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Local Antibiotic Delivery Systems: Current and Future Applications for Diabetic Foot Infections

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Abstract

Foot infections are common among diabetic patients with peripheral neuropathy and/or peripheral arterial disease, and it can be the pivotal event leading to a minor or major amputation of the lower extremity. Treatment of diabetic foot infections, especially deep-seated ones, remains challenging, in part because impaired blood perfusion and the presence of biofilms can impair the effectiveness of systemic antibiotics. The local application of antibiotics is an emerging field in the treatment of diabetic foot infections, with demonstrable advantages. These include delivery of high concentrations of antibiotics in the affected area, limited systemic absorption, and thus negligible side effects. Biodegradable vehicles, such as calcium sulfate beads, are the prototypical system, providing a good elution profile and the ability to be impregnated with a variety of antibiotics. These have largely superseded the nonbiodegradable vehicles, but the strongest evidence available is for calcium bead implantation for osteomyelitis management. Natural polymers, such as collagen sponge, are an emerging class of delivery systems, although thus far, data on diabetic foot infections are limited. There is recent interest in the novel antimicrobial peptide pexiganan in the form of cream, which is active against most of the microorganisms isolated in diabetic foot infections. These are promising developments, but randomized trials are required to ascertain the efficacy of these systems and to define the indications for their use. Currently, the role of topical antibiotic agents in treating diabetic foot infections is limited and outside of routine practice.

Keywords

diabetic foot ulcer, topical antibiotics, diabetic foot infection

Diabetic foot infections (DFIs) represent a frequent and potentially serious complication in the diabetic population and their management remains challenging.[1] DFIs are the most common reason for diabetes-related hospitalization and can precipitate lower extremity amputation.[1] Patients with peripheral artery disease (PAD), which frequently coexists in diabetic patients,[2-4] are particularly at risk.

Diabetic foot ulcers (DFUs) serve as a point of entry for pathogens, with approximately 60% of DFUs infected on presentation.[5] Progression of peripheral neuropathy, with loss of protective sensation, can allow unperceived trauma, and this is the primary cause of skin breakdown. PAD frequently contributes to the development of ulceration and adversely affects healing and outcomes of infection.[4] An impaired cell-mediated immune response and phagocytic function associated with hyperglycemia further contributes to increased frequency and severity of infection in diabetic patients.[6]

DFIs are often polymicrobial, especially in the chronic wound. Recurrence of infection in long-standing ulcers requires repeated courses of antibiotics, but the benefits are frequently hampered by intolerance and adverse effects, especially in frail, diabetic patients with multiple comorbidities.[7,8] Despite the progress in systemic antibiotic usage, its efficacy can be impaired by low tissue penetration due to the PAD, manifested in the more distal vessels, as well as the presence of impaired microcirculation.[7,9,10] The development of biofilms in chronic wounds represents an additional challenge, as biofilms protect pathogens from host immunity and systemically administered antibiotics.[11,12] Thus, a multiplicity of issues have meant that targeting

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antibiotic-resistant organisms has been an increasing problem in recent decades.[13,14]

Rationale for the Use of Topical Antibiotic Therapy

Topical delivery of antibiotics represents an attractive emerging modality in the treatment of DFIs.[7,8,15] A key advantage is the achievement of a high antibiotic concentration in the affected area, which cannot be achieved with the use of systemic antibiotics. This can be of importance in cases where the penetration of the systemically administrated antibiotics in the infected area might be suboptimal, because of compromised vascular perfusion and/or the presence of bacterial biofilms. The limited systemic absorption of the locally applied antibiotic reduces considerably the risk of toxicity and avoids many of the adverse drug reactions caused by systemic antibiotics. Local antibiotics could be especially useful for patients who are intolerant to systemic administration or have impaired renal or liver function. Both the aforementioned complicate systemic antibiotic administration, often requiring additional drug-level monitoring. Moreover, the reduction in exposure of the whole of the body's microbial flora to a topical antibiotic could reduce the development of resistant microorganisms. This could bring significant public health benefits, in view of the current threat of multidrug-resistant microbial strains.

Methods

A literature review was conducted in 2017 using the PubMed database. The English language filter was applied, but no date parameters were set. All types of studies were included in the search, as was human and animal-based research. The search terms and combinations used were the following: local antibiotic delivery +/− diabetic foot infections or diabetic foot osteomyelitis, topical antibiotic delivery +/− diabetic foot infections or diabetic foot osteomyelitis, antibiotic beads +/− diabetic foot infections or diabetic foot osteomyelitis, antibiotic carriers +/− diabetic foot infections or diabetic foot osteomyelitis.

Classes of Local Antibiotic Delivery Systems and Pharmacokinetic Properties

Much of the provenance of topical antibiotic therapies originates from orthopedic-driven interventions. Local antibiotic carriers can elute a high concentration of antibiotics, above the minimum inhibitory concentration, for organisms present at the site of infection by 10 to 100 times, while serum antibiotic levels remain low.[16,17] Several devices loaded with antibiotics have been used for the in situ treatment of chronic osteomyelitis, primarily to fill anatomical defects secondary to surgical debridement. They can be classified as resorbable and nonresorbable antibiotic delivery systems.

Polymethylmethacrylate (PMMA) beads represent the major class of nonbiodegradable carrier systems. Cement beads are impregnated with one or a combination of antibiotics such as glycopeptides and aminoglycosides. Antibiotic release from PMMA is initially high during the first 48 to 72 hours, but quickly falls to lower subtherapeutic levels, eluting for weeks or even years.[17,18] It is a dense, acrylic, nonreabsorbing material that requires surgical removal on completion of drug elution, to avoid becoming a focus for biofilm formation.[19,20] While longevity and structural support are advantageous, removal of the foreign material requires further surgery, incurring associated risks.

Biodegradable vehicles represent an alternative to PMMA cement, and there are several types, namely, bone and bone substitutes, natural protein–based polymers, synthetic polymers, and composite carriers. Perceived advantages are that they gradually resorb and can act as a matrix for new bone growth. With their degradation, additional release of antibiotics occurs, prolonging their action and preventing biofilm formation on their surface.

Cancellous bone autograft or morselized bone allograft, impregnated or soaked in antibiotic solution, has been used extensively in orthopedic surgery. The antibiotics are released from the graft maintaining a bactericidal concentration for 1 to 3 weeks.[21] Calcium sulfate can be loaded with water-soluble antibiotics such as aminoglycosides, glycopeptides, for example, vancomycin, fluoroquinolones such as moxifloxacin, or daptomycin. The elution properties have been studied in vitro and in animal models. Wichelhaus and colleagues investigated the elution of vancomycin, gentamicin, and clindamycin from calcium sulfate beads. They found a high initial elution phase, providing around 45% of vancomycin and about 80% of gentamicin and clindamycin release within the first 24 hours. This was followed by a more gradual second phase of drug delivery over a further 10 days.[22]

Howlin and coworkers studied resorbable synthetic calcium sulfate beads loaded with tobramycin, vancomycin, or both antibiotics in combination. In one study, they demonstrated high bioactivity in preventing early bacterial colonization and biofilm formation by methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* strains.[11] A further study showed the antibacterial and anti-biofilm efficacy of broad-spectrum antibiotics against key gram-negative bacterial species involved in periprosthetic joint infections, such as *Pseudomonas aeruginosa, Klebsiella pneumoniae*, and *Acinetobacter baumannii*.[23] However, some of the antibiotics, such as tobramycin, traditionally used for impregnation, are now known to cause a delay in implant fixation.[24]

Concerns have been raised that calcium sulfate is unable to provide significant long-term mechanical support, or to act as a scaffold for tissue regeneration, since it dissolves relatively quickly.[25] In one case series, the use of a calcium sulfate carrier for the treatment of periprosthetic infection after total hip replacement resulted in transient hypercalcemia in 3 out of 15 patients.[26] Furthermore, calcium sulfate has been implicated in causing local wound leakage at a rate of 15%, which appeared to be a self-limiting side effect.[27]

Collagen, fibrin, and thrombin are naturally occurring protein-based polymers that can be manufactured into a mesh-like structure, creating a scaffold. This allows direct binding of antibiotics, which are then released as the structure is broken down, usually within days.[28] Collagen fleece is a widely used biodegradable carrier system, which stimulates osteoblast proliferation, promoting mineralization and production of collagenous tissue. It is usually impregnated with a broad-spectrum antibiotic such as an aminoglycoside. Changing the porosity of collagen or treating it with chemicals can modify and control drug elution rates.[29]

Chitosan, a polymerized D-glucosamine polysaccharide, can act as a drug carrier with additional antibacterial and antifungal activity. The gentamicin-loaded chitosan bar seems to be a clinically useful method for the treatment of bone and soft tissue infections, delivering effective concentrations of antibiotics for approximately 8 weeks.[30] Chitosan has been developed further as a composite carrier with nanohydroxyapatite and ethyl cellulose microspheres, and has been demonstrated to elute gentamicin above the minimum inhibitory concentration for 45 days.[31] To improve further the elution characteristics of topical systems, synthetic polymers (polyglycolide and polylactide) have been tested as potential antibiotic carriers. They are purported to undergo gradual, controlled degradation and dissolve at physiological pH.[32] However, the current preparations have not progressed to market because of their quick loss of integrity and suboptimal mechanical properties.[33]

Another emerging option for topical treatment is pexiganan cream. Pexiganan is a synthetic analogue of the natural antimicrobial peptide magainin II. It is a broad-spectrum agent, active against most of the microorganisms isolated in DFIs, including MRSA and multidrug-resistant gram-negative strains.[34] It has been submitted to the Food Drug Administration and European agencies for review.

The Evidence Base for Topical Antibiotic Use

A significant amount of orthopedic experience has been acquired in this field, via the use of numerous antibiotic vehicles in the treatment of osteomyelitis, as well as for minimizing the risk of postoperative infections.[35-38]

The nonbiodegradable PMMA delivery system has been most widely used to date. A meta-analysis of 8 randomized control studies compared the use of antibiotic (gentamicin and cefuroxime) impregnated PMMA for revision of infected arthroplasties with control groups (plain cement or systemic antibiotics). The PMMA was shown to be superior, in terms of the incidence of postoperative deep infections.[39] In a study of 100 patients with osteomyelitis, who were followed-up post debridement, the use of gentamicin-impregnated PMMA was associated with better outcomes for primary wound closure and elimination of the need for systemic antibiotics.[40]

However, controversy regarding PMMA as a foreign body, and the need for further procedures for removal, has meant greater focus on biodegradable vehicles.[36] Bone auto/allografts, which are impregnated with antibiotics (vancomycin and tobramycin), were trialed in 17 patients with large infected bone defects. Therapeutic concentrations of antibiotics, along with effective infection clearance with a minimum 2-year follow-up, was confirmed.[41] In another randomized control trial, patients with infected tibial nonunions were managed with either local antibiotic therapy (beads or antibiotic-impregnated autogenous cancellous bone graft) or pure autogenous cancellous bone graft. The former benefitted from improved infection elimination with antibiotic impregnation, without any adverse effect on bone incorporation.[42] However, more studies are required to determine local antibiotic concentrations and its effect on bone incorporation.[43]

Other bone graft substitutes (BGS) were developed, with calcium sulfate being the most studied. In a retrospective study of 337 patients with lower extremity osteomyelitis, treatment with surgical debridement and a local mixture of calcium sulfate with gentamycin and vancomycin achieved successful healing in 86% of patients, without the need for systemic antibiotics.[44] In a small prospective study, a combination of demineralized bone matrix and calcium sulfate mixed with vancomycin was used to fill the bony defect in patients with displaced calcaneal fractures. A reduction in time to bone union, compared with the control group, was shown.[45]

Such interventions are not without problems. Reports of continuous serous drainage from wounds containing the medicated carriers, as well as nonunions, can be found in the literature.[46] In a prospective study, 30 patients with chronic osteomyelitis and infected nonunions were randomized into either surgical debridement with antibiotic-impregnated PMMA or biodegradable BGS. The follow-up mean was 38 months.[47] Both groups showed similar infection eradication rates, but patients treated with BGS required fewer additional surgical procedures. However, the value of this study was limited by the small patient sample. Another BGS studied was hydroxyapatite, but limited clinical data for this are available. However, some retrospective clinical

studies suggest its potential for use in deep-seated infections and prosthetic joint infections.[48]

Further need for biodegradable vehicles led to trials with natural and synthetic gels/polymers.[29] In a systematic review of 15 randomized control trials comprising 6979 patients, gentamicin-impregnated collagen sponges were found to reduce the incidence of surgical site infections.[35] Favorable outcomes have also been reported with application of collagen sponges impregnated with gentamycin in 47 patients following debridement and surgical management for treatment of acute/chronic osteomyelitis.[49]

A recent systematic review incorporating 15 trials, evaluating the usefulness of different types of antibiotic-impregnated synthetic BGS in the treatment of patients with osteomyelitis, found insufficient evidence to come to a clear conclusion. Nonetheless, results have been promising, with high success rates at least in the short term. Infection eradication rates are reported to range from 80% to 100% and bone growth rates of 87.5% to 100%.[38]

Use of Local Antibiotics in DFIs

The available data regarding the usage of local antibiotics in the treatment of DFIs are limited at present (Table 1). There have been case reports of successful treatment of diabetic foot osteomyelitis (DFO) with local administration of antibiotics. Roeder et al have reported the successful use of PMMA beads impregnated either with tobramycin or vancomycin in 3 cases of pedal osteomyelitis including one case of MRSA calcaneal osteomyelitis, in conjunction with local resection of osteomyelitis and systemic antibiotics.[50] Salgami et al reported the treatment of a forefoot osteomyelitis with septic arthritis with tobramycin-impregnated calcium sulfate pellets inserted into a cavity beneath the foot ulcer, in addition to oral antibiotic treatment in a patient declining ray excision.[51] Cases of resolution of forefoot osteomyelitis, after excision of infected bone and local application of calcium sulfate beads impregnated with vancomycin and gentamicin, combined with systemic antibiotics, or vancomycin-loaded calcium sulfate and hydroxyapatite beads have been reported by Morley et al and by Karr, respectively.[7,52]

Ramanujan and Zgonis have also presented the use of tobramycin-impregnated PMMA beads as adjunctive treatment in staged reconstruction for Charcot ankle osteomy elitis.[53] Jogia et al report cures in all 20 members of a series of patients with DFU and underlying forefoot osteomyelitis, who had failed to respond to routine wound debridement, systemic antibiotics, and off-loading.[54] Patients were subsequently treated with minimal surgical intervention, consisting of excision of bone sequestrate and application of biodegradable highly purified synthetic calcium sulfate pellets containing vancomycin and gentamicin. Postoperative systemic antibiotic treatment was decided on an individual basis. Similarly, Panagopoulos et al have reported successful treatment in a series of 8 patients with chronic metatarsal or calcaneal DFO with local delivery of gentamicin. This was either with PMMA cement beads or BGS after minor surgery in combination with systemic antibiotics.[8]

Only a few studies present comparative data between outcomes, with or without the addition of local antibiotics to standard treatment, or between local versus systemic treatment. In a retrospective comparative study, Krause and coworkers assessed the effect of local application of bioabsorbable, tobramycin-impregnated calcium sulfate beads. This was in addition to standard treatment after transmetatarsal amputation in diabetic patients with nonhealing forefoot full-thickness ulcerations with osteomyelitis or skin necrosis.[55] In total, data from 65 cases of amputations were reviewed, including 49 cases in the "beads group" and 16 cases without beads. The wound breakdown rate following transmetatarsal amputation was significantly lower in the "beads group." Although a difference favoring the "beads group" was observed regarding the time to wound healing, this did not reach statistical significance. Length of hospital stay and the proportion of patients who required conversion to transtibial amputation did not significantly differ between groups.

Varga et al investigated the effectiveness of a bioabsorbable gentamicin-impregnated collagen sponge application into wounds after minor amputation for nonhealing ulcer with osteomyelitis.[56] Fifty diabetic patients were randomized, to have or not to have the gentamicin sponge applied. All patients received systemic antibiotics according to the antibiogram profile. The application of a gentamicin sponge significantly shortened wound healing duration by almost 2 weeks. No effect was observed on the length of hospital stay or any difference in the number of revisions for wound breakdown or subsequent amputations between groups.

The results of a randomized controlled trial by Lipsky et al were in keeping with this positive finding.[57] Fifty-six diabetic patients with moderately infected foot ulcers were randomized for the use or nonuse of a gentamicin-collagen sponge in addition to standard care. Significantly higher rates of clinical cure and eradication of baseline pathogens were achieved in the group treated with the gentamicin-collagen sponge.

To date, usage of local antibiotics in the form of cream or ointment has been of limited benefit in the treatment of mild DFIs. This may change with the development of new broad-spectrum antibiotics, such as pexiganan. A large, randomized, controlled double-blind trial compared the topical application of the investigational antimicrobial peptide pexiganan versus oral ofloxacin.[58] Lipsky et al randomized 835 patients with a mildly infected DFU to receive pexiganan cream or oral ofloxacin, plus a respective inactive placebo. Similar clinical improvements rates, microbiological eradication rates, and wound healing rates were

Table 1. Published Clinical Data on Local Antibiotic Delivery in Diabetic Foot Infections.

Roeder et al[50]	2000	Case series	Tobramycin-impregnated PMMA beads in 2 cases of forefoot OM in conjunction with local resection of bone	In conjunction with systemic antibiotic treatment
			Vancomycin-impregnated PMMA beads placed in the dead space after subtotal calcanectomy in a case of MRSA OM of the heel	Healed
Salgami et al[51]	2007	Case report	Tobramycin-impregnated calcium sulfate pellets inserted as part of forefoot OM management	In conjunction with systemic antibiotic treatment
				Healed
Lipsky et al[58]	2008	Randomized controlled double-blind multicenter	835 patients with mild infections of diabetic foot ulcers were randomized	Equivalent result between topical and systemic treatment was reported for microbiological eradication and healing
			One group was treated with topical pexiganan, one group with oral ofloxacin	Development of resistance was reported in some ofloxacin cases
			Each group received the respective inactive placebo	None was found for pexiganan
Krause et al[55]	2009	Retrospective cohort study	Application of tobramycin-impregnated calcium sulfate beads post TMA in 49 patients in addition to standard care	The beads group outcomes were better for lower rate wound breakdown and further surgery
			Compared with 16 TMA cases with no beads applied	No difference in length of hospital stay or rate of conversion to below knee amputation
Ramanujan and Zgonis[53]	2010	Case report	Resection of distal fibula and insertion of tobramycin-impregnated PMMA beads in Charcot ankle OM	In conjunction with systemic antibiotic treatment
				No recurrence of OM
Karr[52]	2011	Case report	Insertion of vancomycin cerement beads with bone resection for forefoot osteomyelitis	Healed without requiring further surgery/removal of beads
Lipsky et al[57]	2012	Randomized controlled multicenter study	Randomly allocated treatment of 38 infected diabetic foot ulcers with gentamicin collagen sponge in addition to standard care	Treatment group had a significantly higher clinical cure rate
			Compared with 18 cases who received standard care alone	
Varga et al[56]	2014	Randomized trial (no placebo group)	50 patients requiring minor amputations were randomized: half received a bioabsorbable collage sponge impregnated with gentamicin and half had no treatment	The topical antibiotic group required significantly less time to healing
				Hospital stay and further surgery were not different between groups
Jogia et al[54]	2015	Case series	20 patients with forefoot ulcers with OM previously failed to respond to systemic antibiotics, regular wound debridement, and off-loading	All healed
			Excision of sequestrate and bone was packed with calcium sulfate pellets impregnated with vancomycin and gentamicin	No recurrence at 12 months
				Need of postoperative systemic antibiotics was decided individually (not clear how many received systemic antibiotics)
Panagopoulos et al[8]	2015	Case series	8 patients with chronic metatarsal or calcaneal OM	In conjunction with systemic antibiotics and minor surgery
			Use of PMMA beads or bone graft substitutes loaded with gentamicin	OM successfully treated in all cases
Morley et al[7]	2016	Case report	A limb-threatening forefoot infection complicated with OM was debrided and drained then packed with calcium sulfate beads impregnated with vancomycin and gentamicin	In conjunction with systemic antibiotic treatment
				Healed

Abbreviations: PMMA, polymethylmethacrylate; OM, osteomyelitis; MRSA, methicillin-resistant *Staphylococcus aureus*; TMA, transmetatarsal amputation.

demonstrated with both active treatments. It is of interest that no significant resistance to pexiganan emerged, while bacterial resistance to ofloxacin was noted in some of the patients.

Conclusions and Future Perspectives

Local antibiotic delivery can yield very high concentrations exclusively in targeted areas, which cannot be achieved by systemic therapy. This is likely to be particularly useful in poorly perfused tissues and in the presence of biofilms. Most experience has been acquired in orthopedic surgery, with local antibiotic therapies in routine use for prophylaxis and treatment of osteomyelitis. In recent years, there has been a significant expansion in the number of local antibiotic delivery systems. Nonbiodegradable vehicles such as PMMA were the first to be widely used, but lately there has been a shift toward biodegradable vehicles such as calcium sulfate beads. These do not require surgical removal and potentially offer a more prolonged elusion profile. Other biodegradable materials, such as synthetic gels and polymers, have been developed but the role of these is unclear.

Limited data exist in the field of DFIs, and a robust body of evidence is missing, in so far as whether local antibiotics are to be used alone, or in conjunction with systemic antibiotics and/or surgical intervention. Local delivery of antibiotics appears to be an effective adjuvant treatment in cases of surgically treated osteomyelitis, and there also appears to be potential for soft tissue infection management. Local antibiotic application could also be especially useful in cases of infected deep ulceration. Finally, the novel broad-spectrum antibiotic, pexiganan, applied topically, is of great interest, since it covers almost all pathogens causing DFIs, including multidrug-resistant strains. This may prove very useful in the future, as an alternative treatment to systemic antibiotic therapy for mild skin and soft tissue infections.

In conclusion, local antibiotic delivery systems represent a promising pharmaceutical option in the treatment of DFIs. Well-designed randomized clinical trials are required to establish their efficacy and to define the framework for their usage.

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References

1. Markakis K, Bowling FL, Boulton AJ. The diabetic foot in 2015: an overview. *Diabetes Metab Res Rev*. 2016;32(suppl 1):169-178.
2. Fisher TK, Wolcott R, Wolk DM, Bharara M, Kimbriel HR, Armstrong DG. Diabetic foot infections: a need for innovative assessments. *Int J Low Extrem Wounds*. 2010;9:31-36.
3. Lipsky BA, Berendt AR, Cornia PB, et al; Infectious Diseases Society of America. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2012;54: e132-e173.
4. Prompers L, Schaper N, Apelqvist J, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE study. *Diabetologia*. 2008;51:747-755.
5. Prompers L, Huijberts M, Apelqvist J, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. *Diabetologia*. 2007;50:18-25.
6. Peleg AY, Weerarathna T, McCarthy JS, Davis TM. Common infections in diabetes: pathogenesis, management and relationship to glycaemic control. *Diabetes Metab Res Rev*. 2007;23:3-13.
7. Morley R, Lopez F, Webb F. Calcium sulphate as a drug delivery system in a deep diabetic foot infection. *Foot (Ednib)*. 2016;27:36-40.
8. Panagopoulos P, Drosos G, Maltezos E, Papanas N. Local antibiotic delivery systems in diabetic foot osteomyelitis: time for one step beyond? *Int J Low Extrem Wounds*. 2015;14: 87-91.
9. Creager MA, Lüscher TF, Cosentino F, Beckman JA. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. *Circulation*. 2003;108: 1527-1532.
10. Skhirtladze K, Hutschala D, Fleck T, et al. Impaired target site penetration of vancomycin in diabetic patients following cardiac surgery. *Antimicrob Agents Chemother*. 2006;50: 1372-1375.
11. Howlin RP, Brayford MJ, Webb JS, Cooper JJ, Aiken SS, Stoodley P. Antibiotic-loaded synthetic calcium sulfate beads for prevention of bacterial colonization and biofilm formation in periprosthetic infections. *Antimicrob Agents Chemother*. 2015;59:111-120.
12. Wolcott RD, Rhoads DD, Bennett ME, et al. Chronic wounds and the medical biofilm paradigm. *J Wound Care*. 2010;19:45-46, 48-50, 52-53.
13. Boyanova L, Mitov I. Antibiotic resistance rates in causative agents of infections in diabetic patients: rising concerns. *Expert Rev Anti Infect Ther*. 2013;11:411-420.
14. Uckay I, Gariani K, Pataky Z, Lipsky BA. Diabetic foot infections: state-of-the-art. *Diabetes Obes Metab*. 2014;16: 305-316.
15. Lipsky BA, Hoey C. Topical antimicrobial therapy for treating chronic wounds. *Clin Infect Dis*. 2009;49:1541-1549.
16. Fleiter N, Walter G, Bösebeck H, et al. Clinical use and safety of a novel gentamicin-releasing resorbable bone graft substitute in the treatment of osteomyelitis/osteitis. *Bone Joint Res*. 2014;3:223-229.
17. Walenkamp GH, Vree TB, van Rens TJ. Gentamicin-PMMA beads. Pharmacokinetic and nephrotoxicological study. *Clin Orthop Relat Res*. 1986;(205):171-183.

18. Wininger DA, Fass RJ. Antibiotic-impregnated cement and beads for orthopedic infections. *Antimicrob Agents Chemother*. 1996;40:2675-2679.
19. Donlan RM, Costerton JW. Biofilms: survival mechanisms of clinically relevant microorganisms. *Clin Microbiol Rev*. 2002;15:167-193.
20. Kendall RW, Duncan CP, Smith JA, Ngui-Yen JH. Persistence of bacteria on antibiotic loaded acrylic depots. A reason for caution. *Clin Orthop Relat Res*. 1996;(329):273-280.
21. Witso E, Persen L, Løseth K, Benum P, Bergh K. Cancellous bone as an antibiotic carrier. *Acta Orthop Scand*. 2000;71: 80-84.
22. Wichelhaus TA, Dingeldein E, Rauschmann M, et al. Elution characteristics of vancomycin, teicoplanin, gentamicin and clindamycin from calcium sulphate beads. *J Antimicrob Chemother*. 2001;48:117-119.
23. Howlin RP, Winnard C, Frapwell CJ, et al. Biofilm prevention of gram-negative bacterial pathogens involved in periprosthetic infection by antibiotic-loaded calcium sulfate beads in vitro. *Biomed Mater*. 2016;12:015002.
24. Gogia JS, Meehan JP, Di Cesare PE, Jamali AA. Local antibiotic therapy in osteomyelitis. *Semin Plast Surg*. 2009;23: 100-107.
25. Inzana JA, Schwarz EM, Kates SL, Awad HA. Biomaterials approaches to treating implant-associated osteomyelitis. *Biomaterials*. 2016;81:58-71.
26. Kallala R, Haddad FS. Hypercalcaemia following the use of antibiotic-eluting absorbable calcium sulphate beads in revision arthroplasty for infection. *Bone Joint J*. 2015;97-B: 1237-1241.
27. Ferguson JY, Dudareva M, Riley ND, Stubbs D, Atkins BL, McNally MA. The use of a biodegradable antibiotic-loaded calcium sulphate carrier containing tobramycin for the treatment of chronic osteomyelitis: a series of 195 cases. *Bone Joint J*. 2014;96-B:829-836.
28. Mehta S, Humphrey JS, Schenkman DI, Seaber AV, Vail TP. Gentamicin distribution from a collagen carrier. *J Orthop Res*. 1996;14:749-754.
29. Rao KP. Recent developments of collagen-based materials for medical applications and drug delivery systems. *J Biomater Scie Polym Ed*. 1995;7:623-645.
30. Aimin C, Chunlin H, Juliang B, Tinyin Z, Zhichao D. Antibiotic loaded chitosan bar. An in vitro, in vivo study of a possible treatment for osteomyelitis. *Clin Orthop Relat Res*. 1999;(366):239-247.
31. Shi P, Zuo Y, Li X, et al. Gentamicin-impregnated chitosan/nanohydroxyapatite/ethyl cellulose microspheres granules for chronic osteomyelitis therapy. *J Biomed Mater Res A*. 2010;93:1020-1031.
32. Makinen TJ, Veiranto M, Lankinen P, et al. In vitro and in vivo release of ciprofloxacin from osteoconductive bone defect filler. *J Antimicrob Chemother*. 2005;56:1063-1068.
33. Hanssen AD, Osmon DR, Patel R. Local antibiotic delivery systems: where are we and where are we going? *Clin Orthop Relat Res*. 2005;(437):111-114.
34. Flamm RK, Rhomberg PR, Simpson KM, Farrell DJ, Sader HS, Jones RN. In vitro spectrum of pexiganan activity when tested against pathogens from diabetic foot infections and with selected resistance mechanisms. *Antimicrob Agents Chemother*. 2015;59:1751-1754.
35. Chang WK, Srinivasa S, MacCormick AD, Hill AG. Gentamicin-collagen implants to reduce surgical site infection: systematic review and meta-analysis of randomized trials. *Ann Surg*. 2013;258:59-65.
36. 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.
37. Nandi SK, Bandyopadhyay S, Das P, et al. Understanding osteomyelitis and its treatment through local drug delivery system. *Biotechnol Adv*. 2016;34:1305-1317.
38. 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.
39. Wang J, Zhu C, Cheng T, et al. A systematic review and meta-analysis of antibiotic-impregnated bone cement use in primary total hip or knee arthroplasty. *PLoS One*. 2013;8:e82745.
40. Walenkamp GH, Kleijn LL, de Leeuw M. Osteomyelitis treated with gentamicin-PMMA beads: 100 patients followed for 1-12 years. *Acta Orthop Scand*. 1998;69:518-522.
41. McLaren A. Antibiotic impregnated bone graft. *J Orthop Trauma*. 1989;3:171.
42. Chan YS, Ueng SW, Wang CJ, Lee SS, Chen CY, Shin CH. Antibiotic-impregnated autogenic cancellous bone grafting is an effective and safe method for the management of small infected tibial defects: a comparison study. *J Trauma*. 2000;48:246-255.
43. Cancienne JM, Burrus MT, Weiss DB, Yarboro SR. Applications of local antibiotics in orthopedic trauma. *Orthop Clin North Am*. 2015;46:495-510.
44. Gauland C. Managing lower-extremity osteomyelitis locally with surgical debridement and synthetic calcium sulfate antibiotic tablets. *Adv Skin Wound Care*. 2011;24:515-523.
45. Bibbo C, Patel DV. The effect of demineralized bone matrix-calcium sulfate with vancomycin on calcaneal fracture healing and infection rates: a prospective study. *Foot Ankle Int*. 2006;27:487-493.
46. Borrelli J Jr, Prickett WD, Ricci WM. Treatment of nonunions and osseous defects with bone graft and calcium sulfate. *Clin Orthop Relat Res*. 2003;(411):245-254.
47. McKee MD, Li-Bland EA, Wild LM, Schemitsch EH. A prospective, randomized clinical trial comparing an antibiotic-impregnated bioabsorbable bone substitute with standard antibiotic-impregnated cement beads in the treatment of chronic osteomyelitis and infected nonunion. *J Orthop Trauma*. 2010;24:483-490.
48. Yamashita Y, Uchida A, Yamakawa T, Shinto Y, Araki N, Kato K. Treatment of chronic osteomyelitis using calcium hydroxyapatite ceramic implants impregnated with antibiotic. *Int Orthop*. 1998;22:247-251.
49. Wernet E, Ekkernkamp A, Jellestad H, Muhr G. Antibiotic-containing collagen sponge in therapy of osteitis [in German]. *Unfallchirurg*. 1992;95:259-264.
50. Roeder B, Van Gils CC, Maling S. Antibiotic beads in the treatment of diabetic pedal osteomyelitis. *J Foot Ankle Surg*. 2000;39:124-130.

51. Salgami EV, Bowling FL, Whitehouse RW, Boulton AJ. Use of tobramycin-impregnated calcium sulphate pellets in addition to oral antibiotics: an alternative treatment to minor amputation in a case of diabetic foot osteomyelitis. *Diabetes Care*. 2007;30:181-182.
52. Karr JC. Management in the wound-care center outpatient setting of a diabetic patient with forefoot osteomyelitis using Cerament Bone Void Filler impregnated with vancomycin: off-label use. *J Am Podiatr Med Assoc*. 2011;101:259-264.
53. Ramanujan CL, Zgonis T. Antibiotic-loaded cement beads for Charcot ankle osteomyelitis. *Foot Ankle Spec*. 2010;3:274-277.
54. Jogia RM, Modha DE, Nisal K, Berrington R, Kong MF. Use of highly purified synthetic calcium sulfate impregnated with antibiotics for the management of diabetic foot ulcers complicated by osteomyelitis. *Diabetes Care*. 2015;38:e79-e80.
55. Krause FG, deVries G, Meakin C, Kalla TP, Younger AS. Outcome of transmetatarsal amputations in diabetics using antibiotic beads. *Foot Ankle Int*. 2009;30:486-493.
56. Varga M, Sixta B, Bem R, Matia I, Jirkovska A, Adamec M. 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.
57. Lipsky BA, Kuss M, Edmonds M, Reyzelman A, Sigal F. Topical application of a gentamicin-collagen sponge combined with systemic antibiotic therapy for the treatment of diabetic foot infections of moderate severity: a randomized, controlled, multicenter clinical trial. *J Am Podiatr Med Assoc*. 2012;102:223-232.
58. Lipsky BA, Holroyd KJ, Zasloff M. Topical versus systemic antimicrobial therapy for treating mildly infected diabetic foot ulcers: a randomized, controlled, double-blinded, multicenter trial of pexiganan cream. *Clin Infect Dis*. 2008;47:1537-1545.