Chir. Narzadow Ruchu Ortop. Pol., 2018; 83(6) 221-228
DOI: 10.31139/chnriop.2018.83.6.44
ISSN 0009-479X

ORIGINAL PAPER

Antimicrobial biomaterials in the prevention and local treatment of infection in orthopedics

Biomateriały antybakteryjne w zapobieganiu i miejscowym leczeniu zakażeń w ortopedii

Ireneusz Babiak[1,2], Piotr Pędzisz[1], Jakub Janowicz[1], Paweł Małdyk[1]

[1] Department of Orthopedics and Traumatology, Medical University of Warsaw
[2] Department of Orthopedics, Mälarsjukhuset Eskilstuna, Sweden

Abstract

According to current views, infection around the orthopedic implant and in chronic osteomyelitis is associated with the development of a bacterial biofilm, which is a barrier to systemic administered antibiotics. This results in the inability to cure the infection with systemic antimicrobial therapy because the doses guaranteeing activity in the biofilm will be toxic to the patient. The antibiotic concentration effective against bacteria in the biofilm can be achieved by local administration. The main advantage of local antibiotic carriers is the local release of drugs in high concentrations that exceed those achievable after systemic administration, but without systemic toxicity. The vehicle should provide a high local concentration of antibiotic above the minimal inhibitory concentrations (MIC) for the most common pathogens an should be effective against sedentary forms of bacteria. It can not impair the regeneration of bone tissue and the biological integration of the implant with the bone. Carriers that are both a substitute for bone and have osteoconductive or osteoinductive properties protect the bone from re-infection and promote the reconstruction of cavernous defects. Local carriers of antibacterial drugs may be absorbable or non-absorbable and depending on physico-chemical properties include 6 classes of biomaterials. Local carriers of antibacterial substances are currently being and will probably remain the treatment of choice of infections of orthopedic implants and osteomyelitis.

Key words: Antibiotic Loaded Acrylic Cement; Local Antibacterial Carriers, bone substitutes, periprosthetic joint infection, osteomyelitis, orthopedic infections

Streszczenie

Według obecnych poglądów infekcja w okolicy implantu ortopedycznego i w przewlekłym zapaleniu kości związana jest z rozwojem bakteryjnego biofilmu, który stanowi barierę dla antybiotyków podawanych ogólnie. Powoduje to niemożność wyleczenia infekcji za pomocą ogólnej antybiotykoteraii, ponieważ dawki gwarantujące aktywność w biofilmie będą toksyczne dla pacjenta. Skuteczne wobec bakterii w biofilmie stężenie antybiotyku można osiągnąć przez ich miejscowe podanie Główną zaletą miejscowych nośników antybiotyków jest miejscowe uwalnianie leków w wysokich stężeniach, które przekraczają stężenia osiągalne po podaniu ogólnoustrojowym, jednak bez toksyczności ogólnoustrojowej. Nośnik powinien zapewnić wysokie stężenie miejscowe antybiotyku powyżej MIC dla najczęstszych patogenów, powinien być skuteczny wobec osiadłych form bakterii, a zarazem nie upośledzać regeneracji tkanki kostnej oraz biologicznej integracji implantu z kością. Nośniki będące jednocześnie substytutem kości i mające właściwości osteokondukcyjne lub osteoindukcyjne chronią kość przed ponownym zakażeniem i sprzyjają odbudowie ubytków jamistych. Miejscowe nośniki leków antybakteryjnych mogą być wchłanialne lub niewchłanialne i zależnie od właściwości fizykochemicznych obejmują 6 klas biomateriałów. Miejscowe nośniki substancji antybakteryjnych stały się obecnie i zapewne pozostaną w przyszłości postępowaniem z wyboru w profilaktyce i leczeniu infekcji implantów ortopedycznych i zapaleń kości.

Słowa kluczowe: złamania okołoprotezowe, złamania okołoprotezowe z infekcją, endoprotezoplastyka stawu biodrowego, endoprotezoplastyka stawu kolanowego

Author's address: Ireneusz Babiak, Department of Orthopedics and Traumatology, Medical University of Warsaw, Poland
e-mail: ibabiak@wum.edu.pl

Received: **27.07.2018**
Accepted: **22.11.2018**
Published: **04.01.2019**

Introduction

Growing number of implanted orthopedic implants is accompanied by a number of complications, including infection. Orthopedic device related infection (ODRI) is one of the most serious. Despite the growing number of publications on infections in orthopedics, and particularly periprosthetic joint infection (PJI), there are no EBM-based guidelines for the treatment of ODRI, osteomyelitis (OM) and native joints infection. Dominant views are based on the experience of large centers and studies covering small groups of patients. This can be- in the "antibiotic era" – result of the lack of a control group – bone and joint infections treated only surgically, without the systemic antibiotic therapy [1, 2].

In the area of treatment of ODRI, experimental and clinical observations have been conducted since the 1970s to improve the results. These objectives are in focus of scientific societies: the European Bone and Joint Infection Society (EBJIS) and the Musculoskeletal Infection Society (MIS). In Poland, in 2005, the National Consultant in Orthopedics was published "Principles of prevention, diagnosis, and treatment of bone and joint infections", which was updated in 2008, and in 2013 issued a new version of guidelines developed by the National Consultants in Orthopedics and in Medical Microbiology [3,4]. PJI can lead to the failure of arthroplasty, and even limb amputation or death due to sepsis. Despite the current low PJI percentage, their absolute number increases each year. The dominant form of PJI is so-called low grade – chronic low-invasive implant infection [5]. People after joint arthroplasty undergoing other invasive procedures are at risk of developing a hematogenous PJI. Considering early and late infections, the incidence of all PJIs is estimated at around 3-3.5% [6].

According to the Swedish National Hip Arthroplasty Register from 2010, PJI was the third reason for the revision, after aseptic loosening and dislocation of the prosthesis, and accounted for 11.8% of all hip revisions [7]. The prevalence of the problem in Poland is indicated by data from the National Health Fund (NFZ) for the period 2009-2013. At 260 030 hip and knee prostheses, 4221 revisions were performed due to PJI, which constituted on average 844 new cases each year. Revisions for PJI accounted for 14.67% of all hip and 30.23% of all of knee prosthesis revisions [8].

According to current views, the development of ODRI, and chronic OM is associated with the formation of biofilm by bacteria on the surface of the tissue or implant [9]. Transforming planktonic forms to sedentary and diversifying microorganisms in a mature biofilm increases bacterial resistance to antibiotics. Antibiotic doses effective in vitro against planktonic forms are ineffective against the same bacteria in biofilm conditions. In this case, 200-1000 times higher concentrations of the same antibiotic may be necessary. The consequence of biofilm formation on the surface of implants is the inability to cure PJI with antibiotics administered systematically because the doses active in the biofilm will be toxic to the patient. Because the inflammatory process with biofilm formation takes place mainly in the interface between bone and implant surface, local carriers of antibacterial substances seems currently treatment of choice in case of ODRI.

Historically, local antibacterial treatment has outpaced systemic antibiotic therapy. In 1892, Dressman used "plaster of Paris" soaked in antiseptic. In 1947 DeGrood applied bone graft soaked with penicillin. In the 1960s, absorbable carriers of polyglycolic acid (PGA) and polylactidic acid (PLA) were introduced [10]. In 1970, Buchholz and Klemm initiated the use of Antibiotic Loaded Acrylic Cement (ALAC). In the 1980s, Buri and Lob promoted the topical use of Tauroline gel. In 1987, Ascherl and Stemberger introduced a collagen sponge with gentamicin into clinical practice. The breakthrough in the change of views on the topical use of antibacterials was the experience of Scandinavian orthopedics in the treatment of OM in children published in 1987 [11]. It was one of the first but little known randomized trials on topical use of antibiotics in bone infection, conducted in Nepal. After surgical debridement the focus of OM in 45 children, pellets of ALAC with gentamicin were randomly administered locally, and compared with standard open treatment with wet dressing. The randomization was discontinued taking into account the very good local treatment results with ALAC pellets, that prompted researchers to discontinue inefficient and unethical alternative treatment. A more known randomized trial was published in 1983 in which Walenkamp compared ALAC pellets with gentamicin with suction-irrigation drainage and general antibiotic therapy in OM and PJI. The randomized trial was discontinued after 27 cases, due to the obvious advantage of topical treatment compared to the suction-irrigation drainage [12]. In the late 90's of the 20th century began the more widely use of bone grafts and graft substitutes loaded with antibiotics.

The ideal carrier should provide a high local concentration of the antibiotic above the MIC for the most common pathogens, without systemic toxicity. Should be effective against sedentary forms of bacteria and does not impair the regeneration of bone tissue and biological integration of the implant with bone. The osteoinductive and osteoconductive properties of the antibiotic carrier are also desirable. Despite the studies, questions about the optimal and maximum local concentration of the drug necessary to achieve the therapeutic effect, the time of maintaining the achieved concentration and activity of the drug in tissues, as well as the influence of antibacterial substances on bone regeneration remain open. From a practical point of view, currently used local antibacterial biomaterials are divided into resorbable and non-resorbable. The first one provides a high initial concentration, which decreases with degradation

of the carrier. The non-resorbable carriers provide a therapeutic concentration immediately after implantation, which persists for a long time [10].

Depending on the physicochemical properties, local antibiotic carriers used in bone and joint infections include 6 classes of biomaterials.

1. ALAC. There are two types of ALAC – with a low and high dose of an antibiotic. Low-dose ALAC contain less than 1 g antibiotic in 40 g of polymer, most often aminoglycosides, colistin, or erythromycin, and are commonly used as prophylaxis of infection in primary arthroplasty [2, 7].

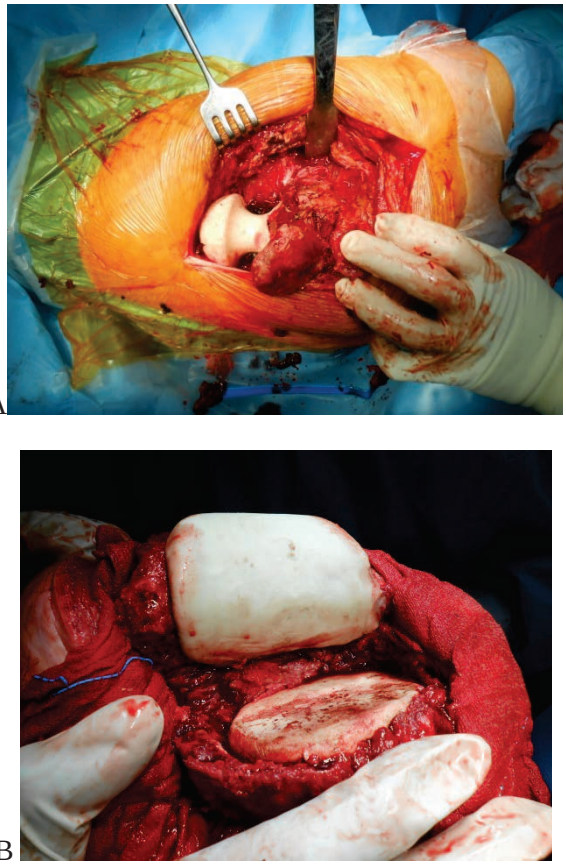

Fig. 1. ALAC spacer in hip (A) and knee joint (B).

Lidwell's studies showed that the use of low-dose ALAC led to an 11-fold decrease in infection rate after hip replacement [13]. Animal studies, however, did not show the protective effect of ALAC with gentamicin against hemetogenous PJI [14]. Higs-dose ALAC is mainly used for the construction of spacers in a two-stage revision of PJI [15]. Depending on the preferences and experience of the surgeon, spacers can be made by hand, or in molds during surgery [16]. They are also ready for use spacers - often modular, replacing the original prosthesis. The spacer is releasing the antibiotic in the lodge after removed prosthesis and prevents the formation of hematome in the remaining dead space. There are static - non-articulating and dynamic – articulated spacers. The antibiotic remains in the cement in the form of inclusions and thus gives ALAC a porous structure, which allows the elution of the antibiotic from its porous surface. A release of the antibiotic from ALAC occurs in two phases: at the beginning, the antibiotic quickly releases from the external surface of the cement, and then the antibiotic diffuses from the center of the spacer to its surface. ALAC containing 5% antibiotic complies with the ISO standard for cement compressive strength (minimum 70 mPa, cement with 5% vancomycin – 95 mPa). The optimal experimentally confirmed antibiotic content in ALAC intended for the implantation of prostheses is 2.5-7.5%. The dose of 10% antibiotic is considered in Europe as suitable for use in spacers, while in the US doses of up to 20% are used. In animal studies, it has been proven that gentamicin can diffuse from ALAC to adherent bone at concentrations 4 times the MIC for the most common pathogens, for a period of at least 6 months [17]. In another study, it was found that the elution from the spacer is on average 20% of the total dose added to the ALAC and that 15% of the antibiotic is released from ALAC within the first 2 weeks after the spacer implantation. After implantation of a joint prosthesis using a low dose ALAC, the concentration of gentamicin in the post-operative hematoma in the area of the hip joint prosthesis may exceed MIC 20-fold [17]. The release process of the added antibiotic is more effective if it is added to the cement already commercially loaded with any antibiotic. Despite the advantages of ALAC, the occurrence of the toxic action of the released gentamicin has been reported In patients with renal insufficiency [18]. The addition of vancomycin in ALAC requires monitoring of serum concentrations to avoid oto- and nephrotoxic effects of the released antibiotic. ALAC is also used in the reconstruction of segmental bone defects in the Masquelet technique and for fabrication of antibacterial coating of intramedullary nails in the treatment of infections after intramedullary osteosynthesis [19]. In the treatment of chronic OM, ALAC may be used in form of pellets, nown in the Europe as Septopal and Miniseptopal, while in the USA, where Septopal is not registered, pellets are produced intraoperatively in a different way [20]. The disadvantage of this form of antibiotic therapy is the necessity of surgical removal of chains (pellets) after the end of antibiotic release [21].

2. Bone grafts with antibiotics. Autografts or allogeneic bone grafts were originally used to fill cavities and dead space in the bone after sequestrectomy. The advantage of bone grafts is the combination of their osteoconductive properties with the local release of antibiotics The antibiotic may be added to the morselised cancellous bone in powder form or added to the solution in which the bone graft is immersed, and the antibiotic itself is adsorbed on the graft surface [22]. Allogenic grafts impregnated with vancomycin, netilmycin or tobramycin were used with good results in two-stage revision of infected hip prosthesis. From the technological

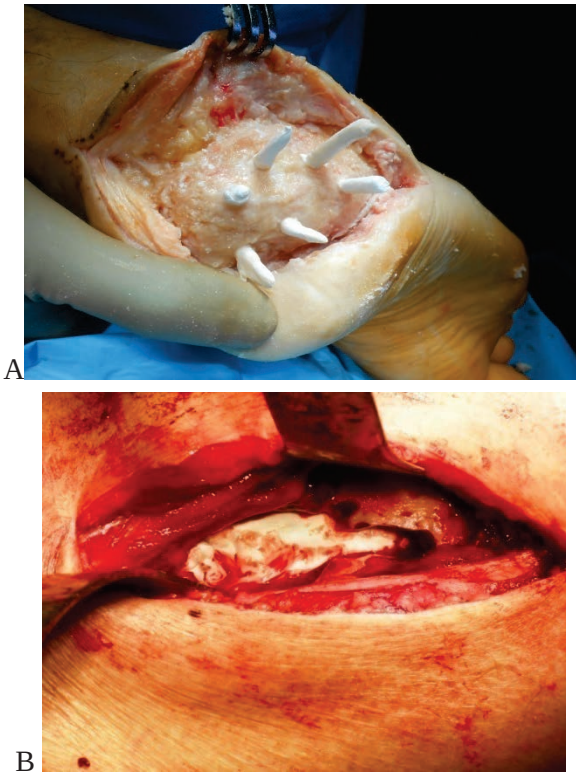

Fig. 2. Garamycin collagen sponge within calcaneus after debridement of superficial bone infection (A) and as securing „clot" in the port off application of other biometerial into the inflamattory void in the bone (B).

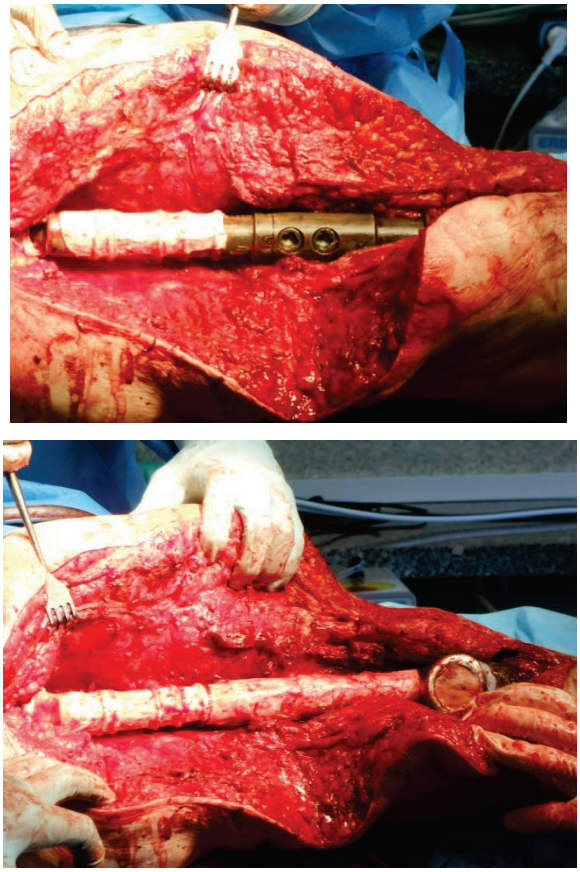

Fig. 3. Garamycin collagen sponge as antibacterial coating of the surface of megaprosthesis of the femur after debridement of the prosthesis and surrounding tissues (DAIR procedure) due the infection.

side, a method of impregnating 50 g of cancellous bone in a solution containing 100 mg of netilmycin in 1 ml of solution has proved to be safe and effective [23]. At the given concentrations neither netilmycin nor vancomycin did not impair bone healing and remodeling of the bone graft. In contrast, the addition of ciprofloxacin, gentamicin, or rifampicin exerts an inhibitory effect on the remodeling of the graft [23]. Similar good results were obtained using 1 g vancomycin powder as an additive to allogenic bone graft made of one femoral head, then compacted in the femur or acetabulum [24].

3. Bone graft substitutes. Just like bone grafts, their substitutes are dedicated to filling non-segmental, cavernous bone defects and at the same time to close the dead space inside the bone, which protects the post-operative defect against hematoma and reinfection. These materials provide a high local concentration of antibiotic, while some also participate in bone regeneration, undergo resorbtion and replacement by bone. It is possible in cavities with limited volume and depends also on bone quality in the walls of the defect. The advantage of substitutes – in contrast to bone allografts – is the lack of the risk of transmission of pathogens. This group of biomaterials includes, for example products under brand-names: Osteoset T, Herafil, PerOssal, Stimulan, BonaLive (bioactive glass in pellets). The products available have the form of pellets and may consists of calcium sulphate, calcium carbonate or calcium phosphate with addition of e.g. vancomycin, teicoplanin, tobramycin, or gentamicin [10, 25]. Some, such as Stimulan, is registered not as drug, but as bone graft substitute and the manufacturer gives the possibility of adding an antibiotic. This biomaterial is a completely absorbable, purified calcium sulphate with a microcrystalline structure and can be used in the form of pellets or paste injected into the bone. Pellets with a 6 mm diameter are released of gentamicin at therapeutic concentrations (MIC 10ug / mL) up to about 40 days, while vancomycin is released even longer. It seems that due to the size and shape of pellets, and their rapid resorption after implantation, this material in most cases is not suitable as a substitute for bone grafts in load-bearing sites in a revision of PJI [26]. A separate biomaterial is synthetic bioactive glass (BonAlive). It does not contain any antibiotic and the inhibition of colonization of the surface of the implanted material by the bacteria is related to its physicochemical properties. Bioactive glass is resorbable after injection into the bone, it has the ability to chemically bind to the bone and stimulate bone tissue regeneration [27].

4. Natural polymers contain antibiotic-enriched collagen (in the past bovine, now equine), fibrin, thrombin, or hyaluronic acid [10]. Protein-based products has the form of flat sponges or foils (eg Septocol, Garamycin Schwam),

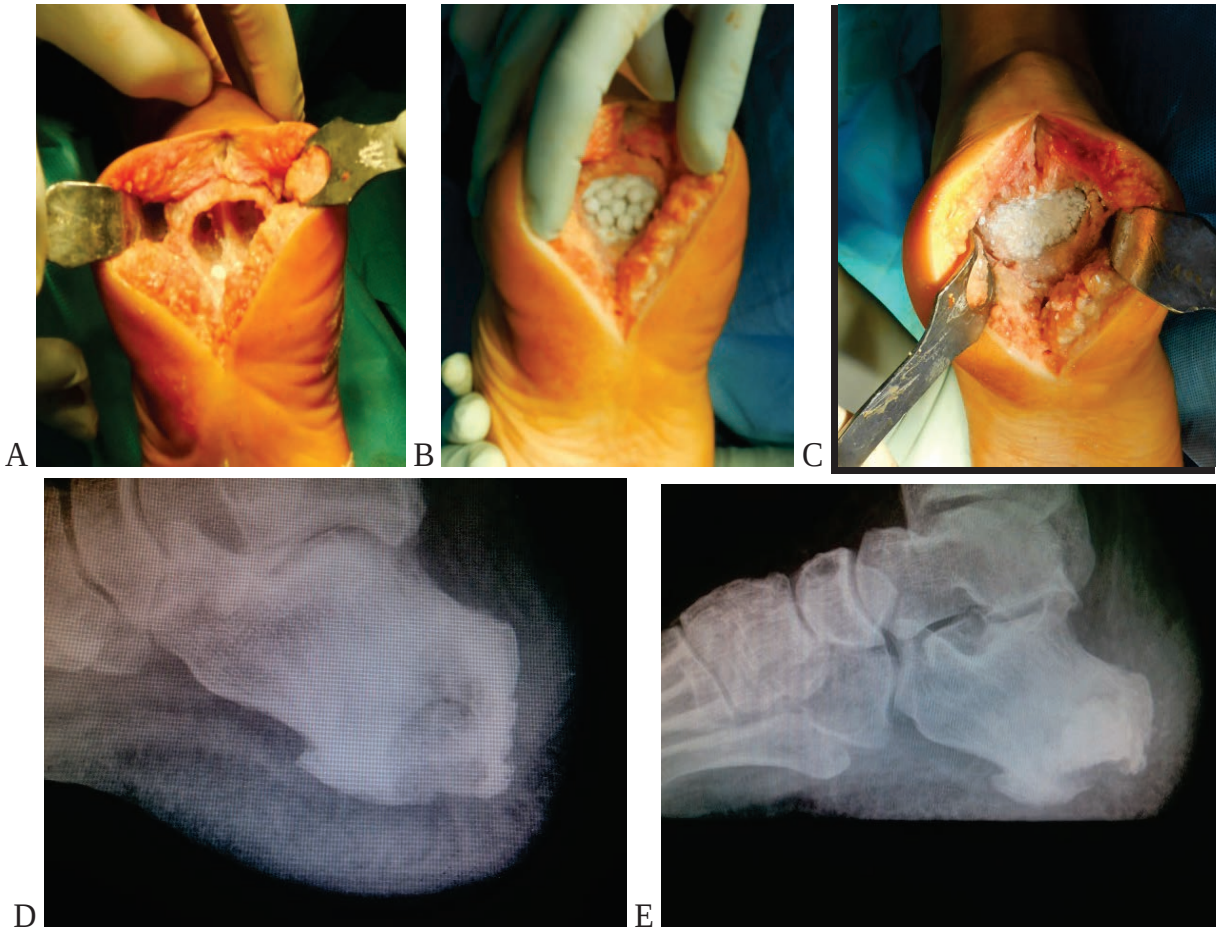

Fig. 4. A-C: filling of cavitary bone defect with Herafil pellets after debridement of infectious focus in calcaneus; preoperative (D) and postoperative radiographs (E).

which after debridement of the inflammatory focus are given to small, cavernous bone defects, or to the bone marrow of long bones. They are also suitable for coating the surface of the ostheosynthesis plate or the nonarticulating surface of the prosthesis, which in the postoperative period will be protected against bacterial colonization. The collagen carrier is releasing the antibiotic at the site of implantation for several hours or days. As a result, the antibiotic does not wash-out of the wound or bone through the postoperative hematoma. Each product has an individual release profile of the antibiotic. After implantation of a collagen sponge containing 130 mg gentamycin (Garamycin Schwam), the local therapeutic concentration of gentamicin can persist up to 5 days. A few hours after implantation the gentamicin concentration in the tissue is about 1000 μg/ml, while in serum it is about 1000 times smaller. On the fourth day after implantation, the gentamicin concentration in the tissue is approx. 10 μg/ml, while in the serum 50 times less [28]. One should avoid using a large volume of sponge in the wound, because after elution of the antibiotic a large volume of the carrier will remain in the wound. It will separate the edges of the wound, making it difficult to heal "per primam", which is unfavorable, especially in the subcutaneous tissue and may cause wound dehiscence. Septocol with a dose of 130mg gentamicin should not be implanted more than 5 sponges. The advantage of a collagen sponge compared to other antibiotic carriers is the possibility of application into a native joint. The simultaneous use of absorbable polymer carrier and ALAC with a high dose of antibiotic can be dangerous because of the potential risk of antibiotic accumulation and its toxic systemic effects. Natural polymers also pose a potential risk of transmitting prion diseases or inducing allergic reactions to proteins, which was found in 8% of patients. Acute renal failure associated with a toxic concentration of gentamicin has also been reported, after the use of a collagen sponge [29]. Another biomaterial, currently developed is the coating of hyaluronic acid with the addition of antibiotics, so-called DAC (Defensive Antibacterial Coating) [30]. It has strong adhesive properties and is completely resorbable. It is used as a prophylactic coating on the surface of cementless prosthesis, as well as in the treatment of PJI during the implantation of a new cementless prosthesis, or for coating implants in ODRI [31].

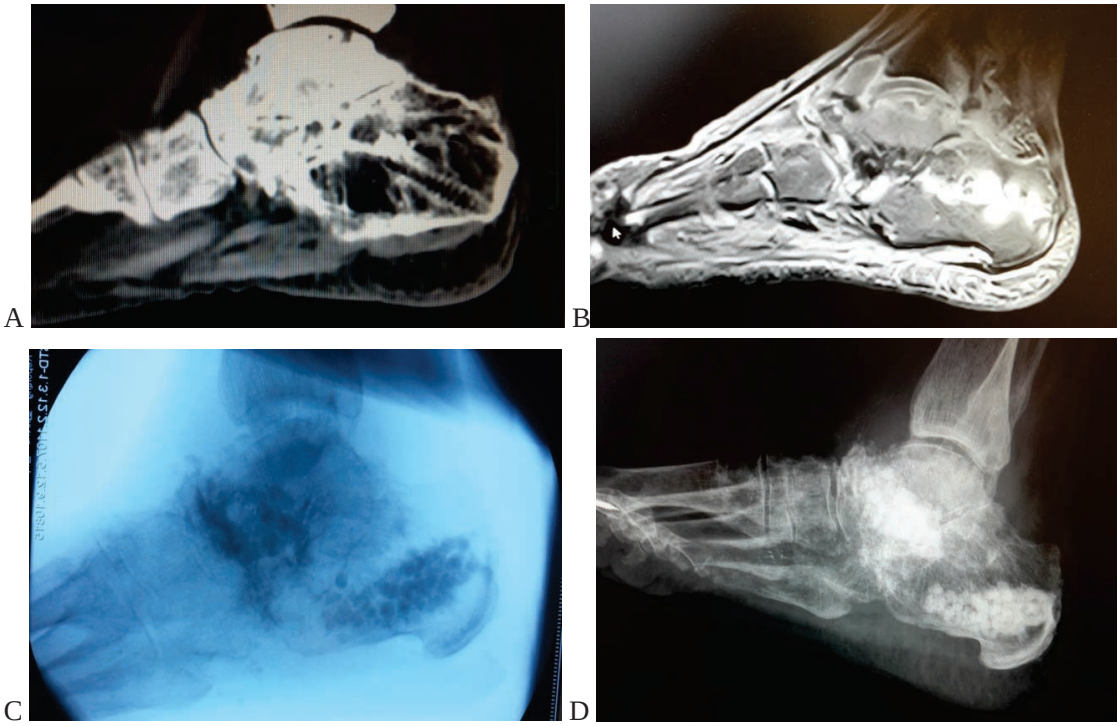

Fig. 5. Filling of cavitary bone defect with Stimulan bone substitute in pellets after debridement of infectious focus in calcaneus; preoperative CT (A) and MR (B); intraoperative controll of placement of pellets with fluoroscopy (C); postoperative radiograph (D).

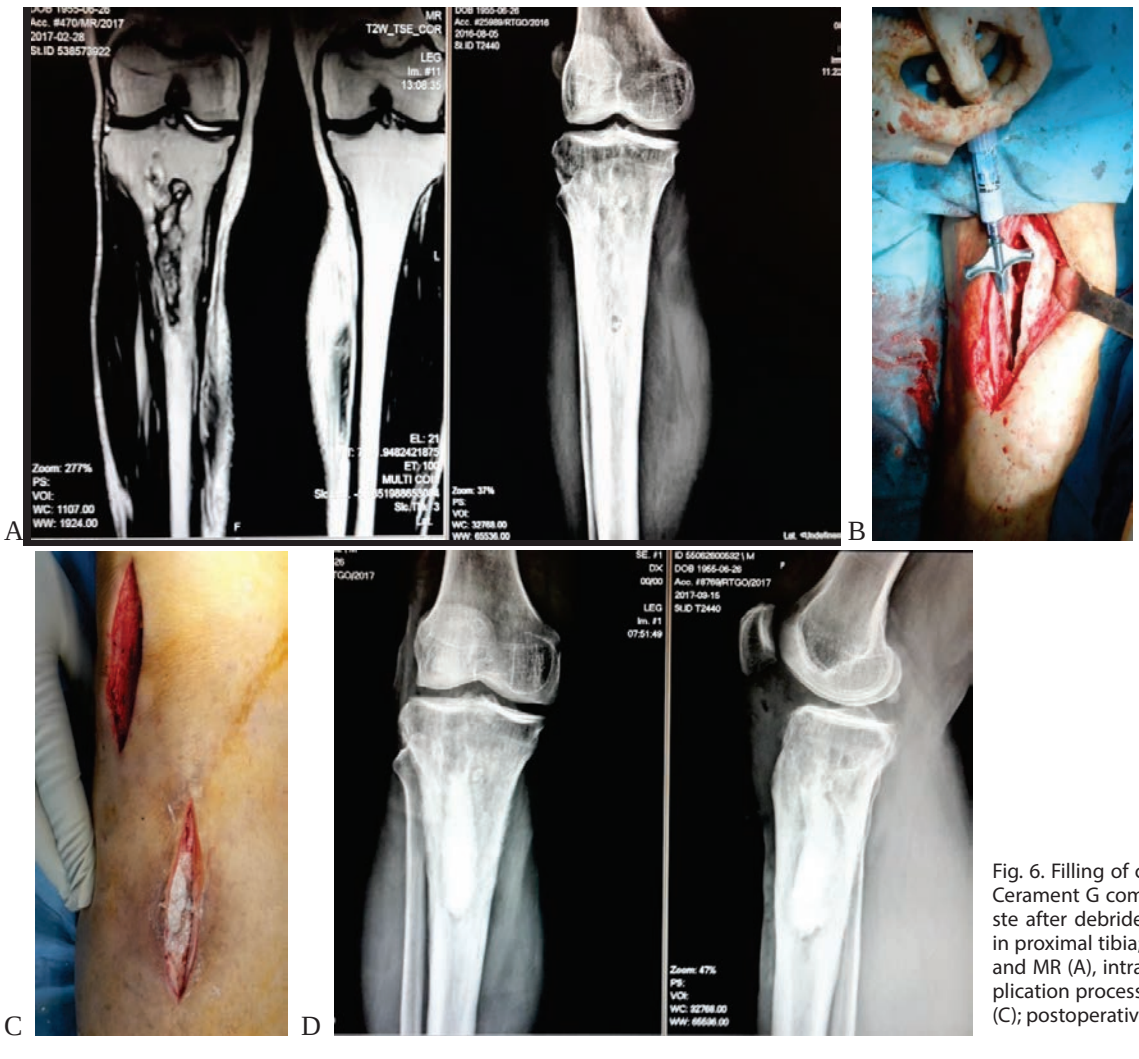

Fig. 6. Filling of cavitary bone defect with Cerament G composite biomaterial in paste after debridement of infectious focus in proximal tibia; preoperative radiograph and MR (A), intraoperative viev of the application process (B) and material in place (C); postoperative radiograph (D).

5. Synthetic polymers include a group of absorbable carriers of antibiotics such as: polyanhydrides, polylactic acid (PLA), polylactide-co-glycolide (PLGA), polycaprolactone, or crosslinked polydimethylsiloxane (PDMS). In clinical practice, PLA and PLGA were used in orthopedics [32]. They enable local, controlled delivery of antibiotics over the period of degradation of the carrier. Due to problems with maintaining their structure after implantation, they were mainly used in the treatment of OM. Since 2005, prefabricated titanium nails with a biodegradable PLA coating with gentamicin has been studied. The advantages of this coating were demonstrated in a group of 21 patients treated with such nails due to complex fractures of the tibia, and due to complications. No deep infection was found in any case, and bone union after 6 months was obtained in 11 from 21 fractures [33].

6. Composite biomaterials. They have a structure of scaffolds and have osteoinductive and osteoconductive properties. They enable delivery of an antibiotic, repair of closed, non-critical bone defects, and enable maintaining a permanent shape during the biomaterial resorbtion. They release the antibiotic in different doses and at different times. An example of a composite biomaterial is CeramentG consisting of calcium sulfate and hydroxyapatite with gentamicin. In a prospective Oxford study of 100 patients with chronic OM, including 10 with an infected pseudoarthrosis, a one-stage surgical treatment of bone infection was performed and CeramentG has been used [34]. After an average of 20 months of observation, only 4 recurrences occurred. There was no correlation between the cure of bone infection and the result of bacteriological sensitivity proves, classification of OM according to Cierny and Mader, or the presence or absence of bone union before surgery.

Summary

Since the introduction of ALAC by Buchholz and Engelbrecht, it is the most commonly used local antibiotic carrier. The main advantage of local antibiotic carriers is the local release of high concentrations of drugs that significantly exceed systemic concentrations, but without systemic toxicity. In combination with good bone stabilization, e.g. in the form of a coating on intramedullary nails, providing stability at the site of an infected fracture or non-union, they promote healing of the infection and fracture, while closing the dead space after debridement of the infection. Bone substituting antimicrobial carriers protect the bone from re-infection and enable reconstruction of cavernous bone defects. Local carriers of antibiotics allow the use of antibacterial drugs based on pre-operative microbiological tests. Mechanisms for the release of antibiotics and to improve the total amount of drug delivered are still under investigation. The results of short- and medium-term use of topical antibiotics published since the 1980s-XX are convincing, but further clinical trials are necessary to resign from concurrent systemic treatment with antibiotics.

References

1. Langlais F.: Can we improve the results of revision arthroplasty for infected total hip replacement? J Bone Joint Surg. 2003;85-B:637-40.
2. Osmon D, Berbari E, Berendt A et al.: Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice Guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2013;56:e1-25
3. Górecki A, Marczyński W, Babiak I.: Zasady profilaktyki, rozpoznawania i leczenia nieswoistych zakażeń kości i stawów. Ortop. Traumatol. Rehabilit, 2008;4(10):396-415.
4. Hryniewicz W, Małdyk P, Ozorowski T, Babiak I, Krogulec Z.: Profilaktyka, diagnostyka i terapia zakażeń w ortopedii. Rekomendacje Konsultanta Krajowego 2013. Narodowy Instytut Leków, Warszawa, Ministerstwo Zdrowia Warszawa, ISBN: ISBN 978-83-932196-3-6. http://www2.mz.gov.pl/wwwfiles/ma_struktura/docs/rekomendacjeortopedia_20131122
5. Mangram AJ, Horan TC, Pearson ML et al.: Guideline for prevention of surgical site infection. Centers for Disease Control and Prevention Hospital Infection Control Practices Advisory Committee. Am J Infect Control 1999;27:97-132.
6. Peersman G, Laskin R, Davis J, Peterson M.: Infection in total knee replacement: a retrospective review of 6489 total knee replacements. Ciln Orthop Relat Res 2001;392:15-23.
7. Swedish Hip Arthroplasty Register Annual Report 2010. Available from: http://www.kvalitetsregister.se/register/rorelseorganen/svenska_hoftprotesregistret
8. Babiak I, Pędzisz P, Janowicz J, Kulig M, Małdyk P.: Economic Analysis of 4221 Revisions Due to Periprosthetic Joint Infection in Poland. Ortop Traumat Rehab 2017;19(1):33-44.
9. Costeron WJ.: Biofilm theory can guide the treatment of device related orthopaedic infections. Clin Orthop Rel Res 2005;437:7-11.
10. Hanssen A.: Local antibiotic delivery vehicles in the treatment of musculoskeletal infection. Clin Orthop Rel Res 2005;437:91-96.
11. Höök M, Lindberg L.: Treatment of chronic osteomyelitis with gentamicin-PMMA beads. A prospective study in Nepal. Tropical Doctor 1987;17:157-63.
12. Walenkamp G.H.I.M.: Gentamicin PMMA beads. A clinical, pharmacokinetic and toxicological study. Thesis, Catholic University of Nijmegen 1983.
13. Lidwell L.: Effect of ultraclean air in operating rooms on deep sepsis in the joint after total hip or knee replacement: a randomised study. BMJ 1982:10-14.
14. Blomgren G, Lindgren U.: Late hematogenous infection in total joint replacement. Studies of gentamicin and bone cement in the rabbit. Clin Orthop Rel Res 1981;155:244-248.
15. Duncan CP, Beauchamp C.: A temporary antibiotic-loaded joint replacement system for management of complex infections involving the hip. Orthop Clin North Am 1993;24:751-759.
16. Babiak I.: Application of individually performed acrylic cement spacers containing 5% of antibiotic in two-stage revision of hip and knee prosthesis due to infection. Chir Narz Ruchu i Ortopedia Pol 2012;77(1):29-37.
17. Langlais F.: Antibiotic cements in articular prostheses: current orthopaedic concepts. International journal of Antimicrobial Agents 2004;28:84-89.
18. Raaij van TM, Visser LE et al.: Acute renal failure after local gentamicin treatment in an infected total knee arthroplasty. J Arthroplasty 2002;17(7):948-950.
19. Masquelet AC, Begue T.: The concept of induced membrane for reconstruction of long bone defects. Orthop Clin North Am 2010;41(1):27–37.
20. Kanellakopoulou K, Giamarellos-Bourboulis EJ.: Carrier systems for the local delivery of antibiotics in bone infections. Drugs 2000;59(6):1223-1232.
21. Mendel V, Simanowski HJ, Scholz HC, Heymann H.: Therapy with gentamicin-PMMA beads, gentamicin-collagen sponge and cefazolin for experimental osteomyelitis due to Staphylococcus aureus in rats. Arch Orthop Trauma Surg 2005;125(6):363-368.

22. Winkler H, Kaudela K, Stoiber A, Menschik F.: Bone grafts impregnated with antibiotics as a tool for treating infected implants in orthopedic surgery – one stage revision results. Cell Tissue Banking 2006;7:319-323.
23. Witso E., Engesaeter L.B.: Revision of Infected total hip prostheses in Norway and Sweden. In: Walenkamp G.H.I.M, editor. Local antibiotics in arthroplasty. Stuttgart New York: Thieme Verlag; 2007. p. 145-146.
24. Buttaro M., Pusso R, Piccaluga F.: Vankomycin-supplemented impacted bone allografts in infected hip arthroplasty. Two – stage revision results. J Bone Joint Surg Br 2005;87: 314-319.
25. Lazarettos J, Efstathopoulos N et al.: A biodegradable calcium phosphate delivery system with teicoplanin for treating MRSA osteomyelitis. Clin Orthop Rel Res 2004;423:253-258.
26. Lei D et al.: treatnment of chronic osteomyelitis using vancomycin impregnated calcium sulphate bone cement. in Bone grafting, A. Zorzi, Editor, InTech. 2012. p. 147-156.
27. Drago L, Romanò D, De Vecchi E, et al.: Bioactive glass BAG-S53P4 for the adjunctive treatment of chronic osteomyelitis of the long bones: an in vitro and prospective clinical study. BMC Infectious Diseases 2013;13:584.
28. Stemberger A, Schwabe J et al.: New antibiotic carriers and coatings in surgery. In: Walenkamp G.H.I.M, editor. Local antibiotics in arthroplasty. Stuttgart New York: Thieme Verlag; 2007. p. 13-21.
29. Swieringa AJ, Tulp NJ: Toxic serum gentamicin levels after use of gentamicin-loaded sponges in infected total hip arthroplasty. Acta Orthop 2005;76(1):75-77.
30. Giavaresi G, Meani E, Santori M, et al.: Efficacy of antibacterial-loaded coating in an in vivo model of acutely highly contaminated implant. International Orthopedics 2013;38:1505-12.
31. Drago L, Boot W, Dimas K, et al.: Does implant coating with antibacterial-loaded hydrogel reduce bacterial colonisation and biofilm formation in vitro? Clin Orthop Relat Res, 2014; 472:3311-3323
32. Garvin K, Feschuk C.: Polylactide-polyglycolide Antibiotic Implans. Clin Orthop Rel Res 2005;437:105-110.
33. Fuchs T, Stange R, Schmidmaier G, Raschke MJ.: The use of gentamicin-coated nails in the tibia: preliminary results of a prospective study. Arch Orthop Trauma Surg 2011;131:1419-1425.
34. McNally MA, Ferguson JY, Lau ACK et al.: Single stage treatment of chronic osteomyelitis with a new absorbable gentamicin loaded, calcium sulphate/hydroxiapatite biocomposite. Bone Joint J, 2016;98-B:1289-96.