] Tomford WW, Thongphasuk J, Mankin HJ, Ferraro MJ. Frozen musculoskeletal allografts. A study of the clinical incidence and causes of infection associated with their use. J Bone Joint Surg Am. 1990;72:1137–1143.
[8] Eward WC, Kontogeorgakos V, Levin LS, Brigman BE. Free vascularized fibular graft reconstruction of large skeletal defects after tumor resection. Clin Orthop Relat Res. 2010;468:590–598. doi:10.1007/s11999-009-1053-x.
[9] Tsuchiya H, Tomita K. Distraction osteogenesis for treatment of bone loss in the lower extremity. J Orthop Sci. 2003;8:116–124. doi:10.1007/s007760300020.