**Abstract**

This is a review of the current and emerging topical antibiotic systems and formulations, with potential applications for the management of diabetic foot infections.

Foot infections are common among diabetic patients with peripheral neuropathy and/or peripheral arterial disease, and 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 including 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 These have largely superseded the non-biodegradable vehicles, but the strongest evidence available is for calcium bead implantation for osteomyelitis management.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 is limited. There is recent interest in the novel antimicrobial peptide pexiganan in the form of cream, which is active against most of the micro-organisms 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.

**Introduction**

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 co-exists 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 hyperglycaemia 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 co-morbidities.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 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 of which complicates systemic administration, often requiring additional drug level monitoring. Moreover, the reduction in exposure of the whole of the body’s microbial flora to the antibiotic could reduce the development of resistant microorganisms. This could bring significant public health benefits, in view of the current threat of multi-drug 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: 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 orthopaedic-driven interventions. Local antibiotic carriers can elute a high concentration of antibiotics, above the minimum inhibitory concentration (MIC), for organisms present at the site of infection by 10-100 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 non-resorbable antibiotic delivery systems.

Polymethylmethacrylate (PMMA) beads represent the major class of non-biodegradable 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 48-72 hours, but quickly falls to lower, sub-therapeutic levels, eluting for weeks or even years.17,18 It is a dense, acrylic, non-reabsorbing material which requires surgical removal upon 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 require further surgery and, potentially, 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 orthopaedic surgery. The antibiotics are released from the graft maintaining a bactericidal concentration for 1-3 weeks.21 Calcium sulfate can be loaded with water- soluble antibiotics such as aminoglycosides, glycopeptides, e.g. vancomycin, fluoroquinolones such as moxifloxacin, or daptomycin. Their 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, and 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 co-workers 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 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 in 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 mineralisation 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 drug elution rates.29

Chitosan, a polymerised 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 eight 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 MIC for 45 days.31 To further improve elution characteristics of topical systems, synthetic polymers (polyglycolide and polylactide) have been tested as potential antibiotic carriers, because 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 sub-optimal 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 FDA and European agencies for review.

**The evidence base for topical antibiotic use**

A significant amount of orthopaedic 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 non-biodegradable 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 non-unions 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 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 (DBM) 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 to 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 non-unions, can be found in the literature.46 In a prospective study, 30 patients with chronic osteomyelitis and infected non-unions were randomized into either surgical debridement with antibiotic impregnated PMMA, or biodegradable bone graft substitutes (BBS). The follow-up mean was 38 months.47 Both groups showed similar infection eradication rates, but patients treated with BBS required fewer additional surgical procedures. However, the value of this study was limited by the small patient sample. Another bone graft substitute studied was hydroxyapatite, but limited clinical data for this is 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 bone graft substitutes 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% - 100% and bone growth rates of 87.5% - 100%.38

**Use of local antibiotics in DFIs**

The available data regarding the usage of local antibiotics in the treatment of DFIs is limited at present. There have been case reports of successful treatment of diabetic foot osteomyelitis (DFO) with local administration of antibiotics. 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.50 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.7,51

Ramanyjam and colleagues have also presented the use of tobramycin- impregnated PMMA beads as adjunctive treatment in staged reconstruction for Charcot ankle osteomyelitis.52 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.53 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 bone graft substitutes, 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 co-workers assessed the effect of local application of bioabsorbable, tobramycin impregnated calcium sulfate beads. This was in addition to standard treatment after transmetatarsal amputation (TMA) in diabetic patients with non-healing forefoot full thickness ulcerations with osteomyelitis or skin necrosis.54 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 TMA 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 trans-tibial 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 non-healing ulcer with osteomyelitis.55 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 two 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.56 56 diabetic patients with moderately infected foot ulcers were randomized for the use or non- use 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 oflaxocin.57 Lipsky et al randomized 835 patients with a mildly infected DFU to receive pexiganan cream or oral oflaxocin, plus a respective inactive placebo. Similar clinical improvements rates, microbiological eradication rates and wound healing rates were 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 orthopaedic 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. Non-biodegradable vehicles such as PMMA were the first to be widely used but lately there has been a shift towards 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 exists 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 multi-drug 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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