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Review

Antimicrobial delivery systems for local infection prophylaxis in orthopedic- and trauma surgery

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ABSTRACT

Infectious complications occur in a minor but significant portion of the patients undergoing joint replacement surgery or fracture fixation, particularly those with severe open fractures, those undergoing revision arthroplasty or those at elevated risk because of poor health status. Once established, infections are difficult to eradicate, especially in the case of bacterial biofilm formation on implanted hardware. Local antibiotic carriers offer the prospect of controlled delivery of antibiotics directly in target tissues and implant, without inducing toxicity in non-target organs. Polymeric carriers have been developed to optimize the release and targeting of antibiotics. Passive polymeric carriers release antibiotics by diffusion and/or upon degradation, while active polymeric carriers release their antibiotics upon stimuli provided by bacterial pathogens. Additionally, some polymeric carriers gelate in-situ in response to physiological stimuli to form a depot for antibiotic release. As antibiotic resistance has become a major issue, also other anti-infectives such as silver and antimicrobial peptides have been incorporated in research. Currently, several antibiotic loaded biomaterials for local infection prophylaxis are available for use in the clinic. Here we review their advantages and limitations and provide an overview of new materials emerging that may overcome these limitations.

1. Introduction

Developments in the field of trauma and orthopedic biomaterials have improved the life of millions of patients undergoing surgery. However, infectious complications can delay successful healing. Infection after orthopedic or trauma surgery occurs when bacteria enter the surgical site and cause pathological conditions or diseases [1]. Surgical site infections (SSI) are infections that encompass the surgical wound and all other tissues involved in the operation [2]. Clinical studies have identified several risk factors for the development of SSI, which may be classified into patient-related factors and operation-related factors (Table 1) [2,3].

One of the most significant risk factors for the development of infection is the presence of an implant. The reasons why implanted medical devices are at such high risk for developing infection has been a topic of research for decades. In 1957, Elek and Conen showed that the presence of a single silk suture could reduce the number of bacteria required to cause an infection in human subjects by 10,000 fold [4]. Zimmerli et al. showed similar data in a guinea pig model, whereby the minimal infectious dose of *Staphylococcus aureus* (*S. aureus*) was 100,000 fold lower when a device was implanted subcutaneously compared to the situation in which no implant was inserted [5]. This increased susceptibility to infection appears to be partly due to a localized deficiency in phagocytosis of bacteria in the vicinity of an implant, and to the growth of bacteria in a biofilm on the surface of the implanted device [6,7]. Published infection rates of about 5% have been reported for internal fracture fixation devices (FFDs) [8]. Increased infection rates have been reported within certain high-risk groups: for example, the infection rate in patients with open fractures may exceed 30% [9], in comparison with 0.5–2% for equivalent closed fractures [9]. Similarly, the infection rate for revision of failed prosthetic joints

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Table 1
Risk factors for surgical site infection [2,14].

	Risk factors for the development of SSI
Patient factors	Extremes of age
	Poor nutritional state
	Obesity (>20% of ideal body weight)
	Diabetes mellitus
	Smoking
	Infections at sites other than the surgical site
	Inflammatory arthritis
	Malignancy
	Bacterial colonization (e.g. nares colonization)
	Immunosuppression (steroids, other immunosuppressive drug use, cytotoxic drugs or previous antibiotics)
	Preoperative hospitalization
	Prolonged postoperative hospital stay (nosocomial infection)
Operation factors	Too short surgical scrub (shorter than 2 min)
	Poor skin antisepsis
	Preoperative shaving
	Type of agent used for preoperative skin preparation
	Emergency procedure
	Length of operation
	Antimicrobial prophylaxis
	Operating theater ventilation
	Inadequate instrument sterilization
	Traumatic or unfamiliar surgical technique (hematoma, devitalized tissue, dead space, electro cautery etc.)
	Foreign material in surgical site (orthopedic implant, fracture fixation devices)
	Surgical drains
	Surgical technique (hemostasis, poor closure, tissue trauma)
	Postoperative hypothermia

may be up to 40% [9], whereas the rate for primary joint replacement is approximately 1–4% [3,10–12].

A guideline document outlining best clinical practice for the prevention of SSI has been published by the U.S. department of health and human services [13]. Several key-actions for surgical personnel are described which are based upon well-designed studies that have proven to reduce the risk of SSI significantly. Most importantly, preoperative intravenous administration of antimicrobial agents that are effective against the most common species causing SSI should be provided. The timing of the administration should be such that the minimal bactericidal concentration of the antimicrobial agent for these species should be reached and that it stays above this level at least until a few hours after the incision is closed. Finally, surgical personnel should adhere to the principles of asepsis when placing intravascular devices, spinal or epidural anesthesia catheters or when providing intravenous drugs [13].

Most infections associated with orthopedic implants are caused by opportunistic pathogens and bacteria that are regularly found within the microflora of the human skin [15]. The initial colonization of the wound tissues may occur preoperatively, in the case of open wounds, or perioperatively, i.e. after incision but before complete healing of the surgical wound [8]. Considering the large number of bacterial species present on the human skin, only relatively small percentages have been implicated in SSI infections involving orthopedic hardware. The staphylococci account for the majority of cases of device related infections for most classes of implants. *Staphylococcus aureus* and various coagulase negative staphylococci such as *Staphylococcus epidermidis* account for more than 50% of infection cases related to FFDs and for up to 65% of prosthetic joint infections (PJIs) [8,16–19].

The increasing prevalence of multiple antibiotic resistant bacteria such as methicillin resistant *S. aureus* (MRSA), both in the community and in the hospital setting, has been attributed to the misuse of antibiotic agents in the medical and agricultural sector [20,21]. This has an additional downstream impact upon the treatment of infections associated with implanted orthopedic hardware. Even when medically required, antibiotic use can have secondary consequences. For example, colonization of the hip joint with antibiotic-resistant bacteria may reach up to 88% upon hip revision surgery in which antibiotics had been used in bone cement at a previous operation [22].

Infection of the bone and bone marrow, osteomyelitis, can be divided into different types according to the origin of the condition: 1) osteomyelitis from hematogenous spread of infection, 2) osteomyelitis secondary to a contiguous focus of infection, 3) osteomyelitis associated with vascular insufficiency [23] and 4) osteomyelitis from iatrogenic inoculation during surgery or trauma.

If symptoms appear early and are correctly diagnosed, treatment of acute osteomyelitis is usually successful [24]. If the diagnosis is delayed, or infection of the bone progresses without successful treatment, a significantly more challenging complication arises. Chronic osteomyelitis may involve bacterial biofilm formation on the implant and devitalized bone fragments, which become sequestra [25]. The bacterial biofilm is a central factor in implant related osteomyelitis. A biofilm consists of adherent bacteria within a polymeric matrix made out of exopolysaccharides surrounded by interstitial voids in which nutrients circulate between cells [26]. These polysaccharides are required for intercellular adhesion so that bacteria can accumulate in an adherent muli-layered biofilm [27]. Besides these polysaccharides, the extracellular polymeric substances in which bacteria live, are composed out of proteins, nucleic acids (extracellular DNA), lipopolysaccharides, glycolipids and lipids [28,29]. Biofilms readily form on surfaces such as prostheses and implants [30] as well as on the surface of dead bone and living tissue [31,32].

The presence of bacteria in a biofilm drastically reduces their susceptibility to antimicrobial drugs and host defense cells. Reduced susceptibility seems not to be caused by limited antibiotic penetration, but the reduced growth rate of bacteria in a biofilm makes them less susceptible to growth-dependent antimicrobial killing [17,26,33]. Sub-populations may also differentiate into a phenotypically resistant state and bacteria might express biofilm-specific antimicrobial resistance genes [34,35].

The treatment of chronic osteomyelitis is difficult, time-consuming and expensive. A standard treatment protocol for chronic osteomyelitis and infected non-unions may involve: identification of the bacterial species and antibiotic susceptibility testing, removal of orthopedic or fracture fixation devices, debridement of infected bone and soft tissue and systemic delivery of antibiotics for a 4–6 week period. Antibiotic-loaded spacers may be placed in the area where infected bone is removed. Irrigation with abundant antiseptic after debridement of infected bone may be an adjunct to this standard procedure [36]. Furthermore, a viable and stable soft-tissue environment has to be created and reconstruction, alignment and stabilization of the skeleton has to be performed [25].

The average costs for removing infected internal fixation devices and subsequent treatment of these infections were estimated to be $ 15,000 on average per case around the year 2000 in the United States [37]. A similar figure was obtained from a large survey from hospitals located in New York City in 1995, where 13,550 cases of *S. aureus* infection were reported with a total cost of $ 435.5 million for treatment; on average $ 32,100 per case [38]. Treatment of SSI caused by *S. aureus* cost on average $ 21,800 and treatment of osteomyelitis $ 35,000 [38]. The morbidity and socioeconomic costs of implant related osteomyelitis emphasize the need for effective prophylactic measures to prevent infection in orthopedic- and trauma surgery.

Systemic antibiotic prophylaxis is mandated for certain surgical procedures, though not for all [39]. The requirement for antibiotic prophylaxis is largely based on the risk assessment of the surgeon, regular practice in the hospital in question, and numerous guidelines published on the topic. Antimicrobial prophylaxis is indicated for operations considered to have contamination, as these are associated with a high rate of infection [40]. When an implant is inserted during surgery, it is standard practice that perioperative antibiotic prophylaxis is provided, since the presence of a foreign material at the surgical site is an important risk factor for the development of SSI [41].

For arthroplasty, usually a single dose or 24 h administration of a first or second generation cephalosporin is provided [14,42]. A similar regime is indicated for the fixation of closed fractures [14]. For the fixation of open fractures in trauma surgery, the number of antibiotic doses and the duration of administration are related to the severity of the open fracture and the status of the wound, with greater antibiotic protection required for cases with greater soft tissue damage and greater exposure of bone and higher degree of contamination [43] (Table 2). When there is potential fecal contamination of the wound, either piperacillin/tazobactam, or a carbapenem or a third generation cephalosporin plus metronidazole should be provided [14].

For elective surgery like an arthroplasty, the optimal effect is obtained when sufficient antibiotic tissue levels are achieved at the time of incision. The incidence of SSI during these surgeries increases to 3.8% when prophylaxis is given too early (>2 h before surgery) or to 3.3% when prophylaxis is given too late (>3 h after surgery) in comparison with 0.6% when prophylaxis is given just before surgical incision is made [44]. In the case of severe trauma with open fractures after an accident, one would like to give antibiotic prophylaxis as soon as possible, since the possibility of bacterial colonization of the wound increases over time. In surgical practice, however, the antibiotics are administered upon arrival in hospital.

One of the problems related to systemic delivery of antibiotics is that insufficient concentrations are reached at vascular compromised locations, such as a fracture site or other compromised tissues. In fractures, the bony structure may be affected and the local vascularity may be disturbed [45] making it impossible to achieve appropriate local antibiotic concentrations via systemic delivery via the bloodstream. Increasing the dose of systemically delivered antibiotics is not a suitable approach since high concentrations of antibiotics over an extended period might cause systemic toxicity problems; e.g. like ototoxicity for aminoglycosides [46] and nephrotoxicity for aminoglycosides [46–48], glycopeptides [48,49], polymyxins [48–50], quinolones, rifampicin and sulfonamides [48].

2. Local antibiotic infection prophylaxis

Local delivery of antibiotics maximizes target tissue concentration, and minimizes systemic toxicity risks. Any drug delivery device intended for prophylactic use should have a broad-spectrum antibiotic incorporated in order to prevent both a wide of Gram-positive (e.g. *S. aureus* and *S. epidermidis*) and Gram-negative (e.g. *Pseudomona aeruginosa* and *Escherichia coli*) bacteria from colonizing the surgical site.

Aminoglycosides are broad-spectrum antibiotics covering the species most frequently encountered in trauma surgery such as *S. aureus* and *S. epidermidis* [51]. Aminoglycosides have two mechanisms of action. First of all, aminoglycosides inhibit protein synthesis in bacteria. Sensitive bacteria accumulate aminoglycosides on the 30s subunit of ribosomes associated with the cell membrane. Secondly, aminoglycosides destroy the cytoplasmic membrane [52]. The ability of aminoglycosides to destabilize the outer membrane by creating holes in the cell wall is probably the most important ability of this class of antibiotics, since bacteria are killed even before protein synthesis is disrupted [52]. The aminoglycosides gentamicin and tobramycin, and the glycopeptide vancomycin are the most commonly used antibiotics in local delivery vehicles [53,54].

Gentamicin has a broad-spectrum of activity, rapid concentration-dependent bactericidal effect, a low rate of resistance and low cost [52]. Gentamicin is available for intramuscular and intravenous injection, in antibiotic impregnated poly(-methylmethacrylate) PMMA beads, in sponge-like collagen implants and as antibiotic component in a coating on intramedullary nails for tibial fracture fixation [53,54]. Tobramycin and the glycopeptide vancomycin are also used in PMMA bone cement. The aminoglycosides activity is reduced at low pH, at low oxygen-containing environment, in the presence of calcium and magnesium ions, and in the case of hyperosmolarity [52,55–57]. The suggested mechanism is that an acidic pH impairs gentamicin transport into bacteria, this is because of its larger ionization at lower pH, since the pKa values of the amino groups of gentamicin are between 5.5 and 9 [56].

Vancomycin is active against Gram-positive bacteria such as Staphylococci (including MRSA), Streptococci and Enterococci [2]. Vancomycin interferes with cell wall synthesis in Gram-positive bacteria [58]. It targets the terminal D-Ala-D-Ala of the

Table 2
Guidelines for antibiotic prophylaxis according to AO principles [14].

Open fracture classification	Fracture description	Likely bacterial pathogen	Antibiotic course (IV)	Duration following wound closure
I	Skin wound more than 1 cm Clean Simple fracture pattern	Gram positive cocci	1st or 2nd generation cephalosporin	24 h
II	Skin wound less than 1 cm Soft-tissue damage not extensive No flaps or avulsions Simple fracture pattern	Gram positive cocci	1st or 2nd generation cephalosporin	24 h
IIIA IIIB IIIC	High-energy injury involving extensive soft-tissue damage Or multifragmentary fracture, segmental fractures, or bone loss irrespective of the size of skin wound Or severe crush injuries Or vascular injury requiring repair Or severe contamination including farmyard injuries	Gram positive cocci + Gram negative rod	Amoxicillin/clavulanic acid or ampicillin/sulbactam or 3rd generation cephalosporin	120 h

staphylococcal peptidoglycan stem peptide and inhibits the elongation of the sugar backbone and the crosslinking of the peptidoglycan [59]. The systemic route of administration of vancomycin is oral or intravenous [60]. Vancomycin is often used in the case of β-lactam resistance [59,61]. Another reason for using vancomycin is when the patient is allergic to β-lactams [17]. Staphylococci, both coagulase negative and coagulase positive are susceptible to vancomycin at levels as low as ≤1–5 μg/ml, but susceptibility is drastically lowered in vancomycin-resistant *S. aureus* (VRSA) [62].

One potential side effect of high local concentrations of antibiotics is the risk of cytotoxicity. Rathbone et al. showed the effect of the concentration of various antibiotic agents on osteoblast cell viability and activity [63]. Gentamicin concentrations of 10 μg/ml resulted in a decrease of less than 25% in alkaline phosphatase (ALP) activity and DNA content. At concentrations between 10 μg/ml and 200 μg/ml, a decrease in ALP activity and DNA content of 25%–50% was reported, while for concentrations higher than 2000 μg/ml more than 75% decrease in ALP activity and DNA content was observed [63]. Isefuku et al. used human osteoblast like cells (HOB) to investigate the effect of gentamicin on osteogenesis [64]. ALP activity and DNA content were measured, as well as ^{3}H-thymidine incorporation (measure of cell proliferation) after 4 days of culture. Gentamicin concentrations of 30 μg/ml resulted in no decrease in the aforementioned parameters. Gentamicin concentrations of 100 μg/ml and higher showed a decrease in ALP activity, concentrations of 300 μg/ml resulted in less than 50% decrease of ^{3}H-thymidine incorporation and concentrations of 700 μg/ml showed a decrease in DNA content for all HOB cultures. Haleem et al. showed in an *in vivo* study that systemic administration of gentamicin (1.5 mg/kg intramuscularly) or vancomycin (25 mg/kg intraperitoneally), both to simulate therapeutic peak serum concentrations, resulted in 30 min serum concentration of 4.5 μg/ml for gentamicin and 35.1 μg/ml for vancomycin and did not impair experimental fracture healing in rats [65].

Tobramycin can potentially be applied locally at higher concentrations (>500 μg/ml *in vitro*) than gentamicin without compromising osteoblast viability [50,63]. Vancomycin can be released even at concentrations up to 2000 μg/ml with a decrease of less than 25% in ALP activity and DNA content. However, such high concentrations may not be required, since glycopeptides display time-dependent activity, rather than concentration dependent activity.

Thus, in the local delivery of antibiotics such as gentamicin it is therefore not only necessary to reach concentration levels above the minimal bactericidal concentration (MBC) in order to prevent bacterial resistance, but it is also important to keep peak concentration at a level which does not affect bone healing [63,66]. For instance, local gentamicin levels for prophylaxis against Staphylococcal species (spp.) should be between 128 μg/ml and 200 μg/ml to meet the $MIC_{90\%}$ value and have a reduction of less than 50% in ALP activity and DNA content for osteoblasts as determined *in vitro* [66,67].

Since antibiotics will act for a short term period when injected locally before being cleared, the design of controlled and sustained delivery systems is of equal importance as the choice of antibiotic to be used. In 1970, PMMA bone cement was the first polymeric biomaterial which came to the clinic to serve this purpose [68]. Bone cements are prepared by mixing of a liquid phase and a powder phase containing an initiator, which starts the polymerization process. The liquid phase mainly consists of methylmethacrylate (MMA) monomer. The powder phase consists of either a methylmethacrylate (PMMA) or a methylacrylate (PMA) polymer or a copolymer of one of the two previous compounds with butylmethacrylate (BUMA), ethylmethacrylate (EMA), methylacrylate (MA) or styrene. Furthermore, the powder phase contains an initiator, benzoyl peroxide, which cures the cement upon contact with the activator N,N-dimethyl-p-toluidine (DMpT) from the liquid phase. Radiopacifiers such as BaSO4 and ZrO2 may also be added to the powder to increase cement visibility in radiographs. A dye may also be added to the powder or to the liquid or to both. Chlorophyllin is most commonly used; however in Cobalt™ G-HV indigo carmine is added. Hydroquinone (HQ) is added to the liquid monomer as a stabilizer in order to prevent premature polymerization during storage [69]. Obviously, the composition of the polymer powder and the monomer liquid will influence the properties of the resulting bone cement after curing, such as hydrophilicity (water uptake), mechanical strength and porosity (created by air inclusions in the cement dough) [69,70]. The hydrophilicity of the final polymer components will influence the diffusion of antibiotics from the bone cement into the surrounding tissue and therefore the release rate of the included antibiotic. There are 3 different mechanisms suggested for the release of antibiotics from bone cement *in vitro* [71]. The antibiotics are either released from the bone cement by a surface phenomenon (1), by bulk-diffusion through pores and connecting capillaries in the bone cement (2) or by a combination of the two mechanisms, the mixed-mode model, where initially antibiotics are released from the surface followed by bulk-diffusion (3) [71]. However, in all PMMA bone cement compositions, the antibiotics are not completely released [69]. A large amount stays encapsulated within the bone cement and is therefore not released during the lifetime of the implant, which would support the theory that antibiotics are mainly released from the bone cement by a surface phenomenon. In fact, Frutos Cabanillas et al. performed a release study with CMW1 Gentamicin bone cement which supports this phenomenon [72]. The *in vitro* release was tracked for 8 weeks and it was found that most of the gentamicin was released during the first 2 h, but then the antibiotic concentration dropped very quickly afterwards to almost no release.

Kühn compared the release of 12 different bone cements *in vitro* over 7 days [69]. Between the different commercial bone cements there was a large difference in release with a several fold higher release of gentamicin [mg/g bone cement] of the bone cements prepared from MMA/MA copolymer compared to PMMA homopolymer, most likely because of the higher hydrophilicity of the copolymer composition. The gentamicin content in different commercial bone cement powders and the amount of gentamicin released after 7 days from several commercial available bone cements can be seen in Fig. 1 [69].

PMMA is used as a carrier material for antibiotics as bead chains (Fig. 2), blocks (Fig. 3) and putty. A commercial gentamicin loaded PMMA bead chain is produced by Merck since 1972 under the trading name Septopal®. These bead chains are primarily used in the treatment of infections but they are also used in prophylaxis [55], although this is not standard practice. They are used for treating prosthetic joint infections, septic arthritis and osteomyelitis. In prophylaxis they may be used when there is an elevated risk of SSI [55].

The combined action of a systemically administered antibiotic and local delivery using PMMA has been shown to be beneficial in reducing the infection rate upon hip replacement. In a large cohort study of the Norwegian Arthroplasty Register of 22,170 hip replacements, it was shown that local delivery of antibiotics from PMMA bone cement combined with systemic antibiotics had the lowest risk of revision [73]. Patients who received the antibiotics only systemically had a 1.8 times higher revision rate with infection as the endpoint ($p = 0.01$). The systemic antibiotics used were cephalosporins (cephalotin or cefuroxime) or penicillin (cloxacillin or dicloxacillin). The antibiotics used in the PMMA were gentamicin in Palacos cement or colistin/erythromycin in Simplex™ cement [73].

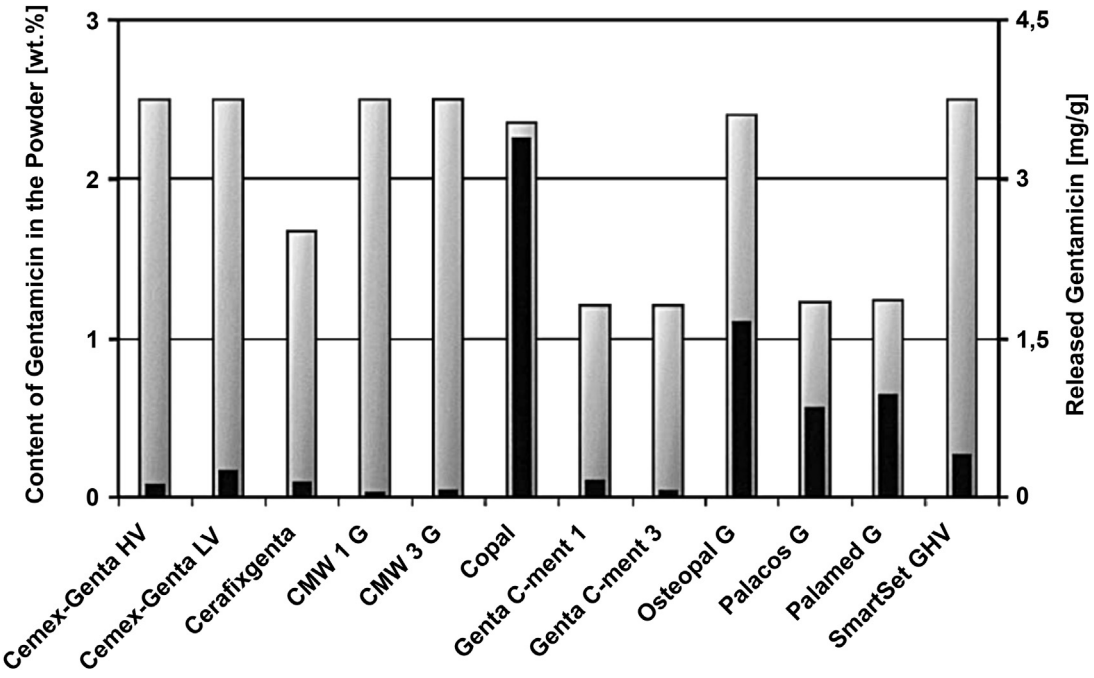

Fig. 1. Gentamicin content in different commercial bone cement powders (gray bars, y-axis on the left) and the amount of gentamicin released after 7 days *in vitro* as expressed in mg/g bone cement (black bars, y-axis on the right) [69].

Polymeric bone cement has also several drawbacks as a local delivery vehicle for antibiotics. The drawbacks are primarily the rapidly reducing local antibiotic levels, and the permanent presence of a foreign body, which may be colonized by bacteria. Low, sub-inhibitory antibiotic levels over an extended period can induce bacterial resistance. For example, studies show increased gentamicin resistance after use of impregnated bone cement in patients receiving a hip implant [67]. In a study published by Weber and Lautenbach, the percentage of bacteria resistant to gentamicin increased from 29% for bacteria which were isolated preoperatively to 41% for bacteria isolated after surgery in which gentamicin-impregnated cement was used [74]. Furthermore, in a study of 34 cases of revision surgery of hip implants, at least one strain of gentamicin-resistant coagulase negative staphylococci (CNS) was found on 88% (30) of the implants in which gentamicin-impregnated cement was used. In 57 cases of revision surgery of hip implants where no gentamicin was included in the cement only 16% (9) grew gentamicin-resistant CNSs [75].

PMMA beads are non-degradable and need to be removed during follow-up surgery, which is an additional risk for acquiring a new intraoperative infection [53]. Unreacted methacrylate monomer can cause toxicity issues, with toxicity directly related to the lipophilicity of the respective methacrylate [76]. Furthermore, the heat generated during polymerization limits the choice of antibiotics: most antibiotics as opposed to gentamicin are heat labile [66]. *In vitro* maximum temperatures reached according to the standards ISO 5833 and ASTM F 451 for curing of bone cement are between 60 °C and 80 °C. Clinical trials, however, showed lower temperatures between 40 °C and 47 °C at the bone-cement interface *in vivo* [69]. Although heat necrosis due to high local temperatures, which is suspected to lead to aseptic loosening, might not occur at the interface *in vivo*, the temperature within the curing bone cement might still be much higher than at the interface and affect heat labile antibiotics [69].

Collagen, in contrast to PMMA, is biodegradable. In the body, collagen is degraded by phagocytosis and enzymatic degradation [10]. Collagen fleece loaded with antibiotics is used in contaminated wounds to prevent infection. Several antibiotic-loaded collagen fleeces are commercially available (Fig. 4) [77], differing in collagen source, amount of antibiotic loaded and type of

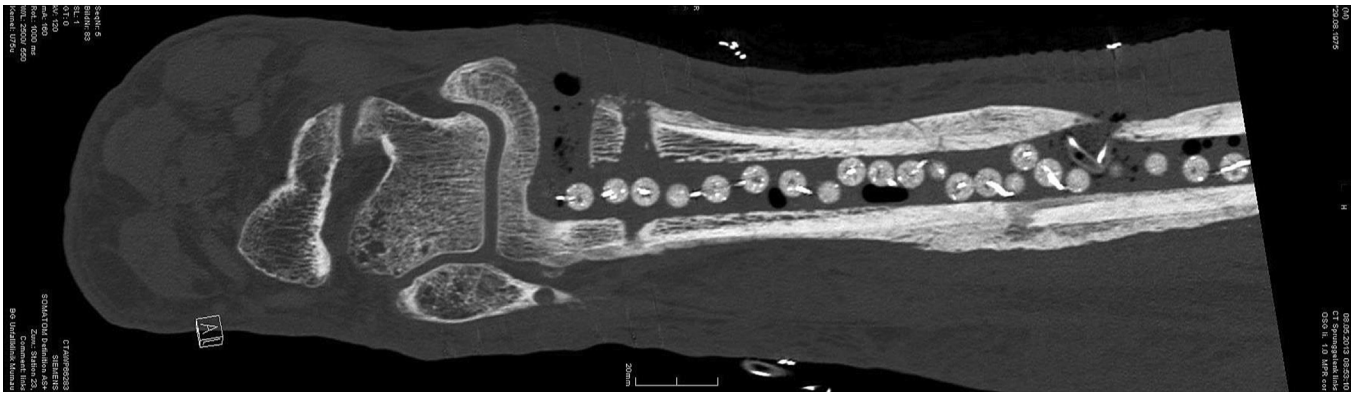

Fig. 2. Gentamicin loaded PMMA beads, placed after infection of a plated tibial fracture (Image courtesy of Dr. Mario Morgenstern, Trauma Center Murnau, Germany).

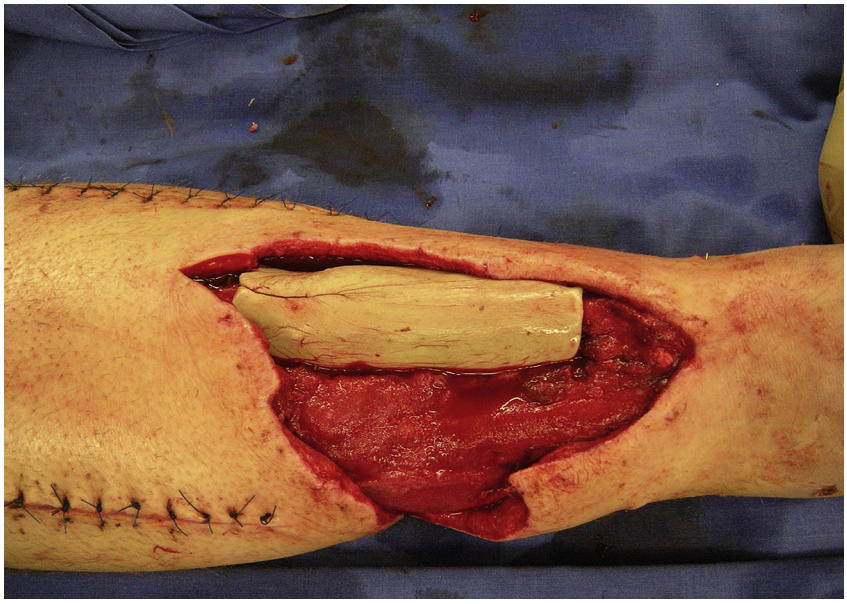

Fig. 3. Antibiotic loaded PMMA spacer (Image courtesy of Dr. Mario Morgenstern, Trauma Center Murnau, Germany).

antibiotic loaded. Controlled randomized clinical studies in which antibiotic-loaded collagen fleece (1–3 sponges per case with 200–600 mg of gentamicin sulfate) was used for intra-abdominal-related surgeries or wound infections, had a positive outcome in 95.6% compared to 72.5% for standard therapy, in which patients healed by primary intention or without evidence of post-operative infection [78].

When using collagen fleece, the antibiotic is released very rapidly [79]. An *in vitro* study with pepsin-treated bovine collagen, 0.5 g of collagen containing 130 mg gentamicin, showed a release of 95% of the antibiotic in 1.5 h [79]. However, the full resorption of the collagen carrier takes 8 weeks [80]. Antibiotic delivery rates are highly dependent on the fluid supply *in vivo*. Effective local concentrations might be reached during less than 24 h in well perfused sites and up to 1 week in bony structures [81]. *In vivo*, the mismatch between the rate of antibiotic release and the rate of degradation of the collagen might allow bacteria to attach to the collagen via microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) [82], serving as substrate for bacterial adhesion.

High water solubility of particular antibiotics might limit the application and the prolonged release from biomaterials. Therefore, research has also focused on formulations with reduced solubility. One approach is to create lipophilic salts of the antibiotic, e.g. for gentamicin: gentamicin sodium dodecyl sulfate (SDS), gentamicin sodium bis(2-ethylhexyl)sulfosuccinate (AOT), gentamicin crobefate, gentamicin laurate, gentamicin myristate and gentamicin palmitate [83–87].

For the use of collagen fleece longer prophylactic antibiotic levels are maintained, when gentamicin crobefate is incorporated in addition to gentamicin sulfate [88]. A prolonged release period

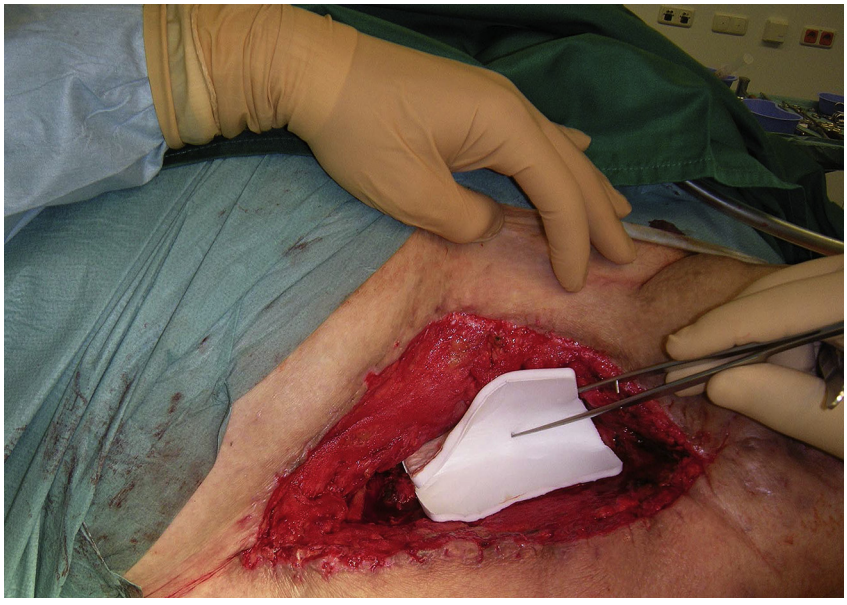

Fig. 4. Antibiotic loaded collagen fleece applied at the surgical site before insertion of the implant (Image courtesy of Dr. Mario Morgenstern, Trauma Center Murnau, Germany).

(about 12 days *in vivo*) is thereby established, since gentamicin crobefate is hydrophobic as opposed to the sulfate salt of gentamicin which is hydrophilic and thus readily diffuses. However, the degradation rate of the fleeces themselves is not modified [80]. Overall, the main drawback of antibiotic loaded collagen fleece is the non-matching degradation rates and release times. Another drawback is the complicated handling of the collagen fleeces, and the covering of all infected areas by the fleece. Furthermore, although rare, biological responses such as localized hypersensitivity to- and circulation of antibodies against bovine collagen can be elicited [89].

The use of biodegradable synthetic implants avoids these biological responses. For instance synthetic coatings containing antibiotics have been applied on metal implants to prevent infection. Coatings can be applied on a wide variety of materials, turning an implant into a drug delivery device. So far, only poly(D,L-lactide) (PDLLA) coatings have made it to the clinic (Fig. 5). Clinical trials with metal implants coated with PDLLA with gentamicin incorporated were started in July 2003 [54]. Intramedullary nails with a PDLLA coating containing gentamicin were implanted in the tibia of patients with complex fractures. Indications for use of a gentamicin-containing PDLLA coated intramedullary nail were the presence of a type III open fracture or the performance of a re-osteosynthesis, because the incidence of infection is very high for these cases. In a case study of a 17 year old man with a type III open tibia fracture, this PDLLA gentamicin-coated nail was inserted. All the wounds healed without complications and after 25 days the patient was fully mobilized. In 2011, this PDLLA gentamicin-coated intramedullary nail was released on the market. *In vitro* release studies in deionized water showed that these PDLLA gentamicin-coated implants released 40% of the gentamicin-sulfate payload within 1 h, 70% within 24 h and 80% within 48 h [90].

There are several drawbacks related to the use of coated implants. One of the drawbacks is that part of the coating can delaminate during insertion due to applied forces on the implant. Since coating the implant creates a new medical device, the device needs a separate approval before it can be used in the clinic. Furthermore, antibiotic activity and bone healing can be impaired upon release of acidic degradation products of PDLLA which lower the local pH [91]. Low pH values at an implant site might evoke inflammatory foreign body responses with accompanying osteolytic foci in the exposed bone [92]. *In vitro* degradation studies with poly(lactide) based polymers showed pH values between pH 3.0 and pH 7.0 depending on the composition of the polymer, experimental conditions and degradation time [93–95]. The minimum pH is reached at the time that the polymer degrades with the greatest rate of weight loss. *In vivo*, this pH drop might be less dramatic than that *in vitro*, since body fluids surround the implant have a buffering effect. This has been shown *in vivo* in Wistar rats upon implantation of a PDLLA implant. Whereas *in vitro* the pH dropped by 4 pH units after 4 weeks in Ringer solution, *in vivo* the maximum pH drop was 1 pH unit 1 week after implantation [93]. However, buffering the release of these acidic degradation products might not be possible for large size implants or implants located at anatomical regions with restricted access to body fluids [96]. Thus, the development of a better prophylaxis material for implant surfaces and the optimal local delivery of the antibiotics from these surfaces remain major challenges.

3. New developments in the local delivery of antibiotics

Different strategies have been pursued by researchers in order to improve systems for the local delivery of antibiotics. For instance, researchers have tried to improve systems already available in the clinics. Besides changing the polymeric carriers, efforts also have been made to incorporate modified antibiotics, to produce polymeric prodrugs based on conventional antibiotics or to entrap silver (nano)particles or to incorporate antimicrobial peptides or antimicrobial peptide elicitors instead of antibiotics. Another new development is the creation of systems that can be applied minimally invasively and have a sustained antimicrobial release profile. And finally, release systems are being investigated which release their antibiotic or antimicrobial compound in response to a biological stimulus related to an infectious state.

3.1. Biomaterials loaded with 'new' antimicrobial agents

Many new antimicrobial compounds have been incorporated into biomaterials. For instance, polymeric prodrugs have been developed based upon conventional antibiotics. An example is given by the work of Marcus et al. who created a prodrug of gentamicin by grafting poly(ethylene glycol) (PEG) to gentamicin with heterobifunctional linkers, which are cleaved by spontaneous hydrolysis [97]. Upon PEGylation, the half-life of the antibiotic increases *in vivo*. By using reversible PEGylation of gentamicin, PEG_{20}-FMS-gentamicin and PEG_{40}-Fmoc-gentamicin, the inactivated gentamicin becomes active again after the linker has been hydrolytically cleaved, whereas irreversibly bound PEG renders the antibiotic inactive [97].

By covalently grafting the antibiotic to a carrier, additionally to increasing the half-life and retarding the time of release of the antibiotic, special ligands can be incorporated to target the complex

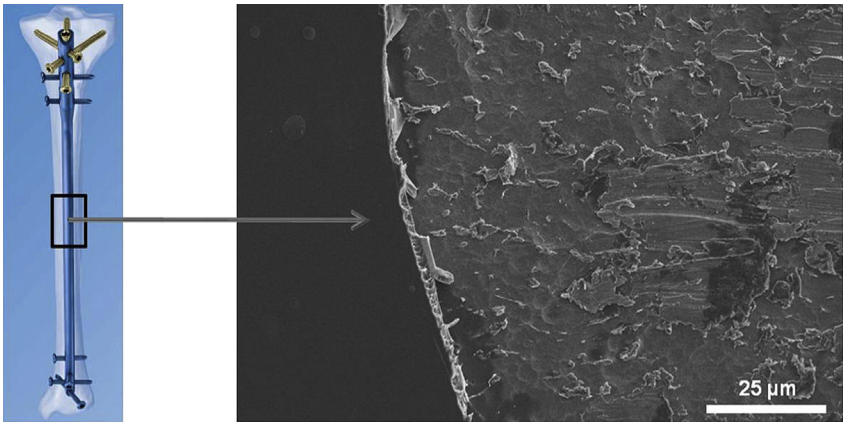

Fig. 5. Tibial nail with gentamicin sulfate containing PDLLA coating visualized by SEM (Coating on the left of the image (image available from www.synthes.com) and scratched implant surface revealing coating on metal implant on the right).

towards specific functionalities on cells in order to target intracellular infections (Fig. 6). As an example, Coessens et al. synthesized a conjugate of streptomycin linked to poly[*N*-(hydroxyethyl)-L-glutamine] (PHEG) and dextran with glycerine hydrazide as linker and a mannose-terminated side group for intracellular targeting [98]. Streptomycin was coupled via Schiff base formation. The release of streptomycin from the carrier is a hydrolytic process and dependents on the pH (acidic environments catalyze the hydrolysis of the linker). The authors hypothesized that the lower pH (pH ~5.2) in endosomes and lysosomes could facilitate the intracellular release of the streptomycin from the prodrug by destruction of the Schiff base. The release of streptomycin from the polyglutamine prodrug was tracked at pH 7.4 and pH 5.2. At pH 5.2 approximately 50% of the streptomycin was hydrolyzed from the prodrug, whereas at pH 7.4 about 30% of the streptomycin was released from the prodrug [98].

Polymeric prodrugs also have been investigated by Choi et al. with the aim of targeting dendrimer-antibiotic conjugates to bacterial cell walls [99]. Poly(amidoamine) (PAMAM) dendrimers of the fifth generation were tethered with vancomycin at the C-terminus. These vancomycin-conjugated PAMAM dendrimers were able to bind to the surface of even vancomycin resistant bacteria in a synthetic model of the bacterial cell wall. Compared to free vancomycin, the PAMAM dendrimer-vancomycin conjugate bound to these synthetic models of the bacterial cell wall tightly through binding to multiple receptor sites, indicating enhancement in avidity of four to five orders of magnitude. In an affinity study by means of surface plasmon resonance spectroscopy, these PAMAM dendrimer-vancomycin conjugates bound tightly to a vancomycin-resistant surface, which shows only weak (millimolar) affinity to free vancomycin [99].

As multi-resistance has become a problem for the use of conventional antibiotics, the use of silver has received new attention in combination with biomaterials. A comprehensive review on the antimicrobial action of silver ions, silver containing compounds and silver nanoparticles in particular has been published by Rai et al. [100]. A book chapter about silver containing biomaterials has been published by Griesser et al. [101]. The bactericidal effect of silver is due to their interaction with biomolecules. Proteins, enzymes and cell-membrane components in bacteria contain nucleophilic functionalities, which are capable of coordinating silver cations (Ag^{+}) [102]. Bacterial cell death is induced by silver cations by reacting and disrupting the function of cell membranes, metabolic proteins and enzymes and also by displacing metal ions, like Zn^{+} and Ca^{2+}, which are essential to bacterial cell survival [102]. The antibacterial effect of PMMA bone cement loaded with silver nanoparticles (0.1%, 0.5% and 1.0%) on *S. epidermidis*, multi-resistant *S. epidermidis* (MRSE) and MRSA was compared with PMMA bone cement loaded with gentamicin sulfate (2%) by Alt et al. [103]. PMMA bone cement loaded with gentamicin or silver nanoparticles both inhibited the proliferation of *S. epidermidis*. Silver nanoparticle-loaded PMMA bone cement was able to clear MRSE and MRSA as well, whereas PMMA bone cement with gentamicin was unable to inhibit the proliferation of the resistant strains.

The advantage of using silver nanoparticles over using larger sized particles is the maximization of the active surface of the silver, while keeping the total amount of silver low [104]. Furthermore, the bactericidal effect seems to be dependent on the shape of the silver nanoparticles as well. Truncated triangular shaped silver nanoparticles were more effective in inhibiting bacterial growth of *E. coli* than spherical silver nanoparticles, which were more effective than rod shaped silver nanoparticles in a study performed by Pal et al. [105]. Although silver-related cytotoxicity towards eukaryotic cells can be limited by using silver with nano-dimensions, the preparation of silver nanoparticles is hindered by their tendency to aggregate [106]. To stabilize silver nanoparticles, Travan et al. encapsulated the particles in hydrogels composed of Chitlac (lactose substituted chitosan) and alginate [106]. Microspheres prepared of this composite with encapsulated silver nanoparticles eluted only 2.6% of the total amount of silver present in the hydrogel over 5 weeks incubation in saline solution, which did not impair the cell viability of 3 different cell lines (mouse fibroblasts, human hepatocarcinoma cells and human osteosarcoma cells). Whereas Chitlac solutions mixed with silver nanoparticles was found to be cytotoxic to all three cell lines, leading to cell death within 24 h. Hydrogels and hydrogel extracts prepared from an alginate-Chitlac mixture with the silver nanoparticles entrapped did not show cytotoxicity towards these cell lines as they are shielded from uptake by mammalian cells [106]. Antibacterial testing was done by adding 20% MH broth as bacterial nutrition to both alginate and Chitlac solutions. The surfaces of alginate-Chitlac gels with and without silver nanoparticles were smeared with 10^{6} CFU/ml *S. epidermidis*. Only the silver nanoparticle loaded gels were free of bacterial colonization [106].

The combination of polymers and nanosilver can solve diverse problems related to the use of nanosilver such as: (1) polymers can prevent aggregation of silver nanoparticles, (2) polymers can act as

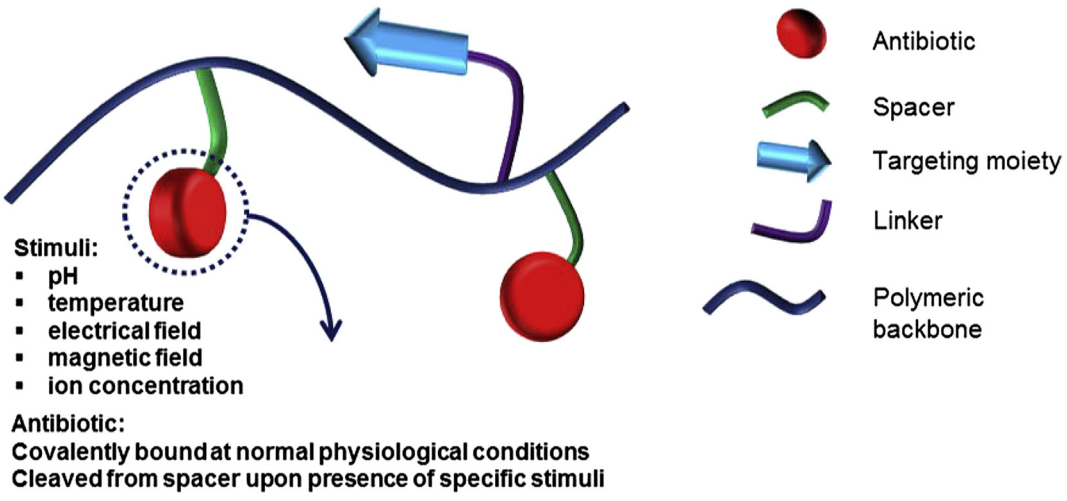

Fig. 6. Schematic of stimuli-responsive prodrug systems for the targeted delivery of antibiotics.

linker for silver nanoparticles in coatings, (3) silver ion release can be tailored by changing the interaction between the polymer and the silver and changing the silver concentration. Several methods for the preparation of polymer/nanosilver composite coatings have been used to incorporate silver in biomaterials as can be found in an extensive review by Guo et al. [107]. Because of the multiple mechanisms of antimicrobial action exploited by silver nanoparticles they are less likely to suffer from resistance mechanisms in bacteria [108], however silver resistance has been observed in clinical isolates from silver exposed sites in patients as well [109].

Antimicrobial peptides (AMPs) have also been incorporated into biomaterials. Antimicrobial peptides are usually rather short peptide sequences, 12 to 100 amino-acids long, positively charged (net charge $+2 - +9$), are amphiphilic, and have been isolated from single-celled microorganisms, insects and other invertebrates, plants, amphibians, birds, fish and mammals, including humans [110]. A special feature of AMPs is that they target a specific feature of the microbial cellular membrane that distinguishes broad species of bacteria from multicellular plants and animals [111]. Microbial cellular membranes possess negatively charged headgroups on the lipids that form the outermost leaflet of the bilayer which is exposed to the outer world. On the contrary, the outer leaflet of the membranes of plants and animals is composed principally of lipids with no net charge [111]. Although there are large variations in the structure of AMPs, a common feature of cationic AMPs is that they have an amphipathic structure, which allows them to bind to the membrane interface. The interaction with, and finally the disruption of the inner and outer membranes of bacteria leads to the bacterial cell death [112].

Unlike resistance towards antibiotics, acquired resistance towards antimicrobial peptides by sensitive bacterial strains is improbable. However, some bacterial species are resistant by nature, since (1) they lack the appropriate density of acidic lipids to provide peptide-binding sites, (2) Some species produce digestive proteases, which destroy AMPs [111]. Furthermore, degradation by human proteases, unknown toxicity profiles and high costs of production have limited the potential application of AMPs [113]. Only few AMPS have made it to clinical phase testing and none is approved by FDA so far [114]. A promising group of AMPs is the indolicidin-analogs such as MBI-226 (Omiganin) for the treatment of catheter-related infection, which have been used in a clinical phase III trial [110,114].

Since development of resistance against AMPs is unlikely, recently the potential of functionalizing biomaterials with AMPs has been explored in research. Issues of short half-lives and cytotoxicity can be circumvented by immobilizing AMPs on the surface of biomaterials. The use of a spacer between a biomaterial and an AMP can influence the orientation of the peptide and hence its bactericidal activity. A comprehensive review on the different strategies for immobilization of AMPs onto biomaterials and its effect on activity, cytotoxicity and long-term stability has been published by Costa et al. [115].

3.2. Improved polymeric carriers for the passive delivery of antibiotics

In order to overcome the drawbacks of non-degradable antibiotic loaded biomaterials such as PMMA beads and spacers, biodegradable polymer based materials for the delivery of antibiotics have been investigated [116]. To prepare biodegradable antibiotic loaded beads or spacers, either PMMA copolymerized with degradable blocks or resorbable polymers have been used. For the latter a wide variety of polymers, especially aliphatic polyesters prepared by ring-opening polymerization such as PDLLA [117–127], poly(lactic-co-glycolic acid) PLGA [128,129] and PCL [130,131] have been used. For example, antibiotic loaded beads from PDLLA and PLGA were prepared by Mader et al. [132]. Clindamycin, tobramycin or vancomycin were released in adequate concentrations for at least 30 days from the PLA and PLGA beads, whereas the PMMA beads released this antibiotics in adequate concentrations for only 12 days [132].

Neut et al. investigated the use of poly(trimethylene carbonate) (PTMC) discs as a delivery system for gentamicin [133]. The advantage of PTMC is that it degrades without acidic degradation products. PTMC degrades primary by enzymatic degradation. Therefore, the degradation *in vitro* is very slow, whereas the degradation *in vivo* is much faster due to the presence of enzymes [134]. Furthermore, the degradation of PTMC by surface erosion might facilitate a more gradual and sustained release depending on the shape of the delivery system, with the possibly for zero-order release kinetics, whereas other biodegradable materials usually degrade by bulk erosion and lack this control. Neut et al. compared the performance of these PTMC discs with conventional gentamicin-containing PMMA beads (Septopal®). PTMC discs loaded with 10 w/w% of gentamicin entrapped were prepared and the *in vitro* release was assessed by immersing the discs in a PBS solution or in a lipase enzyme solution at 37 °C. In the lipase enzyme solution PTMC discs completely degraded in a two week course, whereas the PTMC discs immersed in PBS did not degrade at all. The gentamicin entrapped was released very slowly from the PTMC discs when immersed in PBS solution, with only 10% of the antibiotic being released over two weeks, however in lipase enzyme solution over 50% of the antibiotic was released over two weeks [133]. So, the large difference in degradation and release is the result of the combined enzymatic and hydrolytic degradation mechanism of PTMC. *In vivo* studies of PTMC discs implanted in subcutaneous pockets in the back of rats showed complete degradation of the implant in 1 year [135]. Consequently, in order to find a suitable biodegradable substitute for PMMA beads and spacers, it is important to consider the properties of the material and their mechanism of degradation.

For collagen fleece, most of the research into improvements has focused on sustaining the release of highly water soluble antibiotics. Besides modifying the properties of the antibiotics, the properties of the collagen carrier can be changed to obtain a sustained release. For instance, the release rate of gentamicin from collagen fleece can be modified to a certain extent by varying the porosity of the collagen matrix or by chemical modification, i.e. succinylation of collagen to enhance charge interactions for ionic bonding between the collagen and ciprofloxacin [78,80,136].

Instead of modifying the properties of the collagen fleece itself, a collagen composite can be created by incorporation of microspheres within the collagen matrix. The composite collagen fleece contains antibiotic in the collagen matrix, but also antibiotic entrapped in microparticles. PLGA microspheres made of a 50/50 blend of PLGA of molecular weight (MW) of 13.5 kDa and 36.2 kDa respectively, with gentamicin entrapped were prepared by the water-in-oil-in-water double emulsion technique by Schlapp and Friess [81]. These microspheres were dispersed within a collagen matrix to create the composite fleece. A burst release of 55% of the entrapped gentamicin was observed *in vitro* from these fleeces, followed by a more gradual release of the residual gentamicin during the first 7 days upon immersion in PBS at 37 °C.

3.3. New responsive polymeric carriers for the active delivery of antibiotics

One of the main requirements of a system for the local delivery of antibiotics in prophylaxis is the ability to have a release which is provided over a period of several days. Hydrogels for the delivery of antibiotics combine the advantage of minimally invasive

application (injection with needle, through a tube or application of a spray or foam) with the advantage of having a sustained release without the need of frequent re-administration. Hydrogels are polymeric materials with high water content that can be used to entrap antibiotics. The stimuli sensitive hydrogels are a special group of hydrogels that can respond to chemical or physical stimuli as to change their physical properties and cleave attached chemical groups at the site of action. Thermo-responsive hydrogels can respond to changes in the environmental temperature. Thermo-responsive hydrogels are designed to have low viscosity at room temperature, but turn with change of temperature from a viscous state to an elastic state. So, thermo-responsive hydrogels are designed so that they can be injected at room temperature and form a gel at body temperature. Veyries et al. used Poloxamer 407 (Pluronic® F-127) to encapsulate vancomycin [137]. Poloxamer 407 is a triblock co-polymer with the poly(propylene oxide) (PPO) as a hydrophobic central block with on both ends a hydrophilic block of poly(ethylene oxide) (PEO). Poloxamer can, when used in concentrations higher than 20 w/v%, gel in-situ because of a sol–gel temperature that is lower than the body temperature. However, there is a risk of lipid metabolism alteration because of high doses of Pluronics. Thus, supermolecular structures of Pluronics combined with cyclodextrins have been investigated to decrease the amount of required polymer for gelation while providing a sustained release [138].

Antibiotics can be mixed into these hydrophilic networks at room temperature and become entrapped at higher temperature. Subsequently the drug is released by several mechanisms: diffusion, swelling and erosion. The antibiotics can diffuse out of the hydrogel depending on the concentration difference across the gel and outside the gel and the path length. Swelling of the hydrogel network allows the entrapped antibiotics to more easily diffuse out of the network. Finally, bulk erosion of the hydrogel also causes antibiotics to be released with the eroded parts and decreases the path length for diffusion from the gel.

Suzuki et al. prepared and studied thermo-responsive hydrogels for infection prophylaxis *in vivo*, with hydrophilic blocks composed out of *p*-dioxane (DX) and PEG, the hydrophobic blocks were composed out of PDLLA [123]. This triblock PLA-DX-PEG hydrogel had a MW of 9.8×10^3 Da and a molar ratio of PLA:DX:PEG equal to 5:1:3. This hydrogel degraded in 2–3 weeks in PBS at 37 °C. They encapsulated teicoplanin, a glycopeptide antibiotic, within this hydrogel and next to the antibiotic recombinant human bone morphogenetic protein-2 (rhBMP-2). The rationale behind this was to eradicate an infection and at the same time stimulate bone formation. In a release study, 30 mg of the gel with 4 μg of teicoplanin was used to track the release of the antibiotic *in vitro*. Approximately 40% of the encapsulated teicoplanin was released during the first 24 h and a level above the $MIC_{90\%}$ value for *S. aureus* was maintained for 2 weeks. The polymeric hydrogel was degraded in about 3 weeks. In an *in vivo* experiment of a rat cranial bone defect, the restored area was measured from CT-scans taken 6 weeks upon implantation of the polymeric implant [123]. The implant with rhBMP-2 had a similar size of restored area as compared with the defect, which had been treated with an implant with rhBMP-2 and teicoplanin. The implant with only teicoplanin encapsulated had a smaller restored area as when rhBMP-2 was used, however this area was larger than for the negative control (only the PLA-DX-PEG implant).

Compositions that respond to enzymes have also been investigated. A poly(ester-urethane) based system with covalently bound ciprofloxacin was assessed by Woo et al. [139]. The rationale behind this design is that poly(ester-urethane)s have been shown to be susceptible to degradation by hydrolytic enzymes, which are released by leukocytes and macrophages present at the site of trauma and/or implant site. This way a responsive system would be obtained in which ciprofloxacin would be released from the polymer upon these stimuli. The release was tracked from poly(ester-urethane)-ciprofloxacin coated hollow glass tubes in phosphate buffer (pH 7) and cholesterol esterase (CE) (40 unit/ml) solution for 30 days. Although a higher rate of polymer degradation was observed in the presence of the CE enzyme, there was no difference observed in the release of free ciprofloxacin upon immersion in a CE solution as compared with the phosphate buffer solution. So, the data suggest that the enzyme was unable to specifically cleave the polymer segments required to release free ciprofloxacin, and instead inactive ciprofloxacin with poly(ε-caprolactone) or 1,6-hexane diisocyanate fragments attached were released [139]. Another example of such a responsive system was a poly(vinyl alcohol) (PVA) hydrogel system investigated by Suzuki et al. [140]. This hydrogel had gentamicin covalently grafted to it by a peptide linker susceptible to cleavage by bacterial enzymes released by *P. aeruginosa*. Several peptide sequences were tested for their hydrolytic activity, and the most efficient one (Gly-(D)Phe-Pro-Arg-Gly-Phe-Pro-Ala-Gly-Gly) was selected [140]. The peptide linker and the gentamicin were grafted to a succinylated PVA hydrogel. In an *in vitro* experiment, it was shown that gentamicin was released upon incubation with exudate of a *P. aeruginosa* infected wound, however exudate of a non-infected wound was not able to cleave the peptide linker and release the gentamicin [140].

4. Conclusion. The ideal polymeric delivery system for infection prophylaxis

In order for a polymeric biomaterial to be a good candidate for use in infection prophylaxis, the system has to fulfill several requirements. The materials currently available in the clinic contribute to improved infection prophylaxis, by lowering the number of infections in patients. However, all of these materials have their own limitations. For instance PMMA lacks degradability, which is troublesome due to unfavorable release patterns of the antibiotic as well as permanent presence of a foreign body. Collagen on the other hand, can be biodegraded in the human body; however the inability for true sustained release can be an issue for its use. For the PDLLA coatings, the problem lies in the acidic degradation products that hinder bone regeneration and antibiotic action at the same time. Furthermore, all of these systems are rather passive than active in the sense that they are unable to respond and tailor their antibiotic release upon physiological changes in the human body, like temperature or presence of bacterial enzymes. Also the emergence of resistance in bacteria in hospitals worldwide by use and misuse of antibiotics limits the use of delivery systems that are based on conventional antibiotics. Therefore, research has also focused on encapsulating other antimicrobial compounds into biomaterials, such as modified antibiotics, antibiotic prodrugs, silver or antimicrobial peptides. All of these should have a broad antibacterial spectrum, with coverage of both Gram-positive and Gram-negative organisms.

Finally, a system that can respond to physiological stimuli and therefore can be applied minimal invasively, while sustaining the release of antibiotics over a period of several days can be advantageous. The introduction of linkers in the system, which can be cleaved upon exposure to enzymes produced by bacteria, or other stimuli given by bacterial pathogens, could produce a more effective drug delivery system. In conclusion, there is a wide variety of approaches investigated, all with their specific benefits over traditional delivery systems. But the many requirements for an optimal system make the development of the ideal system a significant challenge.

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References

[1] National Center for Biotechnology I. Infection. 2012.
[2] Scottish Intercollegiate Guidelines N. Antibiotic prophylaxis in surgery. A national clinical guideline. 2008.
[3] Greene LR. Guide to the elimination of orthopedic surgery surgical site infections: an executive summary of the Association for Professionals in Infection Control and Epidemiology elimination guide. Am J Infect Control 2012;40:384–6.
[4] Elek SD, Conen PE. The virulence of Staphylococcus pyogenes for man; a study of the problems of wound infection. Br J Exp Pathol 1957;38:573–86.
[5] Zimmerli W, Waldvogel FA, Vaudaux P, Nydegger UE. Pathogenesis of foreign body infection: description and characteristics of an animal model. J Infect Dis 1982;146:487–97.
[6] Busscher HJ, van der Mei HC, Subbiahdoss G, Jutte PC, van den Dungen JJ, Zaat SA, et al. Biomaterial-associated infection: locating the finish line in the race for the surface. SciTranslMed 2012;4:153rv10.
[7] Rochford ET, Richards RG, Moriarty TF. Influence of material on the development of device-associated infections. Clin Microbiol Infect 2012;18:1162–7.
[8] Trampuz A, Zimmerli W. Diagnosis and treatment of infections associated with fracture-fixation devices. Injury 2006;37:S59–66.
[9] Trampuz A, Widmer AF. Infections associated with orthopedic implants. Curr Opin Infect Dis 2006;19:349–56.
[10] Diefenbeck M, Muckley T, Hofmann GO. Prophylaxis and treatment of implant-related infections by local application of antibiotics. Injury 2006;37(Suppl. 2):S95–104.
[11] Schmidmaier G, Lucke M, Wildemann B, Haas NP, Raschke M. Prophylaxis and treatment of implant-related infections by antibiotic-coated implants: a review. Injury 2006;37:S105–12.
[12] Weinstein RA, Darouiche RO. Device-associated infections: a macroproblem that starts with microadherence. Clin Infect Dis 2001;33:1567–72.
[13] Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. Am J Infect Control 1999;27:97–132.
[14] Zimmerli W. Antibiotic prophylaxis. In: Rüedi TP, Buckley RE, Moran CG, editors. AO principles of fracture management. Davos Platz: AO Publishing; 2007. p. 425–33.
[15] Del Pozo JL, Patel R. Infection associated with prosthetic joints. N Engl J Med 2009;361:787–94.
[16] Boxma H, Broekhuizen T, Patka P, Oosting H. Randomised controlled trial of single-dose antibiotic prophylaxis in surgical treatment of closed fractures: the Dutch Trauma Trial. Lancet 1996;347:1133–7.
[17] Esposito S, Leone S. Prosthetic joint infections: microbiology, diagnosis, management and prevention. Int J Antimicrob Agents 2008;32:287–93.
[18] Glenny A, Song F. Antimicrobial prophylaxis in total hip replacement: a systematic review. Health Technol Assess 1999;3:1–57.
[19] Tamilvanan S, Venkateshan N, Ludwig A. The potential of lipid- and polymer-based drug delivery carriers for eradicating biofilm consortia on device-related nosocomial infections. J Control Release 2008;128:2–22.
[20] Aarestrup FM. Association between the consumption of antimicrobial agents in animal husbandry and the occurrence of resistant bacteria among food animals. Int J Antimicrob Agents 1999;12:279–85.
[21] Kardas P, Devine S, Golembesky A, Roberts C. A systematic review and meta-analysis of misuse of antibiotic therapies in the community. Int J Antimicrob Agents 2005;26:106–13.
[22] Tunney MM, Patrick S, Gorman SP, Nixon JR, Anderson N, Davis RI, et al. Improved detection of infection in hip replacements. J Bone Jt Surg Br Volume 1998;80-B:568–72.
[23] Norden CW. Osteomyelitis. In: Mandell GL, Douglas RG, Bennett JE, editors. Principles and practice of infectious diseases. New York: Churchill Livingstone; 1990. p. 922–30.
[24] Ochsner PE, Sirkin MS, Trampuz A. Acute infection. In: Rüedi TP, Buckley RE, Moran CG, editors. AO principles of fracture management. Davos Platz: AO Publishing; 2007. p. 521–41.
[25] Johnson EE, Buckley RE. Chronic infection and infected nonunion. In: Rüedi TP, Buckley RE, Moran CG, editors. AO principles of fracture management. Davos Platz: AO Publishing; 2007. p. 543–55.
[26] Patel R. Biofilms and antimicrobial resistance. Clin Orthop Relat Res 2005;437:41–7.
[27] Mack D, Fischer W, Krokotsch A, Leopold K, Hartmann R, Egge H, et al. The intercellular adhesin involved in biofilm accumulation of Staphylococcus epidermidis is a linear beta-1,6-linked glucosaminoglycan: purification and structural analysis. J Bacteriol 1996;178:175–83.
[28] Flemming H-C, Wingender J. The biofilm matrix. Nat Rev Micro 2010;8:623–33.
[29] Montanaro L, Poggi A, Visai L, Ravaioli S, Campoccia D, Speziale P, et al. Extracellular DNA in biofilms. Int J Artif Organs 2011;34:824–31.
[30] National Center for Biotechnology I. Biofilm. 2013.
[31] Donlan RM. Biofilms and device-associated infections. Emerg Infect Dis 2001;7:277–81.
[32] Donlan RM. Biofilms: microbial life on surfaces. Emerg Infect Dis 2002;8:881–90.
[33] Anderl JN, Franklin MJ, Stewart PS. Role of antibiotic penetration limitation in Klebsiella pneumoniae biofilm resistance to ampicillin and ciprofloxacin. Antimicrob Agents Chemother 2000;44:1818–24.
[34] Costerton JW. Biofilm theory can guide the treatment of device-related orthopaedic infections. Clin Orthop Relat Res 2005:7–11.
[35] von Eiff C, Heilmann C, Peters G. Staphylococcus epidermidis: why is it so successful? Clin Microbiol Infect 1998;4:297–300.
[36] Peng KT, Chen CF, Chu IM, Li YM, Hsu WH, Hsu RWW, et al. Treatment of osteomyelitis with teicoplanin-encapsulated biodegradable thermosensitive hydrogel nanoparticles. Biomaterials 2010;31:5227–36.
[37] Darouichi RO. Treatment of infections associated with surgical implants. N. Engl J Med 2004;350:1422–9.
[38] Rubin RJ, Harrington CA, Poon A, Dietrich K, Greene JA, Moiduddin A. The economic impact of Staphylococcus aureus infection in New York City hospitals. Emerg Infect Dis 1999;5:9–17.
[39] National Center for Biotechnology I. Antibiotic prophylaxis. 2012.
[40] Kaiser AB. Antimicrobial prophylaxis in surgery. N Engl J Med 1986;315:1129–38.
[41] Haas DW, Kaiser AB. Antimicrobial prophylaxis of infections associated with foreign bodies. In: Waldvogel FA, Bisno AL, editors. Infections associated with indwelling medical devices. Washington DC: John Wiley & Sons; 2000. p. 395–406.
[42] Jaeger M, Maier D, Kern WV, Südkamp NP. Antibiotics in trauma and orthopedic surgery – a primer of evidence-based recommendations. Injury 2006;37:S74–80.
[43] Gustilo RB, Merkow RL, Templeman D. The management of open fractures. J Bone Jt Surg Am 1990;72:299–304.
[44] Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. N Engl J Med 1992;326:281–6.
[45] Ito K, Perren SM. Biology and biomechanics in bone healing. In: Rüedi TP, Buckley RE, Moran CG, editors. AO principles of fracture management. Davos Platz: AO Publishing; 2007. p. 9–31.
[46] Deguchi T, Ishi A, Tanaka M. Binding of aminoglycoside antibiotics to acidic mucopolysaccharides. J Antibiot(Tokyo) 1978;31:150–5.
[47] Mingeot-Leclercq MP, Tulkens PM. Aminoglycosides: nephrotoxicity. Antimicrob Agents Chemother 1999;43:1003–12.
[48] Naughton CA. Drug-induced nephrotoxicity. Am Fam Physician 2008;78:743–50.
[49] Elyasi S, Khalili H, Dashti-Khavidaki S, Mohammadpour A. Vancomycin-induced nephrotoxicity: mechanism, incidence, risk factors and special populations. A literature review. Eur J Clin Pharmacol 2012;68:1243–55.
[50] Kubin CJ, Ellman TM, Phadke V, Haynes LJ, Calfee DP, Yin MT. Incidence and predictors of acute kidney injury associated with intravenous polymyxin B therapy. J Infect 2012;65:80–7.
[51] Durante-Mangoni E, Grammatikos A, Utili R, Falagas ME. Do we still need the aminoglycosides? Int J Antimicrob Agents 2009;33:201–5.
[52] Begg EJ, Barclay ML. Aminoglycosides-50 years on. Br J Clin Pharmacol 1995;39:597–603.
[53] Griffis CD, Metcalfe S, Bowling FL, Boulton AJM, Armstrong DG. The use of gentamicin-impregnated foam in the management of diabetic foot infections: a promising delivery system? Expert Opin Drug Deliv 2009;6:639–42.
[54] Raschke MJ, Schmidmaier G. Biologisierung von Implantaten in der Chirurgie des Stütz- und Bewegungsapparates. Der Unfallchirurg 2004;107:653–63.
[55] Barth RE, Vogely HC, Hoepelman AI, Peters EJ. 'To bead or not to bead?' Treatment of osteomyelitis and prosthetic joint-associated infections with gentamicin bead chains. Int J AntimicrobAgents 2011;38:371–5.
[56] Baudoux P, Bles N, Lemaire S, Mingeot-Leclercq M-P, Tulkens PM, Van Bambeke F. Combined effect of pH and concentration on the activities of gentamicin and oxacillin against Staphylococcus aureus in pharmacodynamic models of extracellular and intracellular infections. J Antimicrob Chemother 2007;59:246–53.
[57] Schlessinger D. Failure of aminoglycoside antibiotics to kill anaerobic, low-pH, and resistant cultures. Clin Microbiol Rev 1988;1:54–9.
[58] Madigan MT, Martinko JM, Parker J. Microbial growth control. Brock; biology of microorganisms. 2000.
[59] Berger-Bächi B, McCallum N. State of the knowledge of bacterial resistance. Injury 2006;37:S20–5.
[60] Lee SH, Lee JE, Baek WY, Lim JO. Regional delivery of vancomycin using pluronic F-127 to inhibit methicillin resistant Staphylococcus aureus (MRSA)

growth in chronic otitis media in vitro and in vivo. J Control Release 2004;96:1–7.
[61] Hajdu S, Lassnigg A, Graninger W, Hirschl AM, Presterl E. Effects of vancomycin, daptomycin, fosfomycin, tigecycline, and ceftriaxone on Staphylococcus epidermidis biofilms. J Orthop Res 2009:1361–5.
[62] Winkler H, Janata O, Berger C, Wein W, Georgopoulos A. In vitro release of vancomycin and tobramycin from impregnated human and bovine bone grafts. J Antimicrob Chemother 2000;46:423–8.
[63] Rathbone CR, Cross JD, Brown KV, Murray CK, Wenke JC. Effect of various concentrations of antibiotics on osteogenic cell viability and activity. J Orthop Res 2011;29:1070–4.
[64] Isefuku S, Joyner CJ, Simpson AH. Gentamicin may have an adverse effect on osteogenesis. J Orthop Trauma 2003;17:212–6.
[65] Halleem AA, Rouse MS, Lewallen DG, Hanssen AD, Steckelberg JM, Patel R. Gentamicin and vancomycin do not impair experimental fracture healing. Clin Orthop Relat Res 2004;427:22–4.
[66] McLaren AC. Alternative materials to acrylic bone cement for delivery of depot antibiotics in orthopaedic infections. Clin Orthop Relat Res 2004;427:101–6.
[67] Tunney MM, Ramage G, Patrick S, Nixon JR, Murphy PG, Gorman SP. Antimicrobial susceptibility of bacteria isolated from orthopedic implants following revision hip surgery. Antimicrob Agents Chemother 1998;42:3002–5.
[68] Buchholz HW, Engelbrecht H. Depot effects of various antibiotics mixed with Palacos resins. Chirurg 1970;41:511–5.
[69] Kuehn KD, Ege W, Gopp U. Acrylic bone cements: composition and properties. Orthop ClinNorth Am 2005;36:17–28. v.
[70] Serbetci K, Hasirci N. Recent developments in bone cements. Biomaterials in orthopedics. 2004. p. 241–86.
[71] Lewis G, Janna S. The in vitro elution of gentamicin sulfate from a commercially available gentamicin-loaded acrylic bone cement, VersaBond AB. J Biomed Mater Res B Appl Biomater 2004;71:77–83.
[72] Frutos CP, Diez PE, Barrales-Rienda JM, Frutos G. Validation and in vitro characterization of antibiotic-loaded bone cement release. Int J Pharm 2000;209:15–26.
[73] Engesaeter LB, Lie SA, Espehaug B, Furnes O, Vollset SE, Havelin LI. Antibiotic prophylaxis in total hip arthroplasty effects of antibiotic prophylaxis systemically and in bone cement on the revision rate of 22,170 primary hip replacements followed 0-14 years in the Norwegian Arthroplasty Register. Acta Orthop 2003;74:644–51.
[74] Weber FA, Lautenbach EEG. Revision of infected total hip arthroplasty. Clin Orthop Relat Res 1986:108–15.
[75] Hope PG, Kristinsson KG, Norman P, Elson RA. Deep infection of cemented total hip arthroplasties caused by coagulase-negative staphylococci. J Bone Jt Surg Br 1989;71:851–5.
[76] Yoshii E. Cytotoxic effects of acrylates and methacrylates: relationships of monomer structures and cytotoxicity. J Biomed Mater Res 1997;37:517–24.
[77] Kilian O, Hossain H, Flesch I, Sommer U, Nolting H, Chakraborty T, 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;90:210–22.
[78] Ruszczak Z, Friess W. Collagen as a carrier for on-site delivery of antibacterial drugs. Adv Drug Deliv Rev 2003;55:1679–98.
[79] Sorensen TS, Sorensen AI, Merser S. Rapid release of gentamicin from collagen sponge. In vitro comparison with plastic beads. Acta Orthop Scand 1990;61:353–6.
[80] El-Husseiny M, Patel S, MacFarlane RJ, Haddad FS. Biodegradable antibiotic delivery systems. J Bone Jt Surg Br Volume 2011;93-B:151–7.
[81] Schlapp M, Friess W. Collagen/PLGA microparticle composites for local controlled delivery of gentamicin. J Pharm Sci 2003;92:2145–51.
[82] Campoccia D, Montanaro L, Speziale P, Arciola CR. Antibiotic-loaded biomaterials and the risks for the spread of antibiotic resistance following their prophylactic and therapeutic clinical use. Biomaterials 2010;31:6363–77.
[83] Imbuluzqueta E, Elizondo E, Gamazo C, Moreno-Calvo E, Veciana J, Ventosa N, et al. Novel bioactive hydrophobic gentamicin carriers for the treatment of intracellular bacterial infections. Acta Biomater 2011;7:1599–608.
[84] Meyer JD, Falk RF, Kelly RM, Shively JE, Withrow SJ, Dernell WS, et al. Preparation and in vitro characterization of gentamycin-impregnated biodegradable beads suitable for treatment of osteomyelitis. J Pharm Sci 1998;87:1149–54.
[85] Obermeier A, Matl FD, Schwabe J, Zimmermann A, Kuhn KD, Lakemeier S, et al. Novel fatty acid gentamicin salts as slow-release drug carrier systems for anti-infective protection of vascular biomaterials. J Mater Sci Mater Med 2012;23:1675–83.
[86] Schnieders J, Gbureck U, Thull R, Kissel T. Controlled release of gentamicin from calcium phosphate-poly(lactic acid-co-glycolic acid) composite bone cement. Biomaterials 2006;27:4239–49.
[87] Vogt S, Kühn KD, Gopp U, Schnabelrauch M. Resorbable antibiotic coatings for bone substitutes and implantable devices. Materialwissenschaft und Werkstofftechnik 2005;36:814–9.
[88] Holzer B, Grüssner U, Brückner B, Houf M, Kiffner E, Schildberg FW, et al. Efficacy and tolerance of a new gentamicin collagen fleece (Septocoll) after surgical treatment of a pilonidal sinus. Colorectal Dis 2003;5:222–7.
[89] Friess W. Collagen–biomaterial for drug delivery. Eur J Pharm Biopharm 1998;45:113–36.
[90] Fuchs T, Stange R, Schmidmaier G, Raschke MJ. The use of gentamicin-coated nails in the tibia: preliminary results of a prospective study. Arch Orthop Trauma Surg 2011;131:1419–25.
[91] Gunatillake PA, Adhikari R. Biodegradable synthetic polymers for tissue engineering. Eur Cell Mater 2003;5:1–16.
[92] Bostman OM. Osteolytic changes accompanying degradation of absorbable fracture fixation implants. J Bone Jt Surg Br Volume 1991;73-B:679–82.
[93] Heidemann W, Jeschkeit-Schubbert S, Ruffieux K, Fischer JH, Jung H, Krueger G, et al. pH-stabilization of predegraded PDLLA by an admixture of water-soluble sodiumhydrogenphosphate—results of an in vitro- and in vivo-study. Biomaterials 2002;23:3567–74.
[94] Sung H-J, Meredith C, Johnson C, Galis ZS. The effect of scaffold degradation rate on three-dimensional cell growth and angiogenesis. Biomaterials 2004;25:5735–42.
[95] Wu L, Ding J. In vitro degradation of three-dimensional porous poly(d,l-lactide-co-glycolide) scaffolds for tissue engineering. Biomaterials 2004;25:5821–30.
[96] Agrawal CM, Athanasiou KA. Technique to control pH in vicinity of biodegrading PLA-PGA implants. J Biomed Mater Res 1997;38:105–14.
[97] Marcus Y, Sasson K, Fridkin M, Shechter Y. Turning low-molecular-weight drugs into prolonged acting prodrugs by reversible pegylation: a study with gentamicin. J Med Chem 2008;51:4300–5.
[98] Coessens V, Schacht E, Domurado D. Synthesis of polyglutamine and dextran conjugates of streptomycin with an acid-sensitive drug-carrier linkage. J Control Release 1996;38:141–50.
[99] Choi SK, Myc A, Silpe JE, Sumit M, Wong PT, McCarthy K, et al. Dendrimer-based multivalent vancomycin nanoplatform for targeting the drug-resistant bacterial surface. ACS Nano 2013;7:214–28.
[100] Rai M, Yadav A, Gade A. Silver nanoparticles as a new generation of antimicrobials. Biotechnol Adv 2009;27:76–83.
[101] Poulter N, Vasilev K, Griesser SS, Griesser HJ. Silver containing biomaterials. In: Moriarty TF, Zaat SAJ, Busscher HJ, editors. Biomaterials associated infection. New York: Springer; 2013. p. 355–78.
[102] Hetrick EM, Schoenfisch MH. Reducing implant-related infections: active release strategies. Chem Soc Rev 2006;35:780–9.
[103] Alt V, Bechert T, Steinrücke P, Wagener M, Seidel P, Dingeldein E, et al. An in vitro assessment of the antibacterial properties and cytotoxicity of nanoparticulate silver bone cement. Biomaterials 2004;25:4383–91.
[104] Montali A. Antibacterial coating systems. Injury 2006;37:S81–6.
[105] Pal S, Tak YK, Song JM. Does the antibacterial activity of silver nanoparticles depend on the shape of the nanoparticle? A study of the Gram-Negative Bacterium Escherichia coli. Appl Environ Microbiol 2007;73:1712–20.
[106] Travan A, Pelillo C, Donati I, Marsich E, Benincasa M, Scarpa T, et al. Non-cytotoxic silver nanoparticle-polysaccharide nanocomposites with antimicrobial activity. Biomacromolecules 2009;10:1429–35.
[107] Guo L, Yuan W, Lu Z, Li CM. Polymer/nanosilver composite coatings for antibacterial applications. Colloids Surfaces A: Physicochem Eng Asp 2013;439:69–83.
[108] Pelgrift RY, Friedman AJ. Nanotechnology as a therapeutic tool to combat microbial resistance. Adv Drug Deliv Rev 2013;65:1803–15.
[109] Silver S. Bacterial silver resistance: molecular biology and uses and misuses of silver compounds. FEMS Microbiol Rev 2003;27:341–53.
[110] Jenssen H, Hamill P, Hancock RE. Peptide antimicrobial agents. Clin Microbiol Rev 2006;19:491–511.
[111] Zasloff M. Antimicrobial peptides of multicellular organisms. Nature 2002;415:389–95.
[112] Epand RM, Vogel HJ. Diversity of antimicrobial peptides and their mechanisms of action. Biochim Biophys Acta 1999;1462:11–28.
[113] Yeung AY, Gellatly S, Hancock RW. Multifunctional cationic host defence peptides and their clinical applications. Cell Mol Life Sci 2011;68:2161–76.
[114] Kang S-J, Park SJ, Mishig-Ochir T, Lee B-J. Antimicrobial peptides: therapeutic potentials. Expert Rev Anti-infective Ther 2014;12:1477–86.
[115] Costa F, Carvalho IF, Montelaro RC, Gomes P, Martins MC. Covalent immobilization of antimicrobial peptides (AMPs) onto biomaterial surfaces. Acta Biomater 2011;7:1431–40.
[116] Daghighi S, Sjollema J, van der Mei HC, Busscher HJ, Rochford ETJ. Infection resistance of degradable versus non-degradable biomaterials: an assessment of the potential mechanisms. Biomaterials 2013;34:8013–7.
[117] Andreopoulos AG, Hatzi EC, Doxastakis M. Controlled release systems based on poly(lactic acid). An in vitro and in vivo study. J Mater Sci Mater Med 2000;11:393–7.
[118] Kanellakopoulou K, Galanakis N, Giamarellos-Bourboulis EJ, Rifiotis C, Papakostas K, Andreopoulos A, et al. Treatment of experimental osteomyelitis caused by methicillin-resistant Staphylococcus aureus with a biodegradable system of lactic acid polymer releasing pefloxacin. J Antimicrob Chemother 2000;46:311–4.
[119] Koort JK, Makinen TJ, Suokas E, Veiranto M, Jalava J, Tormala P, et al. Sustained release of ciprofloxacin from an osteoconductive poly(DL)-lactide implant. Acta Orthop 2008;79:295–301.
[120] Mauduit J, Bukh N, Vert M. Gentamycin/poly (lactic acid) blends aimed at sustained release local antibiotic therapy administered per-operatively. III. The case of gentamycin sulfate in films prepared from high and low molecular weight poly (DL-lactic acids). J Control Release 1993;25:43–9.
[121] Mauduit J, Bukh N, Vert M. Gentamycin/poly(lactic acid) blends aimed at sustained release local antibiotic therapy administered per-operatively. II.

The case of gentamycin sulfate in high molecular weight poly(dl-lactic acid) and poly(l-lactic acid). J Control Release 1993;23:221–30.
[122] Mauduit J, Bukh N, Vert M. Gentamycin/poly(lactic acid) blends aimed at sustained release local antibiotic therapy administered per-operatively. I. The case of gentamycin base and gentamycin sulfate in poly(dl-lactic acid) oligomers. J Control Release 1993;23:209–20.
[123] Suzuki A, Terai H, Toyoda H, Namikawa T, Yokota Y, Tsunoda T, et al. A biodegradable delivery system for antibiotics and recombinant human bone morphogenetic protein-2: a potential treatment for infected bone defects. J Orthop Res 2006;24:327–32.
[124] Vogt S, Kühn KD, Ege W, Pawlik K, Schnabelrauch M. Novel polylactide-based release systems for local antibiotic therapies. Materialwissenschaft und Werkstofftechnik 2003;34:1041–7.
[125] Wei G, Kotoura Y, Oka M, Yamamuro T, Wada R, Hyon SH, et al. A bioabsorbable delivery system for antibiotic treatment of osteomyelitis. The use of lactic acid oligomer as a carrier. J Bone Jt Surg Br Volume 1991;73-B:246–52.
[126] Zhang X, Wyss UP, Pichora D, Goosen MFA. A mechanistic study of antibiotic release from biodegradable poly(D,L-lactide) cylinders. J Control Release 1994;31:129–44.
[127] Zhang XICH, Wyss UP, Pichora DAVI, Goosen MFA. Biodegradable controlled antibiotic release devices for osteomyelitis: optimization of release properties. J Pharm Pharmacol 1994;46:718–24.
[128] Garvin KL, Miyano JA, Robinson D, Giger D, Novak J, Radio S. Polylactide/polyglycolide antibiotic implants in the treatment of osteomyelitis. A canine model. J Bone Jt Surg Am 1994;76:1500–6.
[129] Kim K, Luu YK, Chang C, Fang D, Hsiao BS, Chu B, et al. Incorporation and controlled release of a hydrophilic antibiotic using poly(lactide-co-glycolide)-based electrospun nanofibrous scaffolds. J Control Release 2004;98:47–56.
[130] Chang HI, Perrie Y, Coombes AGA. Delivery of the antibiotic gentamicin sulphate from precipitation cast matrices of polycaprolactone. J Control Release 2006;110:414–21.
[131] Teo EY, Ong SY, Khoon C, Mark S, Zhang Z, Lu J, et al. Polycaprolactone-based fused deposition modeled mesh for delivery of antibacterial agents to infected wounds. Biomaterials 2011;32:279–87.
[132] Mader JT, Calhoun J, Cobos J. In vitro evaluation of antibiotic diffusion from antibiotic-impregnated biodegradable beads and polymethylmethacrylate beads. Antimicrob Agents Chemother 1997;41:415–8.
[133] Neut D, Kluin OS, Crielaard BJ, van der Mei HC, Busscher HJ, Grijpma DW. A biodegradable antibiotic delivery system based on poly(trimethylene carbonate) for the treatment of osteomyelitis. Acta Orthop 2009;80:514–9.
[134] Zhang Z, Kuijer R, Bulstra SK, Grijpma DW, Feijen J. The in vivo and in vitro degradation behavior of poly(trimethylene carbonate). Biomaterials 2006;27:1741–8.
[135] Pego AP, Van Luyn MJ, Brouwer LA, van Wachem PB, Poot AA, Grijpma DW, et al. In vivo behavior of poly(1,3-trimethylene carbonate) and copolymers of 1,3-trimethylene carbonate with D,L-lactide or epsilon-caprolactone: degradation and tissue response. J Biomed Mater Res A 2003;67:1044–54.
[136] Sripriya R, Kumar MS, Sehgal PK. Improved collagen bilayer dressing for the controlled release of drugs. J Biomed Mater Res B Appl Biomater 2004;70:389–96.
[137] Veyries ML, Couarraze G, Geiger S, Agnely F, Massias L, Kunzli B, et al. Controlled release of vancomycin from Poloxamer 407 gels. Int J Pharm 1999;192:183–93.
[138] Simões SMN, Veiga F, Torres-Labandeira JJ, Ribeiro ACF, Sandez-Macho MI, Concheiro A, et al. Syringeable Pluronic-α-cyclodextrin supramolecular gels for sustained delivery of vancomycin. Eur J Pharm Biopharm 2012;80:103–12.
[139] Woo GL, Mittelman MW, Santerre JP. Synthesis and characterization of a novel biodegradable antimicrobial polymer. Biomaterials 2000;21:1235–46.
[140] Suzuki Y, Tanihara M, Nishimura Y, Suzuki K, Kakimaru Y, Shimizu Y. A new drug delivery system with controlled release of antibiotic only in the presence of infection. J Biomed Mater Res 1998;42:112–6.