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Bone graft substitutes in active or suspected infection. Contra-indicated or not?

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ABSTRACT

Treatment of infection in clinical orthopaedic and trauma care is a time consuming and costly endeavour. More than once, it will lead to extraction of implant material and additional surgical interventions. Currently, debridement, implantation of PMMA beads impregnated with antibiotics most often with implant exchange are the gold standard for deep infection treatment. Recently bone graft substitute materials such as calcium phosphate, collagen fleeces and bioglasses have appeared for specific use in infection treatment. Although these materials show great potential, their supporting level of evidence is still limited.

This review paper provides an overview of current understanding and therapies for infection treatment and provides concepts for the use of new developed biomaterials in infection treatment.

Furthermore, the benefits and risks of using biomaterials in infection treatment are discussed and the level of evidence of a number of new materials is presented.

Introduction

Implants are nowadays routinely used in orthopaedics and traumatology, ranging from simple screws, biomaterials and bone substitutes to total joint arthroplasties. Infections are fortunately rare but difficult to treat and due to ever increasing numbers of implants being used as well as an increase in antibiotic resistant bacteria strains,[1] absolute numbers of infection are on the rise.

The incidence of infection after total joint arthroplasty ranges from 1% or less[2,3] in primaries, to 5% in revision settings and 20% or more when revising for infection.[4] Traumatologic interventions show somewhat higher numbers, due to involvement of open fracture treatment.[5,6]

Morbidity, mortality and cost of treatment are severely influenced by the occurrence of infection and therefore infection related to implants remains a challenge.[7] There is also increasing evidence that many revision that are deemed "aseptic" at workup, are in fact infected.[8]

The herein study provides an overview of current understanding and therapies for infection treatment and provides concepts for the use of new developed biomaterials in infection treatment. Furthermore, the benefits and risks of using biomaterials in infection treatment are discussed and the level of evidence of a number of new materials is presented.

Infection: basic concepts

Aetiology of implant related infection has been explained by the concept of the "race for the surface" by Gristina in 1987.[9] Microbial adhesion and biofilm growth compete with tissue integration. If tissue cells are first to cover the surface of the implant, it will be less susceptible to bacterial colonisation. If, on the other hand, the race is won by the bacteria, they will cover the implant by a biofilm and will be less accessible for the natural host immunologic response and also for antibiotics. Therefore, biofilm formation makes antibiotic treatment by itself insufficient for eradication of the infection. Also, device-associated biofilms represent a focus of infection from which individual cells or clusters of cells may detach, resulting in bloodstream infection, emboli and metastatic spread.[10] Diagnosis of infection is also more troublesome and requires new techniques like sonication to break up the biofilm in order to identify the pathogen.[11]

Inoculation of an implant can occur directly at the time of surgery and manifest itself acutely or late. In a later phase, it can also occur through seeding at the time of haematological spread (bacteraemia). A third pathway is through spread from an adjacent infectious focus.[12]

Zimmerli and Ochsner classified periprosthetic joint infections as early (those that develop less than 3 months after surgery), delayed (3–24 months after surgery), or late (more than 24 months after surgery).[13] If infection occurs in the early timeframe, it is most likely due to bacterial contamination at the time of surgery and usually not very likely to hamper the bone-implant interface. Delayed infections are also most likely caused by contamination during implantation and have a low grade character haematogeneous infections in

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general do not display any sign of infection beforehand. Late manifestations of infection may be low grade infections since the operation or as a result of haematogenous spread. The haematogenous infections are due to a bacteremia with a high dose of virulent bacteria, caused mostly by an urinary tract or dental infection, and they can be caused by various pathogens.[14] Treatment options are dictated by this timing and this can be decisive in being able to save an implant or having to remove it.

Infection: treatment modalities

Two distinct clinical type of infections can be distinguished: superficial and deep. A superficial infection is an infection situated above the fascia layer. The criteria for deep infection have been defined by the Centres for Disease Control (CDC) as follows: a major infection extending through the deep fascia with purulent discharge complicated by spreading cellulites, systemic upset, positive or negative cultures from the deep tissues, pockets of pus or wound breakdown.[39] The challenges of dealing with infection become far greater when the infection is deep since the implant itself is then infected and the bone-implant interface is at risk. Diagnosis is through imaging, blood samples and aspiration, although negative aspiration is no proof for absence of infection.[8]

The two different types of infection are tackled with different treatment strategies, so the diagnosis of either is of utmost importance.[15] Superficial infections can usually be managed by systemic administration of antibiotics, but sometimes surgery is needed consisting of debridement and pulsatile lavage. It may be difficult to judge preoperatively or peroperatively if the infection is limited to superficial tissues or is also deep. If the treatment of the superficial infection proves un-successful there is a need for subsequent debridement of the joint.[16] Deep infections require always antibiotics and surgical debridement, with pulse lavage, addition of gentamicin beads or fleeces, exchange of implant parts and in the worst case scenario removal of the implant.[40] In the case of total joint arthroplasty one and two-stage revision can be considered. Literature reports benefits and drawbacks for both strategies, but there are currently no clear guidelines on which is best. It has been shown that when diagnosis is swift and treatment started early, implants can often be saved and remain in situ.[41,42] There is no clear consensus in literature on when an implant has to be removed or how long one can try to save it. Some authors report salvage of implants of up to two months after initial diagnosis of infection, where others advocate immediate removal.[13]

Antibiotics are a crucial part of the treatment in implant-related infections. Generally, intravenous treatment is necessary in the early stages and when inflammatory parameters improve, a switch can be made to oral treatment. Moran et al.[17] found organisms most frequently isolated in implant-related infections to be coagulase-negative staphylococci (CoNS, 47% patients) and methicillin-sensitive Staphylococcus aureus (MSSA, 44% patients). Eight percent grew methicillin-resistant Staphylococcus aureus (MRSA), 8% grew aerobic Gram-negatives and 7% grew anaerobes. Thirty-seven percent grew multiple organisms.

Antibiotic treatment needs to be adjusted and narrowed when the causative organism is identified. Important in implant related infections is the use of rifampicine (in combination with penicillin or cephalosporin) to eradicate bacteria in the biofilm. There is no urgency to add rifampicine from the start, but preferably only after a few days of initial antibiotic treatment, so that most of the bacterial load is already eliminated.

When local antibiotic therapy is indicated, polymethylmetacrylate (PMMA) beads are considered the gold standard. High local antibiotic concentrations can be achieved (exceeding the minimal inhibitory or bactericidal concentrations of most pathogenic organisms) and the rate of release is constant and no nephrotoxicity or other systemic side-effects could be shown.[18–20] Requirements for the antibiotics being used are heat-resistance and water solubility. Beads have to be removed, which requires a second operation, which might be undesirable in some cases. When a total joint arthroplasty has to be removed, another option is a PMMA spacer containing antibiotics. Benefits of such an approach include restoration of the anatomy whilst awaiting reimplantation surgery, and keeping the patient mobile. However, the release of antibiotics is a lot lower than levels obtained by the implantation of beads[20,43]. This is because the total surface area of the beads is a lot larger than a spacer (Fig. 1). Moreover, beads release about 24% (±11%) of their antibiotic content (mini-beads even up to 93 ± 1.4%),[19] whereas the content released by the spacers is significantly smaller.[20,21] Also, unexpected bone loss can occur.[22] We therefore advise the use of beads in a first stage, eradicating the bulk of the bacterial load, and switching to a spacer in the next phase if indicated.

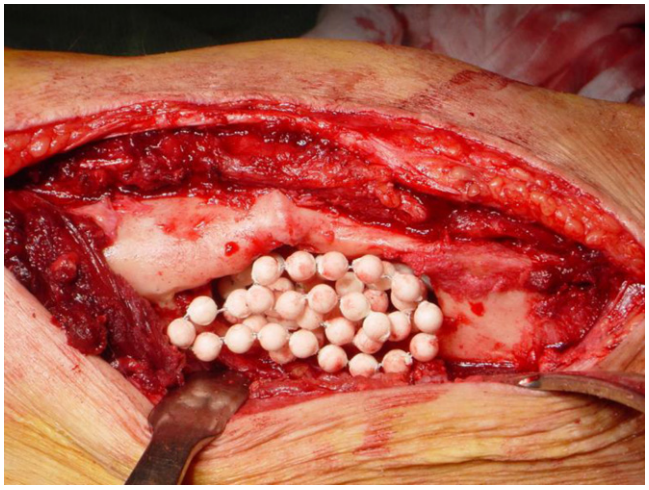

Fig. 1. Cavity of a femur, after debridement of osteomyelitis full packed with gentamicin PMMA beads. The relative large surface of the beads facilitates the diffusion of much gentamicin and the creation of a high local gentamicin concentration in the haematoma and the bone tissue, above the MIC value of most causative bacteria.

Favouring a spacer in some cases is driven by the fact that a spacer can be a definitive treatment for some patients who are unable to undergo any further interventions due to an unacceptable high perioperative risk profile. Using a drain or not when local antibiotics are applied is the surgeon's choice. Having a small residual haematoma increases local concentration of the antibiotic and therefore, in our opinion, a drain is favoured in the first 24 h.

Both beads and spacers can be loaded with a variety of antibiotics. Most common used are gentamicin, tobramycin and vancomycin. The most important prerequisites for antibiotics incorporated in cement are heat-resistance and good water-solubility.

Other methods of local antibiotic release also exist, such as antibiotic-loaded porous hydroxyapatite blocks,[23] gentamicin-collagen fleeces[24] or antibiotic-loaded calcium sulphate pellets.[44,45]

Future developments are also focusing on loading the implant surface with antibiotics and antimicrobial coatings.

Infection: bone graft substitutes in active or suspected infection-the challenges

Concepts

When using biomaterials in active or suspected infection various considerations have to be made. First of all the proper

antibiotic agent should be determined, the desired length of antibiotic release, the depth of antibiotic penetration in surrounding tissues and the release profile of the antibiotic agent (burst or prolonged). Secondly there is a need to assess the effect of bone graft substitute properties such as composition, hydrophilic or hydrophobic behaviour, porosity and surface area on these antibiotic release parameters.

Thirdly the level of evidence of most materials is still limited and this clearly needs to be taken into account.

It is generally accepted that for the treatment of infection, the type of pathogen and the time of infection occurrence determine the antibiotic agent or agents to be administered. Ideally a high concentration (MIC – minimum inhibitory concentration) release pattern of antibiotics is needed in the first 1–2 days and thereafter a prolonged release of a lower MIC should be maintained for another 4 weeks. The penetration depth of the antibiotic agent should be 1 cm in the surrounding tissues and the concentration as high as possible without leading to environmental toxicity.[46] The maximum concentration when using PMMA beads can be as high as 200–400 μg/ml at day three, in general about100 times the MIC value can be achieved.[46] There is a large variance in mechanical and biological behaviour between materials such as bioglass, collagen-fleeces and various calcium phosphate (Ca–P) based materials. Properties of bone graft substitute materials have a profound effect on the antibiotic binding and release profile.

Composition of the bone graft substitute material determines a large proportion of its susceptibility and ability to bind antibiotic agents on its outer surface or throughout its structure and has a direct influence on cellular response.[25] Whether a material is hydrophilic or hydrophobic has a big impact on release profiles.[34] Strength and biological behaviour of bone graft substitutes are much influenced by the porosity and surface area properties and in turn they also have a profound effect on the ability to bind and release antibiotic agents.[26]

Materials

Synthetic bone graft substitutes are usually osteoconductive and consist of calcium phosphate Ca–P (either hydroxyapatite (HA) or tricalcium phosphate (TCP) or a combination of both) components.[25] All Ca–P synthetic porous substitutes share numerous advantages over autografts and allografts including their unlimited supply, easy sterilisation, lack of disease transmission, and long-term storage. Using Ca–P bone graft substitute materials as a scaffold for drug delivery in the treatment of infection has primarily been performed after the development of Ca–P cements.[47] These types of materials are similar in composition to bone mineral content and they are biocompatible, bioactive and osteoconductive and have the unique capability to be able to absorb several chemical (pharmacological) substances on their surface. In contrast to Ca–P granules or beads where pharmacological agents do only absorb on the surface, calcium phosphate cements can incorporate pharmacological agents throughout their entire structure.[48]

Many authors have investigated impregnation of antibiotics onto Ca-P granules and their subsequent antibiotic release profiles.[26–32] However, clinical evidence is still limited. Recently a new resorbable hybrid bead composed of Ca–P and calcium sulphate (Herafill®) containing gentamicin sulphate as a protection against bacterial colonisation was marketed and intended to fill bone voids that result from surgical debridement after post-traumatic, post-operative and hematogenic osteomyelitis.

Although of interest, clinical data in well controlled trials is not yet available. Next to Ca–P materials also bioglass and collagen sponges loaded with antibiotics have been used for infection treatment.[24,36,37]

Bioactive silicate glasses were the first man-made inorganic materials engineered to bind to bone tissue.[33] These inorganic materials provide an ideal environment for colonisation, proliferation, and differentiation of osteoblasts to form new bone exhibiting mechanically strong attachment to the implant surface. Moreover, reactions on the bioactive glass surface induce the release of critical concentrations of soluble ions, for example, Si, Ca, and P, which has been shown to lead to favourable intracellular and extracellular responses promoting rapid bone formation.[49]

Collagen fleeces loaded with antibiotics are able to release a high amount of their antibiotic in the very early stages of implantation and do not have to be removed in a second operation.[24,34] However, they are generally not able to release antibiotics for a sustained time period. Variations between the various products exit (days to 2–4 weeks) and their release can be influenced by the rate of material resorption.

Infection: bone graft substitutes in active or suspected infection – clinical experience

The two key elements of a local antibiotic delivery system are the delivery vehicle and the antimicrobial agent.[35] For adequate local delivery the antibiotic must bind and be released adequately from the delivery vehicle and it should also be active against the targeted microbial pathogens.

To be able to adequately compete for the treatment of infection with PMMA beads and spacers, bone graft substitutes should be able to provide same efficacy, have both a burst and prolonged antibiotic release profile. When they are also resorbed without the need of surgical removal they truly offer beneficial properties in clinical practice.

However, an introduction of Ca–P bone graft substitute materials in an infected or a suspective infected site also brings an inherent risk. The scaffolds might provide bacteria the perfect opportunity to invade and encapsulate themselves into the Ca–P scaffold thereby prolonging the infection.

Soaking up antibiotics into a porous Ca–P scaffold has led to a variety of amounts of antibiotic to be incorporated and different release profiles. In clinical practice a fine balance should exist between antibiotic release and its associated environmental toxicity. Also combination of Ca–P bone graft substitutes with antibiotics is not universal and their performance in one clinical site may not necessarily predict their performance in another clinical indication. Thru level 1 clinical evidence of Ca–P bone graft substitute efficacy in randomised clinical trials is scarce.

Good clinical results in the treatment of osteomyelitis are reported with a bioglass material (BonAlive®) in a small patient cohort.[36] Bioglass is also believed to have angiogenic effect which may be beneficial in late infection healing treatment.[37]

Collagen fleeces (such as Septocoll®) with antibiotics have been extensively used with reasonable results.[34] Concerning collagen fleeces loaded with antibiotics one drawback needs mentioning. Although no reports in literature can be found, a lot of users cite a tendency for fleeces to provoke prolonged wound drainage during week 2–4 postoperative, difficult to distinguish from genuine, persisting infection. The same disturbing secretion has been described with Ca–P bone substitutes.[50]

Ongoing research does not solely focus on bone graft substitute materials. The combination of antimicrobial coatings on implants with biomimetic HA coatings is also rapidly advancing.[32,38] Especially in the early stage of implantation, it should protect the grafted site against microbiological pathogens. Teller et al.[32] reported the release kinetics of gentamicin after loading from a biomimetic HA coating (BONITmatrix). Release kinetics of the loaded Gentamicin was investigated and for BONIT matrix a high

initial release was followed by a continuous release over the investigated 70-day period.[32]

Conclusion and discussion

Infection of any foreign material, implanted in the human body, is a serious and difficult to treat problem. A lot of revisions deemed ''aseptic'', are in fact low-grade infections, so total number of infected implants is most likely underreported. Biofilm formation renders bacteria untouchable for most current antibiotics and poses an added problem in treatment. Since most infections occur at implantation, sterile technique remains of utmost importance. It is also important to differentiate superficial from deep infections, since treatment is different for both and much more invasive and demanding for the patient involved. In this regard we deem that better treatment guidelines from surgical societies are warranted. Larger databases for implant infection registration and subsequent treatment efficacy offer ways to compare different treatment modalities in larger cohorts. They also offer opportunities for further treatment enhancement and we advocate that these should be initiated in a multinational manner. In any infection case, effort must be made to try and retain the original implant. Any surgical treatment requires adjuvant intravenous or oral antibiotic treatment.

The choice of the optimal bone substitutes for treatment of infection is therefore not always an easy one, and largely depends on the clinical application and its associated biological and mechanical needs. Not all bone graft substitutes will perform the same way, and their performance in one clinical site may not necessarily predict their performance in another site. From our perspective PMMA beads remain the golden standard but interesting new materials and treatment techniques are on the brink of clinical implementation. Proper examination of their feasibility and effect in well-designed randomised trials is essential to value their clinical application. It remains important to realize that new treatment options can improve clinical outcomes but cannot replace the need for prophylactic efforts and prevention of infection occurrence.

Conflict of interest statement

The authors state that they received nothing of value with regard to this manuscript. There is no conflict of interest.

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