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The use of custom-made antibiotic-loaded spacer in periprosthetic knee infection caused by XDR organism: case report and review of literature

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Abstract. Periprosthetic knee infection (PKI) remains one of the most challenging complications after total knee replacement, especially if caused by multidrug-resistant (MDR) or extensively drug-resistant (XDR) organisms. Multiple treatment options are available, such as long-term antibiotic suppression, surgical debridement with retention of the prosthesis, definitive resection arthroplasty, arthrodesis, one-stage or two-stage revision procedures, amputation.

We present a rare case of a PKI caused by a XDR *Klebsiella pneumoniae* in a young patient who underwent a prosthetic reconstruction due to an osteosarcoma of the tibia. In this patient, the PKI has been treated using intravenous administration of Amikacin and an Amikacin-impregnated PMMA custom-made spacer.

To our knowledge, only two cases that successfully used hand-mixed antibiotic-loaded spacer based on antibiotic sensitivity for the treatment of PKI caused by MDR and XDR microorganisms have been reported in the literature.

Key Words
Periprosthetic knee infection, XDR, Custom-made spacer, Mega-prosthesis.

Introduction

Peri-prosthetic knee infection (PKI) is a severe complication of total knee arthroplasty that appears to be increasing due to a concomitant rise in total knee replacement[1,2].

In orthopedic oncology, knee prosthetic systems, called mega-prostheses due to the large bone resection and the size of the prosthesis, are commonly used. These mega-prostheses are widely used as a method of reconstruction after segmental resection of long bones in the extremities for their availability, immediate fixation, early weight bearing, and good functional recovery[3].

These mega-prostheses, together with the development of adjuvant chemotherapy, have greatly improved the disease-free survival rate of patients affected by bone tumors, particularly in osteosarcoma patients, for whom amputation was the routine treatment[4-6].

Orthopedic procedures for oncological conditions carry high infection rates. The treatment of infection in these patients is difficult and lengthy, and amputation is the only salvage procedure in case of failure[7].

The prevalence of resistant bacteria, and especially multidrug-resistant (MDR) or extensively drug-resistant (XDR), infecting total knee arthroplasties (TKA) has increased in the last 15 years, making the treatment of infection more challenging[2].

The use of antibiotic-loaded spacers helps in the management of large bone defects while providing a local high concentration of an antibiotic to which the bacterium is sensitive[8,9].

We present a case of a PKI caused by an XDR *Klebsiella pneumoniae* in a young patient who underwent a prosthetic reconstruction due to an osteosarcoma of the tibia.

Case presentation

We report of a 15-year-old woman who underwent TKA mega-prosthesis for an osteosarcoma of the tibia (Figures 1 and 2).

Two months after surgery the patient presented with fever and secretion from the surgical wound.

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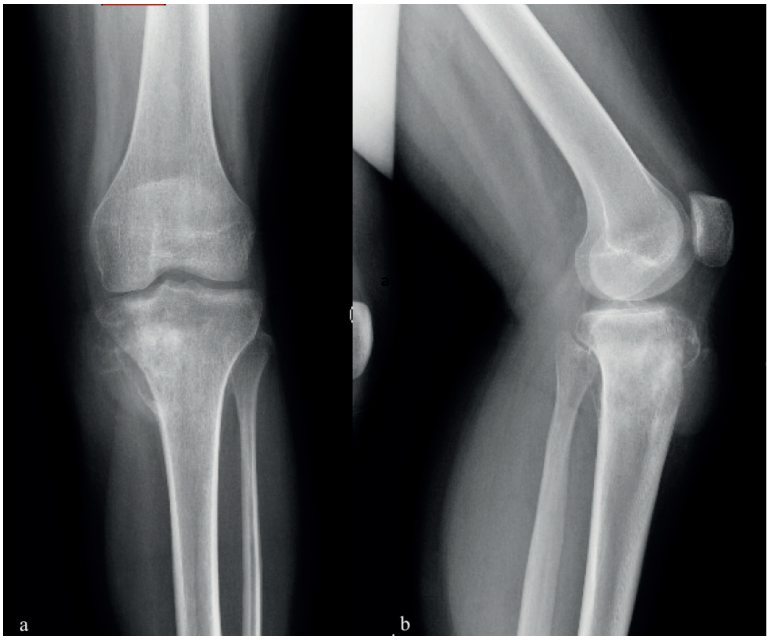

Figure 1. A, Pre-operative X-ray in antero-posterior view (osteosarcoma of the tibia). **B**, Pre-operative X-ray in latero-lateral view.

We performed wound swab culture, with the isolation of *Acinetobacter baumannii*. We decided for a two-stage revision treatment: the first stage was composed of removal of the prosthesis, obtainment of new microbiological samples and positioning of a spacer, handmade with pre-mixed antibiotic-loaded cement, Palacos R + G (Heraeus Medical GmbH, Wehrheim, Germany). The surgical procedure included: removal of all hardware and bone cement, debridement of synovial membrane, pseudomembranes and necrotic tissue, debridement of the bone until healthy bone was exposed, and lavage with 2 L of 1:10 povidone-iodine:saline solution. Before lavage, we obtained 3 samples, sent for microbiological testing, and 1 tissue sample sent for histological examination. The microbiological examination found an XDR *Klebsiella pneumoniae,* only sensitive to Amikacin with a Minimal Inhibitory Concentration

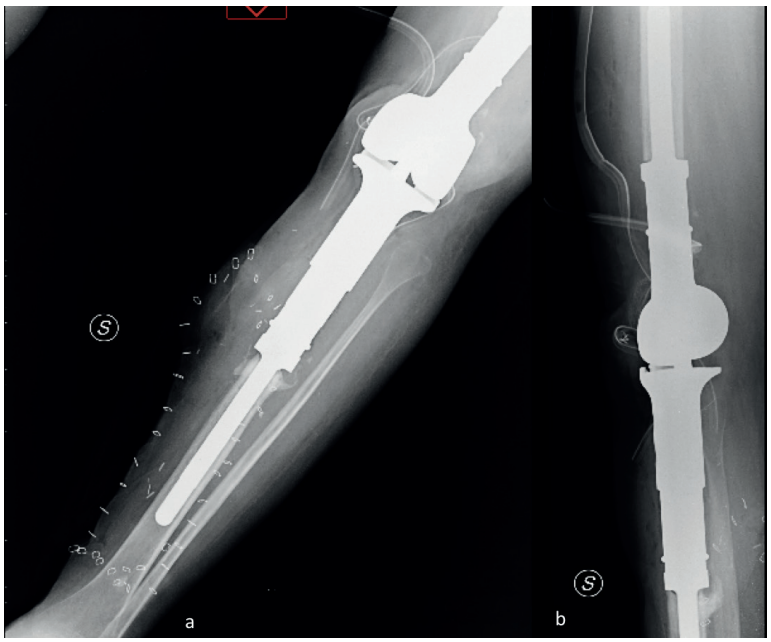

Figure 2. A, Post-operative X-ray of the mega-prosthesis in antero-posterior view. **B**, Post-operative X-ray of the mega-prosthesis in latero-lateral view.

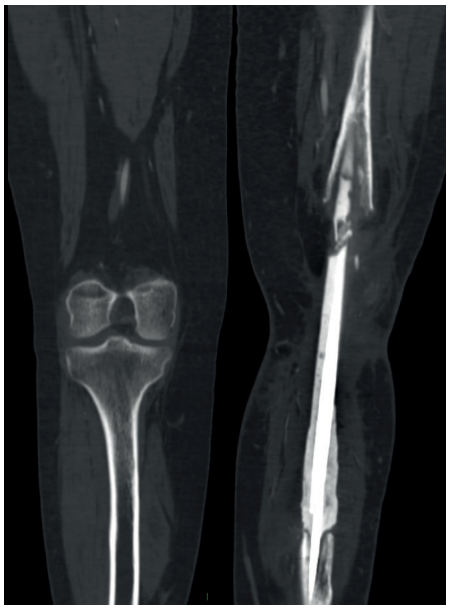

Figure 3. CT coronal section which show the PMMA custom-made spacer.

(MIC) of 8. During the surgical procedure, after obtaining microbiological samples, an intravenous antibiotic therapy was started. The therapy was adjusted according to the microbiological testing results. One month after the surgical debridement, secretion from the surgical wound and fever were still present.

At this stage, we decided to replace the spacer with an antibiotic-loaded hand-made spacer (Figure 3) based on the results of the microbiological tests. During surgery, before implantation of the new spacer, all cement was removed and a thorough debridement and lavage were performed.

The spacer was made of 10 g of Amikacin powder manually mixed with 100 g of polymethylmethacrylate (PMMA) copolymer powder with a plastic spatula for 120 seconds, prior to adding the liquid monomer. We used Simplex bone cement (Stryker, Portage, MI, USA), which is a radio-opaque, low-viscosity cement.

When the cement had reached the right texture, in order to increase the elution of the antibiotic and contact with the tissues, we performed micro-fractures in the spacer with a 2.8 mm drill.

There was a loss of subcutaneous substance, which had been destroyed by infection. Therefore, we decided to use Vacuum Assisted Closure (VAC) therapy in order to improve wound closure and as an aid in infection control. Initially, a negative pressure of 200 mm Hg via VAC had been applied. After 48-72 hours, it has been reduced to 150 mm Hg. VAC therapy was continued until the wound closure that was obtained in 2 months. During this period, we performed a wound debridement, change of the sponge, and microbiological testing every seven days.

The patient continued intravenous antibiotic therapy until the negativization of microbiological tests. When infection markers returned in the normal range, we positioned a knee uncemented arthrodesis implant (Figure 4). In this step, we performed a lavage with 2 L of 1:10 povidone-iodine:saline solution, as well.

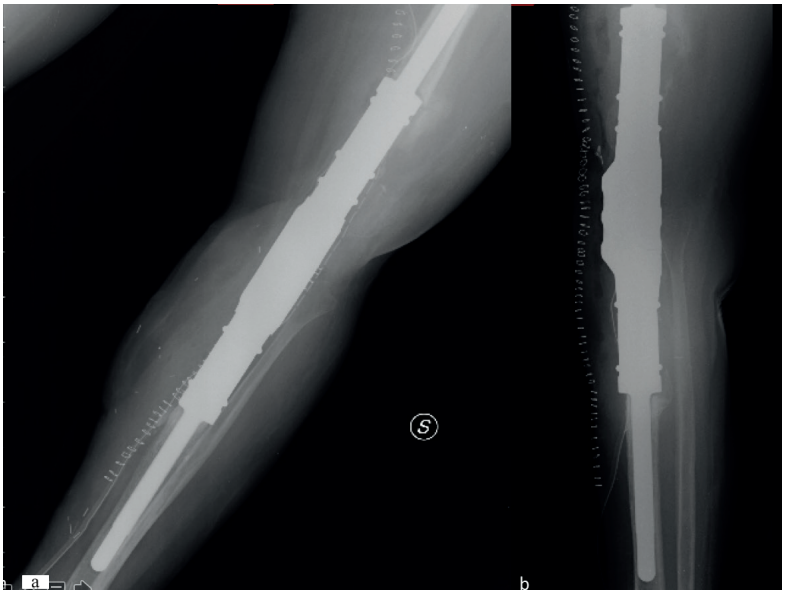

Figure 4. A, Post-operative X-ray of the mega-prosthesis locked in extension in antero-posterior view. **B**, Post-operative X-ray of the mega-prosthesis locked in extension in latero-lateral view.

A multidisciplinary team formed by orthopedic surgeon, infectious disease specialist, and pediatric oncologist followed the patient for 12 months. At the last follow-up, the patient was able to walk with 2 crutches, and the wound was closed.

Discussion and Literature Review

Periprosthetic knee infection is a complication associated with prosthetic failure. Incidence is increasing over the years, ranging from 0.4-2% in primary total knee replacement and 5.6% in revision surgery[10-12]. The infection rate in long-bone tumor surgery with prosthetic reconstruction is higher when compared with rates of conventional replacements[7,13]. The incidence of infection depends on the location in which the prosthesis is implanted: infection occurs in up to 11% of cases in distal femur replacements, and up to 23% of cases in proximal tibia replacements[13].

The higher rate of infection associated with oncologic patients is due to a debilitated status caused by one or more of the following: the tumor itself, chemotherapy-induced immunosuppression and concomitant illness involving other organs, poor soft-tissue situations due to radiotherapy, the often prolonged operating times required, and – particularly with proximal tibia replacement – the difficulty of achieving muscle coverage of the prosthesis[6,7,14,15].

The prevalence of resistant bacteria infecting TKAs has increased in the last 15 years, mainly due to the overconsumption of antibiotics in community and healthcare settings, inappropriate strategies of antibiotic prophylaxis and treatment and increased stay in intensive care units[2]. These microorganisms are resistant to commonly used antimicrobials and sensitive to few antibiotic drugs. In some cases, these microorganisms are sensitive only to high dose of single specific antimicrobials. These high doses are often not possible to administer because of their side effects. In the case reported, the *K. pneumoniae* isolated was sensitive to high dose Amikacin, that could not be administered because of its side-effects such as kidney damage and ototoxicity, occurring in 1-10% of patients.

The two-stage revision could be used in PKI with a resistant organism with a failure rate between 11% and 17%[2,16]. Notwithstanding the high rate of reinfection, two-stage revision remains a viable treatment option for patients infected by a resistant organism at the site of the TKA[16], as an alternative to amputation.

In the literature, two cases of periprosthetic knee infection caused by XDR organism treated with a custom-made PMMA spacer based on the antibiotic sensitivity are reported (Table I). The first case is an infection by *Pseudomonas*

Table I. Review of the literature.

Case	Organism isolated and sensitivity	Spacer used	Concentration	Re-implantation
Reference no. 7	*Pseudomonas aeruginosa* sensitive only to colistin	Colistin-loaded polymethylmethacrylate cement spacer		
Reference no. 16	*Pseudomonas aeruginosa* susceptible only to colistin and tobramycin (MIC = 2 mg/L for both)	Colistin and tobramycin spacer	(200 g of Simplex P containing 60x106 IU of colistin and 5 g of tobramycin after 6 weeks and following measurement of plasma levels of colistin the concentration of the colistin in the spacer was increased to 120x106 IU in 200 g of bone cement	Re-implantation of prosthesis with 100 g of bone cement supplemented with colistin at 50x106IU, so 20x106 IU for each 40 g of bone cement
Our case	Klebsiella pneumonia susceptible only to Amikacin (MIC = 8 mg/L)	Amikacin spacer	10 g of Amikacin powder manually mixed with 100 g	50 g bone cement was supplemented with 2 g of amikacin

aeruginosa sensitive only to Colistin of a revision prosthesis implanted for treatment of pseudarthrosis of a distal femoral fracture. In this patient, a Colistin-loaded PMMA cement spacer was implanted. The concentration of antibiotic has not been mentioned in the paper[9]. The second case reported in the literature is an osteomyelitis caused by *Pseudomonas aeruginosa* susceptible only to Colistin and Tobramycin (MIC = 2 mg/L for both). Before re-implanting of a knee mega-prosthesis, the patient underwent the positioning of three antibiotic-loaded spacers. In the first revision, after the identification of *Pseudomonas aeruginosa* susceptible only to Colistin and Tobramycin, a 200 g of PMMA spacer impregnated with 5 g of tobramycin was used. The microbiological test continued to be positive for *Pseudomonas aeruginosa*. It was, therefore, used a PMMA spacer loaded with high-dose of Colistin and Tobramycin (200 g of Simplex P containing $60x10^6$ IU of Colistin and 5 g of Tobramycin)[8]. At this time, patient's plasma colistin level was below the therapeutic range. Therefore, it was decided to double the colistin concentration in the PMMA spacer ($120x10^6$ IU colistin in 200 g of bone cement) and the intravenous Colistin was increased to $3x10^6$ IU three times a day after a load dose of $9x10^6$ (the previous dosage was of $2x10^6$ IU three times a day). In this way, the infection was eradicated and a re-implantation of a cemented mega-prosthesis with a 100 g of bone cement added to $50x10^6$ IU Colistin (prophylactic dose). In this study, the recommended and tested concentration[19] of colistin for each 40 g of cement wasn't enough to obtain the therapeutic range (measuring the plasma Colistin levels), so authors decided to increase the Colistin concentration in the spacer and the intravenous dose of Colistin.

Regarding hand-made antibiotic-loaded spacers, great attention has been paid to the preparation of antibiotic-loaded acrylic cement, particularly to concentration and elution characteristics of the drug and if single administered or associated with another antibiotic. Relying on data reported by McLaren et al[18], hand-mixed antibiotic-loaded acrylic cement is not less homogeneous than commercially premixed formulations, so this kind of spacer can be used to treat particular PKI as a valid alternative to the traditional spacer.

The recommended concentration that should be used in order to treat PKI is at least 3.6 g for each 40 g of PMMA or $12x10^6$ IU in case of Colistin (Colistin sulfate 2.4% powder)[19-22].

Gasparini et al[19] reported elution characteristics of each antibiotic-loaded cement. They confirmed the burst release of antibiotics in the first hour, followed by a lower elution rate. Considering Amikacin, there is an elution rate similar to that of Gentamicin (the most common drug in antibiotic pre-loaded spacers)[19]. Another characteristic of antibiotic-loaded bone cement is that combining two antibiotics in bone-cement improves elution of both antibiotics[17,19].

We have used 10 g of Amikacin powder manually mixed with 100 g of PMMA copolymer (Simplex bone cement) powder for 120 seconds before adding the liquid monomer.

We used the powder form of Amikacin because Ethell et al[23] showed that elution of Amikacin powder from PMMA was greater than that of Amikacin solution. Moreover, an Amikacin dose effect was observed; in their study, the PMMA beads containing 250 mg of Amikacin powder per 2 g cement eluted significantly more antibiotic than the 125-mg beads.

Two-stage revision remains a viable treatment option for patients with a PKI with a resistant organism. Mittal et al[16] reported some recommendations (Table II) that should be followed in the first procedure of implant removal: removal of all hardware and cement, thorough debridement of the synovial membrane, pseudomembrane, necrotic tissue and curettage of the region of osteomyelitis until encounter of healthy bone. Moreover, multiple specimens should be taken (for aerobic and anaerobic cultures), and tissue should be obtained for frozen and permanent pathologic section. The use of dilute povidone-iodine lavage with a rapport of 1:10 (povidone-iodine:saline solution) has been shown to have a role in acute PJI and to reduce the risk of deep surgical site infection[24]. As shown in some case reports of PKI and in a study of periprosthetic hip infections[25-28], VAC therapy could be a good adjuvant treatment option for periprosthetic infections. It must be applied in case of loss of subcutaneous substance for wound closure and could be applied in a normal tissue for its role in controlling infection. We think that it could increase the elution rate of the antibiotic from the spacer, even if further studies are needed to prove so.

In these rare cases (MDR or XDR microorganism), an antibiotic-loaded bone cement together with a deep debridement, lavage with dilute povidone-iodine, and VAC therapy could be useful to treat these infections.

Table II. Recommendation in case of microorganism MDR or XDR.

Recommendation in case of microorganism MDR or XDR	References
Thorough debridement should be performed: • Removal of all hardware and cement with intraoperative. X-ray should be made to ensure complete cement removal • Debridement of the synovial membrane, pseudomembrane, necrotic tissue, and bone if necessary • Curette of region of osteomyelitis until encounter healthy bone	16
• Use of dilute povidone-iodine lavage with a rapport of 1:10 (at least 2 L)	24
A multiple cultures should be taken (for aerobic and anaerobic cultures) and tissue should be obtained for frozen and permanent pathologic section	16
Concentration recommended is at least 3,6 g for each 40 of bone cement or 12x106 IU in case of colistin • If a preloaded spacer has been used for the fist time and a XDR has been isolated it is important to change with a antibiotic-impregnated PMMA custom-made spacer based on microorganism sensitivity	19, 20, 21, 22
Micro-fractures to the cement of the spacer created with a 2.8 mm drill	Used only in this case report
VAC therapy: it must be applied if there is a loss of subcutaneous substance for wound closure and could be applied in a situation of normal tissue for its role in controlling infection	25, 26
At re-implantation, lavage with dilute povidone-iodine and hand-made antibiotic-impregnated PMMA should be used.	8

Conclusions

This is the first report of an oncologic patient with a periprosthetic knee infection of *Klebsiella* XDR successfully treated using hand-mixed Amikacin-impregnated PMMA spacer.

This case-report with its review of the literature can be a valid help in order to treat PKI due to MDR and an XDR microorganism.

Conflict of Interests

The Authors declare that they have no conflict of interests.

References

1) Segreti J, Parvizi J, Berbari E, Ricks P, Berríos-Torres S. Introduction to the Centers for Disease Control and Prevention and Healthcare Infection Control Practices Advisory Committee Guideline for Prevention of Surgical Site Infection: Prosthetic Joint Arthroplasty Section. Surg Infect (Larchmt) 2017; 18: 394-400.
2) Vasso M, Schiavone Panni A, De Martino I, Gasparini G. Prosthetic knee infection by resistant bacteria: the worst-case scenario. Knee Surg Sports Traumatol Arthrosc 2016; 24: 3140-3146.
3) Pala E, Trovarelli G, Angelini A, Maraldi M, Berizzi A, Ruggieri P. Megaprosthesis of the knee in tumor and revision surgery. Acta Biomed 2017; 88(2Suppl): 129-138.
4) Wang W1, Wang ZC, Shen H, Xie JJ, Lu H. Dose-intensive versus dose-control chemotherapy for high-grade osteosarcoma: a meta-analysis. Eur Rev Med Pharmacol Sci 2014; 18: 1383-1390.
5) Vermesan D, Vermesan H, Dragulescu SI, Bera I, Di Giovanni A, Sabatini R, Santacroce L, Bottalico L, Flace P, Cagiano R. Secondary pathologic fractures in osteosarcoma: prognosis and evolution. Eur Rev Med Pharmacol Sci 2009; 13: 71-76.
6) Ziranu A, Mariotti F, Perisano C, Stomeo D, Maccauro G. Chondroblastoma around the knee: clinical considerations and review of the literature. Minerva Ortop Traumatol 2015; 66: 107-113.
7) 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.
8) Krajewski J, Bode-Böger SM, Tröger U, Martens-Lobenhoffer J, Mulrooney T, Mittelstädt H, Russlies M, Kirchner R, Knobloch JK. Successful treatment of extensively drug-resistant Pseudomonas aeruginosa osteomyelitis using a colistin- and tobramycin-impregnated PMMA spacer. Int J Antimicrob Agents 2014; 44: 363-366.
9) Papagelopoulos PJ, Mavrogenis AF, Giannitsioti E, Kikilas A, Kanellakopoulou K, Soucacos PN. Management of a multidrug-resistant pseudomonas aeruginosa infected total knee arthroplasty using colistin. A case report and review of the literature. J Arthroplasty 2007; 22: 457-463.
10) Fukagawa S, Matsuda S, Miura H, Okazaki K, Tashiro Y, Iwamoto Y. High-dose antibiotic infusion for infected knee prosthesis without implant removal. J Orthop Sci 2010; 15: 470-476.

11) Anagnostakos K. Therapeutic Use of antibiotic-loaded bone cement in the treatment of hip and knee joint infections. J Bone Joint Infect 2017; 2: 29-37.
12) Di Benedetto P, Di Benedetto ED, Buttironi MM, De Franceschi D, Beltrame A, Gissoni R, Cainero V, Causero A. Two-stage revision after total knee arthroplasty. Acta Biomed 2017; 88(2 Suppl): 92-97.
13) Donati F, Di Giacomo G, D'Adamio S, Ziranu A, Careri S, Rosa M, Maccauro G. Silver-coated hip megaprosthesis in oncological limb savage surgery. Biomed Res Int 2016; 2016: 9079041.
14) Schmidt-Braekling T, Streitbuerger A, Gosheger G, Boettner F, Nottrott M, Ahrens H, Dieckmann R, Guder W, Andreou D, Hauschild G, Moellenbeck B, Waldstein W, Hardes J. Silver-coated megaprostheses: review of the literature. Eur J Orthop Surg Traumatol 2017; 27: 483-489
15) Piccioli A, Donati F, Giacomo GD, Ziranu A, Careri S, Spinelli MS, Giannini S, Giannicola G, Perisano C, Maccauro G. Infective complications in tumour endoprostheses implanted after pathological fracture of the limbs. Injury 2016; 47 Suppl 4: S22-S28.
16) Mittal Y, Fehring TK, Hanssen A, Marculescu C, Odum SM, Osmon D. Two-stage reimplantation for periprosthetic knee infection involving resistant organisms. J Bone Joint Surg Am 2007; 89: 1227-1231.
17) Herrmann G, Yang L, Wu H, Song Z, Wang H, Høiby N, Ulrich M, Molin S, Riethmüller J, Döring G. Colistin-tobramycin combinations are superior to monotherapy concerning the killing of biofilm Pseudomonas aeruginosa. J Infect Dis 2010; 202: 1585-1592
18) McLaren AC, Nugent M, Economopoulos K, Kaul H, Vernon BL, McLemore R. Hand-mixed and premixed antibiotic-loaded bone cement have similar homogeneity. Clin Orthop Relat Res 2009; 467: 1693-1698.
19) Gasparini G, De Gori M, Calonego G, Della Bora T, Caroleo B, Galasso O. Drug elution from high-dose antibiotic-loaded acrylic cement: a comparative, in vitro study. Orthopedics 2014; 37: e999-1005.
20) Penner MJ, Masri BA, Duncan CP. Elution characteristics of vancomycin and tobramycin combined in acrylic bone-cement. J Arthroplasty 1996; 11: 939-944.
21) Springer BD, Lee GC, Osmon D, Haidukewych GJ, Hanssen AD, Jacofsky DJ. Systemic safety of high-dose antibiotic-loaded cement spacers after resection of an infected total knee arthroplasty. Clin Orthop Relat Res 2004; (427): 47-51.
22) Parvizi J, Gehrke T, Chen AF. Proceedings of the International Consensus on Periprosthetic Joint Infection. Bone Joint J 2013; 95-B: 1450-1452.
23) Ethell MT, Bennett RA, Brown MP, Merritt K, Davidson JS, Tran T. In vitro elution of gentamicin, amikacin, and ceftiofur from polymethylmethacrylate and hydroxyapatite cement. Vet Surg 2000; 29: 375-382.
24) Ruder JA, Springer BD. Treatment of periprosthetic joint infection usingantimicrobials: dilute povidone-iodine lavage. J Bone Joint Infect 2017; 2: 10-14.
25) Kelm J, Anagnostakos K, Schmitt E. Closed subfascial V.A.C.-therapy in periprosthetic hip infections. Zentralbl Chir 2004; 129 Suppl 1: S49-52.
26) Neagoe VI, Zytoun S, Neuhaus HJ. First case report of a late onset knee periprosthetic joint infection caused by Lactococcus garvieae. Case Rep Orthop 2016; 2016: 5053640.
27) Chen Z, Cheng L, Feng G. Bone inflammation and chronic recurrent multifocal osteomyelitis. Eur Rev Med Pharmacol Sci 2018; 22: 1380-1386.
28) Li J, Zhao QH, Huang KC, Li ZQ, Zhang LY, Qin DY, Pan F, Huang WX. Linezolid vs. vancomycin in treatment of methicillin-resistant staphylococcus aureus infections: a meta-analysis. Eur Rev Med Pharmacol Sci 2017; 21: 3974-3979.