Meeting Proceedings

OTA ORTHOPAEDIC TRAUMA ASSOCIATION

OTA INTERNATIONAL THE OPEN ACCESS JOURNAL OF ORTHOPAEDIC TRAUMA

OPEN

Collagen fleece in orthopaedic infections

Susan M. Ge, MD, Edward J. Harvey, MD*

Abstract

Collagen fleece is a relatively new development. It represents another option in the battle against infection. It is a cheap, biocompatible, and resorbable local antibiotic delivery mechanism with favorable drug release kinetics and low risk of adverse effects or toxicity. Benefit may be conferred when used in contaminated cases. Significantly more research is still needed before the adoption of collagen fleece as the standard of care. However, we can likely conclude that there are no major adverse effects and it can be safely used as an adjunct in addition to conventional therapies for the prophylaxis and treatment of infections.

Keywords: antibiotics, biomaterial, infection, nonunion, osteomyelitis

History of local antimicrobial therapy

Infections have been a challenge to orthopaedic surgeons since the beginning of the profession itself. In the 1970s, Patzakis[1] along with Gustilo and Anderson[2] was the first to show the utility of systemic antibiotics to decrease infection in open fractures. Their work helped lead the development of modern-day antibiotic guidelines. Although systemic antibiotics have been a mainstay of treatment, very high doses are often needed to reach an adequate concentration at the local site to be effective, sometimes resulting in systemic toxicity.[3] Discussion around local therapy has a long history. Local antimicrobial therapy has been used since Lister's time to treat surgical wounds.[4] Antibiotic impregnated polymethylmethacrylate (PMMA) cement was first used to treat infections for revision total hip arthroplasties.[5] It has then been expanded to aid the treatment of chronic osteomyelitis and septic arthritis.[6] Prior to that, local treatment was limited to drainage. Despite numerous advancements over the past 100 years, infections in orthopaedic surgery remain an unsolved problem.

Studies suggest that local application of antibiotics is a useful adjunct to systemic antibiotics in treating implant-related infections and osteomyelitis, particularly those that are chronic.[3,7,8] The higher availability of antibiotics with local application combats scarring and poor vascularity at the fracture site, and better penetrates biofilms.[8–10] Antibiotic impregnated PMMA cement has been the mode in longest usage. Antibiotic cement can provide structural support where there is bone loss, can be molded to fit into specific spaces, or formed into a string of beads to increase the surface area for antibiotic release.[3,6] However, despite the versatility of antibiotic cement, studies have shown variable rates of antibiotic release depending on the amount of antibiotics used, surface porosity, and roughness of the specific cement.[11] The high initial release followed by a prolonged release at a much lower dose over weeks to months, often below the minimum inhibitory concentration[12] means that the antibiotic cement itself over time may become a nidus of infection.[13,14] Moreover, a second surgery is always required to remove the cement.

To tackle some of the drawbacks of antibiotic cement, various bioabsorbable antibiotic delivery vehicles have been developed for use in orthopaedics. These include bone graft substitutes such as antibiotic-impregnated biodegradable ceramics made from various combinations of hydroxyapatite and calcium phosphate or sulfate,[15] and bioactive glass[15,16] with intrinsic antimicrobial properties. Other bioabsorbable delivery vehicles include hydrogels,[17] as well as collagen matrices or fleece.[18]

Gentamicin impregnated collagen fleece

Collagen fleeces are a lyophilized collagen implant of either bovine, equine, or porcine origin composed of mainly Type I collagen.[19,20] They were initially used for hemostasis in surgery[21,22] but were subsequently impregnated with gentamicin to treat surgical infections. Their ability to aid in hemostasis is still marketed as one if its functions by manufacturers. The benefits of collagen fleece include its low cost, biocompatibility, and adjustable drug release characteristics. The stiff mouldable foam characteristic of collagen fleece also makes it easy to handle, allowing surgeons to cut, manipulate, and suture it as needed.

Cost

The cost of collagen fleeces is relatively cheap costing approximately $75 for a 5x5 sheet or $200 for a 10x10 or 5x20 sheet in Canadian dollars which converts to $50 and $140 USD respectively. For most cases, up to three 10×10 sheets may be used for a total cost of $420.[19] To bring this into perspective, antibiotic-impregnated cement costs $650 USD for a 40 g packet containing 1 g of antibiotics.[23] This dose, under 2 g/40 mg packet is generally used for prophylaxis. For treatment of

The authors have no funding and no conflicts of interest to disclose.

McGill University, Dept of Surgery, Division of Orthopedic Surgery, Montreal Quebec Canada

* *Corresponding author. Address: Edward J. Harvey, Montreal General Hospital, 1650 Cedar Ave Room B5.159.5, Montreal Quebec H3G1A4 Tel: +514 934 1934; E-mail address: edward.harvey@mcgill.ca*

OTA (2021) e111

Received: 28 September 2020 / Received in final form: 5 November 2020 / Accepted: 11 December 2020

Published online 15 June 2021

http://dx.doi.org/10.1097/OI9.0000000000000111

infection, a dose of over 2 g/40 mg is recommended. In that case, a regular 40 g packet of PMMA cement costs $65 USD[23] plus the cost of approximately 4.8 g of gentamicin powder[24,25] at $160 USD per gram, results in a total cost of over $1000 USD.

Biocompatibility and biodegradation

Collagen is biocompatible and is degraded by macrophage phagocytosis as well as through enzymatic degradation by extracellular proteases.[21,26] The rate of degradation can take between 1 and 7 weeks depending on local fluid dynamics, pH, and vascularity.[20,26] Some also argue that collagen can attract and stimulate osteoblasts and promote callus formation and granulation tissue in both bone and wound healing.[12,27,28] The effects of collagen fleece on wound healing has not been thoroughly studied, but this characteristic may also play a possible role in decreasing infection.[29]

Drug release kinematics

Gentamicin is uniformly incorporated into the fleece by lyophilization, allowing for an equal dose of antibiotics per centimeter square.[19] Each sponge contains approximately 130 to 200 mg of gentamicin sulfate.[30,31] The structure of the collagen fleece allows both rapid, intermediate, and long-term release of antibiotics. The release kinetics can be altered by changing pore size and porosity. Partial open porosity allows immediate release of antibiotics, partially closed porosity allows for a slower secondary release, whereas the antibiotics trapped within the collagen's fibrillar structure results in an even more gradual tertiary release.[19] Although much research has been put into extending antibiotic release from these collagen sponges, the initial massive release in the first 24 to 48 h is likely still the most important for the treatment of infections.

The combination of hydrophilic gentamicin sulfate with hydrophobic gentamicin crobefate also allows for further optimization of release kinetics.[27,32] Gentamicin sulfate is water soluble and gets released almost immediately after implantation, with the majority of the antibiotics released within first hours or days depending on the rate of collagen degradation.[30,32] This rapid initial release of gentamicin sulfate allows high concentrations of gentamicin to accumulate in the local tissue rapidly to levels as high as 700 to 9000 μg/mL, well above the minimal inhibitory concentration[12] for most organisms (4 μg/mL for sensitive organisms and 8 μg/mL for low sensitive organisms).[19,20,27] In animal models, this has been found to drop to 10 μg/mL from about day 2 through day 10, and by day 28 to 2.7 μg/mL.[20] In humans, concentrations detected in wound exudate were found to be below therapeutic after approximately 7 days.[15] In comparison, beads made from antibiotic cement containing 1 g of gentamicin reached a peak concentration of approximately 1000 μg/mL, whereas spacers reached a peak of 21 μg/mL.[33] Antibiotic concentration for both dropped rapidly for the first 3 days down to about 3.9 μg/mL for beads and 1.9 μg/mL for spacers by day 13.[33] Moreover, only about 4% to 17% of total antibiotics were released after 1 week with a lower rate of release for the remainder of the time, likely resulting in less antibiotics released overall.[11] The addition of gentamicin crobefate to collagen fleeces in addition to gentamicin sulfate leads to a more gradual release of antibiotics over 10 to 12 days, allowing the local concentration of antibiotics to be maintained at 100 μg/mL, and providing a potential advantage over antibiotic cement.[20,27,30,32]

Other ways to increase controlled antibiotic release by altering the physical characteristics of the fleece include; chemical crosslinking to increase the tensile strength of the collagen, making it more resistant to proteolysis[26]; or by manufacturing matrices with a multilayer or compressed design to increase diffusion restriction.[19] There is also work looking at or adding gentamicin enriched biodegradable polylactic-co-glycolic acid (PLGA) to achieve a constant release of antibiotics over 7 to 10 days.[19,30,34]

Adverse effects and toxicity

The therapeutic levels of gentamicin in the serum with intravenous antibiotic administration is 4 to 10 μg/mL. With local antibiotic delivery using collagen fleece, very high local antibiotic concentrations can be obtained without systemic toxicity. When two to five 10×10 collagen fleeces containing 130 mg of gentamicin each were used in humans, serum levels peaked at 3.2 to 7.2 μg/mL, 4.5 to 6 h post-application.[31] These levels further decreased after 24 h to below 2 μg/mL, well below the toxic threshold of 10 to 12 μg/mL for nephro- or ototoxicity.[19,31] When up to 6 collagen sponges have been used to treat infected hip arthroplasty, there have been reports of persistently high serum gentamicin levels with an associated decreased creatinine clearance in several patients, however, baseline renal function was not reported.[35] Another study found that that the increase in mean serum creatinine was significantly higher when collagen fleece was added to the wound although this was not clinically significant.[36]

Generally, the use of collagen in humans is considered safe and most studies report no significant adverse effects or systemic toxicity.[19] There have been rare reports of localized hypersensitivity reactions to animal collagen presenting as erythema, swelling, and pruritis,[26] as well as local wound complications such as fistulas and exudate.[15] Some have reported increased wound secretion for up to 6 weeks as the collagen fleece dissolves.[37] However, it is not clear what the implications of this are on wound healing.[29] One study has shown that collagen fleece buffered to a neutral pH may mitigate these wound complications.[38]

Clinical studies

Prophylaxis

Collagen fleece has been studied extensively for the prevention of wound infections after cardiac and general surgical procedures. Studies have shown conflicting results. However, a meta-analysis of randomized controlled trials from 1992 to 2012 looking at preventing surgical site infections in sternal wounds, colorectal surgery, pilonidal sinuses, and perianal abscesses among other types of surgical wounds, showed that the use of these implants was associated with a significant decrease in surgical site infections in clean and clean-contaminated wounds.[28] They did not have enough contaminated wounds to draw a conclusion. Another study looking at prophylaxis of surgical site infections in general surgery procedures found a larger difference in contaminated cases compared to clean or clean-contaminated cases; a 16% incidence of infection with the use of collagen fleece compared to 30% without. The sample size was however not large enough to be statistically significant.[39] A more recent meta-analysis showed 45% and 38% reduced risk of superficial sternal and deep sternal wound infections respectively, as well

as a 33% risk reduction of mediastinitis, with no difference in mortality.[40] Friberg et al[41] was also able to show that collagen fleece in addition to prophylactic intravenous antibiotics was cost effective to use in all patients undergoing cardiac surgery.

In orthopaedics, collagen fleece has been used as prophylaxis after amputations, open fractures, arthroplasty, and spine surgery.[18] Application of collagen fleece to the wound after forefoot amputation in diabetic patients resulted in more rapid wound healing with a difference of 2 weeks between the fleece group and the control group.[42] Despite this, there was no significant difference in the re-amputation rate. In a series of patients undergoing lumbar discectomy, the rate of postoperative spondylodiscitis diagnosed by laboratory studies and imaging was 3.7% (19/508) in a group without antibiotic prophylaxis, whereas there were no infections (0/1134) in the group that had collagen fleece placed in the cleared disc space.[43] In arthroplasty, a randomized controlled trial of 684 patients across five sites looking at intravenous antibiotics after hemiarthroplasty versus intravenous antibiotics plus the local application of two collagen fleece was conducted. Results showed no significant difference between the groups with an infection rate of 2.7% to 7.6%.[36] In this study, baseline low rates of infection in arthroplasty in addition to variations between the different centers likely obscure any small differences that might exist. A large retrospective study looking at collagen fleece application at wound closure as part of a care bundle along with chlorhexidine prep and a single dose of intravenous antibiotics showed a decrease in surgical site infections compared to previous bundles without collagen fleece application.[44] However, it is difficult to separate the contribution of the collagen fleece from other changes to the care bundle. Unlike arthroplasty and lumbar discectomy, the baseline infection rate of open fractures can be as high as 30%.[2,45] Out of 35 patients with Gustilo IIIA open fractures treated with open reduction internal fixation (ORIF) and local collagen fleece application in addition to 3 to 5 days of systemic antibiotics, 4 (9.67%) had local wound complications, 2 (6.45%) had a deep infection requiring repeat debridement and collagen fleece application.[32] This study did not have a control however and is thus difficult to interpret.

In summary, it appears that the use of gentamicin impregnated collagen fleece does convey some advantages in addition to systemic antibiotics for the prophylaxis of infections, however, the evidence is far from conclusive. In cardiac surgery, a meta-analysis of randomized controlled trials shows that collagen fleece was found to significantly decrease surgical site infections in clean and clean-contaminated cases. In orthopaedics, fewer studies have been done. Studies seem to show favorable or at least non-inferior results compared to conventional treatment alone, particularly in cases in which no metal is implanted.

Treatment of infection

There have been many early case series, mostly out of Germany, looking at the use of collagen fleeces to treat acute and chronic osteomyelitis in orthopaedic surgery. These showed effectiveness and good safety profile.[15,18] However, well-powered prospective comparative studies have been lacking. The most recent cohort study of a group of 50 patients with osteomyelitis treated with surgical resection, intravenous antibiotics (which was converted to oral antibiotics on discharge), and collagen fleece application over a 7-year period found that when compared to a historical cohort treated with surgical resection and 6 weeks of intravenous and 6 weeks of oral antibiotics, the collagen fleece group had a lower probability of recurrence.[46] A systematic review of clinical studies using collagen fleece to treat chronic osteomyelitis showed an overall success rate of 91% in 10 included studies with a total of 413 patients[15] The studies looking at gentamicin sulfate sponges had a success rate of 63% to 100% with the use of anywhere between 1 and 7 sponges. Studies had different treatment protocols, not all studies reported whether systemic antibiotics were used, and all had poor reporting of complications or treatment failures. Only 1 study looked at sponges also containing gentamicin crobefate. This showed a success rate of 93.5% for infection eradication. However, follow-up only went up to 6 weeks with only 93 of the 123 patients completing the study. The included studies were highly heterogeneous with only two higher level randomized control trials, so conclusions remain difficult to draw. When comparing collagen fleece with PMMA, studies showed no difference in the eradication of infection, although as expected the PMMA group had a higher rate of re-operation.[47,48] Outside of orthopaedics, a study looking at the treatment of osteomyelitis in cranio-maxillo-facial surgery found that local collagen sponge application resulted in shorter length of stay as well as fewer local wound complications independent of whether systemic antibiotics were used.[12] There has also been a retrospective study looking at the use of collagen fleece and PMMA to treat periprosthetic total knee and total hip infections with prosthesis retention, however, some patients received only PMMA or only collagen fleece, whereas others received both. The authors also did not differentiate between the two in their analysis.[37]

In summary, gentamicin impregnated collagen fleece appears to confer some benefit to the treatment of osteomyelitis however, there have been no high-powered studies accomplished to make any conclusive recommendations. Direct comparisons to the current standard of care, antibiotic PMMA beads, show no difference in infection eradication but benefits include lower re-operation rate and cost. Prospective randomized controlled trials are needed.

4 Current use in orthopaedics

Commercially available products

There are currently a number of collagen fleeces commercially available and are marketed under different names. These include collagen of equine, porcine, or bovine origin combined with either gentamicin sulfate or a mix of gentamicin sulfate and crobefate[15,19,38] (See Table 1). Studies comparing these various brand names and formulations have shown no significant differences.[29] Collatamp G is the only 1 currently available in North America.

Table 1

Types of gentamicin impregnated collagen fleece and their composition.

Name	Collagen origin	Gentamicin composition
Collatamp G (US), Garacol (Netherlands), Garamycin (Switzerland), Sulmycin (Austria), Gentacoll (Germany), Syntacoll (Germany)	Equine or bovine	2.0 mg gentamicin sulfate
Septocoll (Germany, UK)	Equine	1.5 mg gentamicin sulfate 4.4 mg gentamicin crobefate
Jason G (Germany)	Porcine	1.7 mg gentamicin sulfate

Use by surgeons

Surveys of the use of local antimicrobials to prevent surgical site infection found that 55% of all surgeons questioned do not use any local antimicrobials.[49] However, out of those that do, collagen fleece was the most commonly used. Only 4 (12%) respondents worked in orthopaedic surgery in this survey so it may not be reflective of the orthopaedic practice. This survey concluded that there was no agreement regarding the usefulness of local antimicrobials, particularly among surgeons. In orthopaedic surgery, collagen fleece seems to be the most well studied for use in the treatment of osteomyelitis although there has been work in its use for prophylaxis, particularly in open fractures. In a survey of international orthopaedic trauma surgeons from 112 different countries regarding preventing fracture-related infections, the most used local antimicrobial agent for Gustilo Type III fractures was antibiotic cement beads (33% of respondents) or antimicrobial wound dressings (30% of respondents). When asked whether and when they used antibiotic-impregnated collagen fleece/sponge, 12% of respondents said they use it in Gustilo Type IIIA fractures, 14% for Gustilo Type IIIB fractures, and 16% in Gustilo Type IIIC fractures.[50] This was similar to those that said they would use antibiotic powder. From this survey, it seems that the higher the risk for infection, the more likely surgeons will use collagen fleece.

Conclusions

Collagen fleece is a cheap, biocompatible, and resorbable local antibiotic delivery tool with favorable drug release kinetics and low risk of adverse effects or toxicity. Currently, published studies are heterogeneous and inconsistent with regards to the efficacy of collagen fleece for either the prophylaxis or treatment of infection within orthopaedics. This is clearly reflected in the practice of orthopaedic surgeons. There does seem to be non-inferiority demonstrated in most studies. Additionally, more benefit may be conferred in more contaminated cases. Significantly more research is still needed before the adoption of collagen fleece as the standard of care. However, we can likely conclude that there are no major adverse effects and it can be safely used as an adjunct in addition to conventional therapies for the prophylaxis and treatment of infections.

References

1. Patzakis MJ, Harvey JPJr, Ivler D. The role of antibiotics in the management of open fractures. J Bone Joint Surg Am. 1974;56:532–541.
2. Gustilo RB, Anderson JT. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones: retrospective and prospective analyses. J Bone Joint Surg Am. 1976;58:453–458.
3. Metsemakers WJ, Fragomen AT, Moriarty TF, et al. Evidence-based recommendations for local antimicrobial strategies and dead space management in fracture-related infection. J Orthop Trauma. 2020;34:18–29.
4. Pitt D, Aubin JM. Joseph Lister: father of modern surgery. Can J Surg. 2012;55:E8–E9.
5. Buchholz HW, Elson RA, Engelbrecht E, et al. Management of deep infection of total hip replacement. J Bone Joint Surg Br. 1981;63-B:342–353.
6. Hedstrom SA, Lidgren L, Torholm C, et al. Antibiotic containing bone cement beads in the treatment of deep muscle and skeletal infections. Acta Orthop Scand. 1980;51:863–869.
7. Morgenstern M, Vallejo A, McNally MA, et al. The effect of local antibiotic prophylaxis when treating open limb fractures: a systematic review and meta-analysis. Bone Joint Res. 2018;7:447–456.
8. Metsemakers WJ, Morgenstern M, Senneville E, et al. General treatment principles for fracture-related infection: recommendations from an international expert group. Arch Orthop Trauma Surg. 2019;140:1013–1027.
9. Habash M, Reid G. Microbial biofilms: their development and significance for medical device-related infections. J Clin Pharmacol. 1999;39:887–898.
10. Castaneda P, McLaren A, Tavaziva G. Biofilm antimicrobial susceptibility increases with antimicrobial exposure time. Clin Orthop Relat Res. 2016;474:1659–1664.
11. van de Belt H, Neut D, Uges DR, et al. Surface roughness, porosity and wettability of gentamicin-loaded bone cements and their antibiotic release. Biomaterials. 2000;21:1981–1987.
12. Zawadzki PJ, Perkowski K, Kotlarski M. Comparative study on usefulness of gentamycin-containing collagen implants in the treatment of patients with osteitis and osteomyelitis of the craniofacial skeleton. Ann Agric Environ Med. 2017;24:299–302.
13. Neut D, van de Belt H, Stokroos I, et al. Biomaterial-associated infection of gentamicin-loaded PMMA beads in orthopaedic revision surgery. J Antimicrob Chemother. 2001;47:885–891.
14. Hake ME, Young H, Hak DJ, et al. Local antibiotic therapy strategies in orthopaedic trauma: practical tips and tricks and review of the literature. Injury. 2015;46:1447–1456.
15. van Vugt TA, Geurts J, Arts JJ. Clinical application of antimicrobial bone graft substitute in osteomyelitis treatment: a systematic review of different bone graft substitutes available in clinical treatment of osteomyelitis. Biomed Res Int. 2016;2016:6984656.
16. Lindfors N, Geurts J, Drago L, et al. Antibacterial bioactive glass, S53P4, for chronic bone infections - a multinational study. Adv Exp Med Biol. 2017;971:81–92.
17. Malizos K, Blauth M, Danita A, et al. Fast-resorbable antibiotic-loaded hydrogel coating to reduce post-surgical infection after internal osteosynthesis: a multicenter randomized controlled trial. J Orthop Traumatol. 2017;18:159–169.
18. Knaepler H. Local application of gentamicin-containing collagen implant in the prophylaxis and treatment of surgical site infection in orthopaedic surgery. Int J Surg. 2012;10 (suppl 1):S15–S20.
19. Ruszczak Z, Friess W. Collagen as a carrier for on-site delivery of antibacterial drugs. Adv Drug Deliv Rev. 2003;55:1679–1698.
20. Mehta S, Humphrey JS, Schenkman DI, et al. Gentamicin distribution from a collagen carrier. J Orthop Res. 1996;14:749–754.
21. Diefenbeck M, Muckley T, Hofmann GO. Prophylaxis and treatment of implant-related infections by local application of antibiotics. Injury. 2006;37 (suppl 2):S95–S104.
22. Schonauer C, Tessitore E, Barbagallo G, et al. The use of local agents: bone wax, gelatin, collagen, oxidized cellulose. Eur Spine J. 2004;13 (suppl 1):S89–S96.
23. Cummins JS, Tomek IM, Kantor SR, et al. Cost-effectiveness of antibiotic-impregnated bone cement used in primary total hip arthroplasty. J Bone Joint Surg Am. 2009;91:634–641.
24. Bistolfi A, Massazza G, Verne E, et al. Antibiotic-loaded cement in orthopedic surgery: a review. ISRN Orthop. 2011;2011:290851.
25. Jaeblon T. Polymethylmethacrylate: properties and contemporary uses in orthopaedics. J Am Acad Orthop Surg. 2010;18:297–305.
26. Friess W. Collagen–biomaterial for drug delivery. Eur J Pharm Biopharm. 1998;45:113–136.
27. El-Husseiny M, Patel S, MacFarlane RJ, et al. Biodegradable antibiotic delivery systems. J Bone Joint Surg Br. 2011;93:151–157.
28. Chang Y, Tai CL, Hsieh PH, et al. Gentamicin in bone cement: a potentially more effective prophylactic measure of infection in joint arthroplasty. Bone Joint Res. 2013;2:220–226.
29. de Bruin AF, Gosselink MP, van der Harst E, et al. Local application of gentamicin collagen implants in the prophylaxis of surgical site infections following gastrointestinal surgery: a review of clinical experience. Tech Coloproctol. 2010;14:301–1310.
30. ter Boo GJ, Grijpma DW, Moriarty TF, et al. Antimicrobial delivery systems for local infection prophylaxis in orthopedic- and trauma surgery. Biomaterials. 2015;52:113–125.
31. Swieringa AJ, Goosen JH, Jansman FG, et al. In vivo pharmacokinetics of a gentamicin-loaded collagen sponge in acute periprosthetic infection: serum values in 19 patients. Acta Orthop. 2008;79:637–642.
32. Chaudhary S, Sen RK, Saini UC, et al. Use of gentamicin-loaded collagen sponge in internal fixation of open fractures. Chin J Traumatol. 2011;14:209–214.
33. Anagnostakos K, Wilmes P, Schmitt E, et al. Elution of gentamicin and vancomycin from polymethylmethacrylate beads and hip spacers in vivo. Acta Orthop. 2009;80:193–197.
34. Schlapp M, Friess W. Collagen/PLGA microparticle composites for local controlled delivery of gentamicin. J Pharm Sci. 2003;92:2145–2151.
35. Swieringa AJ, Tulp NJ. Toxic serum gentamicin levels after the use of gentamicin-loaded sponges in infected total hip arthroplasty. Acta Orthop. 2005;76:75–77.

36. Westberg M, Frihagen F, Brun OC, et al. Effectiveness of gentamicin-containing collagen sponges for prevention of surgical site infection after hip arthroplasty: a multicenter randomized trial. Clin Infect Dis. 2015;60:1752–1759.
37. Geurts JA, Janssen DM, Kessels AG, et al. Good results in postoperative and hematogenous deep infections of 89 stable total hip and knee replacements with retention of prosthesis and local antibiotics. Acta Orthop. 2013;84:509–516.
38. Kilian O, Hossain H, Flesch I, et al. Elution kinetics, antimicrobial efficacy, and degradation and microvasculature of a new gentamicin-loaded collagen fleece. J Biomed Mater Res B Appl Biomater. 2009;90:210–222.
39. Chia CL, Shelat VG, Low W, et al. The use of Collatamp G, local gentamicin-collagen sponge, in reducing wound infection. Int Surg. 2014;99:565–570.
40. Kowalewski M, Pawliszak W, Zaborowska K, et al. Gentamicin-collagen sponge reduces the risk of sternal wound infections after heart surgery: meta-analysis. J Thorac Cardiovasc Surg. 2015;149:1631.e1-6–1640.e1-6.
41. Friberg O, Dahlin LG, Levin LA, et al. Cost effectiveness of local collagen-gentamicin as prophylaxis for sternal wound infections in different risk groups. Scand Cardiovasc J. 2006;40:117–125.
42. Varga M, Sixta B, Bem R, et al. Application of gentamicin-collagen sponge shortened wound healing time after minor amputations in diabetic patients - a prospective, randomised trial. Arch Med Sci. 2014;10:283–287.
43. Rohde V, Meyer B, Schaller C, Hassler WE. Spondylodiscitis after lumbar discectomy. Incidence and a proposal for prophylaxis. Spine (Phila Pa 1976). 1998;23:615–620.
44. Johnson B, Starks I, Bancroft G, et al. The effect of care bundle development on surgical site infection after hemiarthroplasty: an 8-year review. J Trauma Acute Care Surg. 2012;72:1375–1379.
45. Dellinger EP, Miller SD, Wertz MJ, et al. Risk of infection after open fracture of the arm or leg. Arch Surg. 1988;123:1320–1327.
46. Leung AH, Hawthorn BR, Simpson AH. The effectiveness of local antibiotics in treating chronic osteomyelitis in a cohort of 50 patients with an average of 4 years follow-up. Open Orthop J. 2015;9:372–378.
47. Letsch R, Rosenthal E, Joka T. Local antibiotic administration in osteomyelitis treatment–a comparative study with two different carrier substances. Aktuelle Traumatol. 1993;23:324–329.
48. Bettin D, Winkler H. Comparative evaluation of results after local antibiotic therapy with gentamycin in form of beads and fleece. Orthop Proc. 2009;91-B (supp_II):311.
49. Cooper C, Horner C, Barlow G, et al. A survey of practice and opinions on the use of topical antibiotics to prevent surgical site infection: more confusion than consensus. J Antimicrob Chemother. 2018;73:1978–1983.
50. Puetzler J, Zalavras C, Moriarty TF, et al. Clinical practice in prevention of fracture-related infection: an international survey among 1197 orthopaedic trauma surgeons. Injury. 2019;50:1208–1215.