Applications of local antimicrobial delivery systems in veterinary medicine

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Local application of antimicrobials to treat or prevent infections is not a new concept. Irrigation of wounds with an antimicrobial solution has, for instance, been used for years and may be appropriate for prophylaxis.[1] With this method, however, the antimicrobial is absorbed almost immediately, with no prolongation of effect. Furthermore, the potential for toxicoses is no different than with systemic administration, because there is no control over the rate of absorption. For these reasons, local antimicrobial delivery systems that allow continuous release of antimicrobials over an extended period have been developed. Such systems are typically used to treat localized infections in which tissues are devitalized and ischemic, preventing penetration of antimicrobials following systemic administration,[2-6] such as post-traumatic osteomyelitis. With these types of infections, the causative bacteria often produce glycocalyx that, in turn, helps create a biofilm that further protects the bacteria from systemically administered antimicrobials.[7,8] Use of local antimicrobial delivery systems circumvents these obstacles, producing high antimicrobial concentrations at the site of infection with low concurrent systemic concentrations.[5,6,9-12]

In addition to treatment, local antimicrobial delivery systems have been used for prophylaxis. In particular, they have been used to prevent infection of implants expected to remain in the body for prolonged periods, such as total joint implants, vascular grafts, pacemaker leads, and IV catheters.

There are 2 essential components for any local antimicrobial delivery system: an appropriate antimicrobial directed against the causative bacteria and a compatible delivery system. The present article provides a detailed look at the appropriate construction and application of a system for local antimicrobial delivery.

Antimicrobials

Antimicrobials used in local delivery systems must be effective against the causative bacteria and compatible with the delivery system. In most instances, the antimicrobial to be used should be chosen on the basis of results of bacterial culture and susceptibility testing. When this is not possible, or when the system is used for prophylaxis, a broad-spectrum antimicrobial effective against the pathogens most likely to be at the site should be chosen. Particularly when the system is used for prophylaxis, a bactericidal antimicrobial should be chosen.

The antimicrobial used must be water-soluble if delivery is dependent on ready diffusion or controlled expulsion from an implant. It should be stable during formation of the implant, as well as at body temperature over time, and should not directly affect the structural or mechanical properties of the implant or have any adverse effects on local tissues. Ideally, concentration of the antimicrobial at the site of implantation should greatly exceed the minimum inhibitory concentration for the causative organism, but the antimicrobial would be only slowly absorbed or not absorbed into the systemic circulation.[13]

Various classes of antimicrobials have been studied to determine whether they are appropriate for use in local delivery systems, and results suggest that not all antimicrobials can be used in such systems. However, there is no clear consensus as to which antimicrobial is the most ideal, and it appears that the specific antimicrobial that is most appropriate will depend on the situation. Factors such as speed and adequacy of elution, duration of activity, and local reactions or toxicoses must be considered.

Delivery Systems

The delivery system should be chosen on the basis of its intended use. Regardless of use, the system should be nonreactive in the body and stable for as long as antimicrobial therapy is desired. Some systems are designed to provide mechanical strength; others are designed to degrade over time, avoiding the need for removal of the implant. The system should allow the antimicrobial to diffuse out via a concentration gradient,[14] ideally maintaining a constant release so that a steady-state antimicrobial concentration can be achieved. Some systems consist of implantable pumps that provide a continuous infusion, but the pump reservoir must be refilled periodically and eventually removed.

Two main types of delivery systems are available: biodegradable and nonbiodegradable. Antimicrobials

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are typically contained within a reservoir or within the matrices of the implant material making up the delivery system.[15] With matrix implants, antimicrobial is incorporated evenly throughout the material and is released by diffusion. These types of implants are typically characterized by an initial rapid release of antimicrobial followed by a slow steady rate of release. With reservoir implants, antimicrobial is located in a central core surrounded by a permeable polymer (with or without incorporation of antimicrobial in the surrounding material). Antimicrobial is released by diffusion, and the thickness of the polymer helps dictate the rate of release. One major drawback of reservoir implants is the possibility of rapid release of a large amount of antimicrobial if the integrity of the polymer is compromised. In addition to matrix and reservoir implants, implantable pumps and other atypical delivery systems are available.

Nonbiodegradable implants—The most commonly used nonbiodegradable matrix implant is **polymethyl methacrylate (PMMA)**, a type of bone cement. Characteristics of antimicrobial-impregnated PMMA have been extensively studied, and most of the considerations applicable to use of this material are relevant to other local antimicrobial delivery systems.

Polymethyl methacrylate is manufactured by mixing powdered polymer with a liquid monomer. The material hardens in approximately 5 to 10 minutes into a porous adhesive material. The powdered polymer can be mixed with liquid or powdered antimicrobial before the monomer is added, resulting in suspension of the antimicrobial throughout the PMMA matrix. However, the polymerization process is exothermic[6,16-18]; therefore, any antimicrobial incorporated into PMMA must remain stable at temperatures up to 100 C.

Antimicrobial-impregnated PMMA beads can be prepared in the surgical suite at the time of implantation or can be prepared ahead of time and sterilized with ethylene oxide gas. Commercially prepared antimicrobial beads are available in Europe but not in the United States, and in an in vitro study[19] of the release of antimicrobial from PMMA beads, a greater amount of gentamicin eluted from commercially prepared beads over a longer period than from handmade beads. Beads can be fabricated by hand or by injecting the material into a mold before it hardens. Individual beads can be made, or the beads can be fashioned around a piece of surgical steel wire or other strong suture material so that they are strung together, making it easier to remove them from the surgical site. Polymethyl methacrylate beads must eventually be removed from the surgical site, necessitating a second surgical procedure. Although antimicrobial-impregnated PMMA beads are most often used in orthopedic procedures, use in soft-tissue procedures has also been reported.[20]

Release of antimicrobials from PMMA is bimodal. There is rapid release during the first 24 hours after implantation followed by continuous sustained release that can last from weeks to years.[6,21-24] Rate of release of antimicrobials from PMMA is partially dependent on pore size and permeability of the cement,[25] and because the various brands of PMMA differ in regard to pore size and permeability, rate of release of antimicrobials also varies. There are conflicting reports[2,3,12,17,19,21,23,25-28] concerning which brand of PMMA offers the most consistent rate of antimicrobial elution. In addition, some studies have found that a particular brand of PMMA[a] appears to yield better elution characteristics with aminoglycoside antimicrobials, whereas another[b] is better with penicillins. Still other studies have found no significant differences among brands of PMMA. Other factors that have been shown to alter the rate of elution of antimicrobials from PMMA include the size and surface area of the implant, the amount of fluid flowing past the implant, and the amount of antimicrobial added to the implant.[6,22,29] More antimicrobial will be released from small rough beads with a greater surface-to-volume ratio[30]; large smooth implants may release less antimicrobial at a slower rate. More vascular tissue such as granulation tissue will result in faster elution than will less vascular tissue such as bone, and the greater the amount of antimicrobial added to beads, the greater and longer the release will be.[4,6,9,31]

Many studies[2-4,32-38] have found that the amount of powdered antimicrobial added to PMMA can affect the mechanical strength of the implant. Polymethyl methacrylate is typically available in 20-g packages, and addition of 0.25 to 1 g of antimicrobial to a 20-g package of PMMA has been shown to have no effect on the mechanical strength of the implants that are produced. However, addition of > 2.25 g of antimicrobial powder to a 20-g package of PMMA will negatively affect mechanical strength.[36] In addition, use of liquid antimicrobial rather than antimicrobial powder compromises mechanical strength. Cefazolin apparently affects the mechanical strength of PMMA implants less than gentamicin does[39]; however, gentamicin is only available as a liquid in the United States.

Mechanical strength is not an issue when using antimicrobial-impregnated PMMA beads. Therefore, higher concentrations of antimicrobials can be used, provided there is no effect on polymerization.[40] An antimicrobial powder-to-PMMA powder ratio > 1:5 will prevent hardening of the cement.[6]

Polymethyl methacrylate implants impregnated with aminoglycoside antimicrobials, predominantly gentamicin and tobramycin, have been used successfully to control infection.[10,21,22,27,29,31,38,39,40-52] These antimicrobials are heat stable, bactericidal, and effective against most pathogens commonly encountered during surgery.[5] Gentamicin-impregnated PMMA beads are commercially available in Europe but not in the United States. In the United States, tobramycin is available in powdered form and is effective against gentamicin-resistant organisms.[5] In an in vitro study,[53] tobramycin beads were associated with higher antimicrobial concentrations throughout the 28-day study period than were beads containing cefazolin, ciprofloxacin, clindamycin, ticarcillin, or vancomycin. In vivo, tobramycin concentrations exceeded the breakpoint susceptibility concentration for 28 days in seroma fluid and granulation tissue of dogs in which impregnated beads were placed in an experimentally created tibial defect[53]; serum tobramycin concentrations were less

than the toxic concentration. In a separate study,[12] bactericidal concentrations of tobramycin were eluted from total hip arthroplasty components for 48 hours in 20 people, although serum and urine concentrations remained low. A recent in vivo study[52] involving human patients found no significant difference in infection rate between patients with acute open fractures treated with tobramycin-impregnated beads or IV administration of antimicrobials. However, because numbers and types of fractures and initial treatment with antimicrobials varied, comparisons may not have been accurate. Beads impregnated with gentamicin have been shown in vitro to release bactericidal concentrations of the drug for at least 30 days,[54] and although gentamicin-impregnated PMMA implants have been used in Europe for many years, there have been no reports of renal toxicoses associated with their use.

Similarly, PMMA implants impregnated with cephalosporin antimicrobials have been widely used.[5,21,22,39,55-57] The most commonly used cephalosporins are cephalexin and cefazolin, first-generation cephalosporins with excellent activity against gram-positive organisms such as *Streptococcus* spp and *Staphylococcus* spp. Cephalexin-impregnated PMMA implants have been shown to have antibacterial activity for as long as 26 weeks in vitro.[56] Cefazolin is rapidly eluted from PMMA implants in vitro,[53] and in dogs (3 dogs for each antimicrobial tested), concentrations in seroma fluid and granulation tissue were high for 2 weeks after implantation. Implantation of PMMA beads impregnated with ceftazidime, a third-generation cephalosporin, eradicated *Pseudomonas* osteomyelitis in 8 rabbits after 15 days of treatments.[57] Although release of cephalosporins appears to be more rapid than the release of aminoglycoside antimicrobials, cephalosporin-impregnated PMMA appears to be useful in controlling infection.

Impregnation of PMMA with other antimicrobials has met with varying success. Fluoroquinolones, clindamycin, penicillins, clavulanic acid-amoxicillin, and lincosamides have all been evaluated, with inconsistent results[5,16,21-24,36,38,40,48,53,55,58,59]; chloramphenicol and tetracycline, on the other hand, apparently cannot withstand the polymerization process.[34,36] Few studies of impregnating PMMA with a mixture of antimicrobials have been performed. In some studies,[3,6] mixing 2 antimicrobials changed the elution rates of both, often by increasing the rate of 1 and slowing the rate of the other. In other studies,[31,49] combining antimicrobials did not have any effect on elution rates or enhanced the elution rates of both. Because so little is known about antimicrobial combinations, it is probably wise to use only 1 antimicrobial at a time and select the antimicrobial on the basis of results of bacterial culture and susceptibility testing or on the basis of the pathogens most likely to be encountered.

Although PMMA has been shown to be an effective matrix for local antimicrobial delivery systems, it has its disadvantages. Polymethyl methacrylate beads are not biodegradable and, therefore, must eventually be removed, requiring a second surgical procedure. Additionally, PMMA in a wound may incite fluid accumulation, which could impede successful delivery of antimicrobials to surrounding tissues. Finally, because the antimicrobial is suspended throughout the PMMA matrix, which does not degrade, release will never be 100%. It has been demonstrated that biologically active antimicrobial was present in PMMA discs even after in vitro elution levels had tapered off, suggesting that small undetectable amounts of antimicrobial will continue to be released for the duration of the implant's life in situ.[44]

Other nonbiodegradable materials have also been used for local antimicrobial delivery systems. Magnetically controlled release systems have been developed and consist of magnetic beads dispersed in an antimicrobial impregnated polymer.[15] External application of a magnetic frequency near the implant causes antimicrobial to be released faster than with simple diffusion. This allows for somewhat more controlled delivery, but again, the implant must be removed at some time after implantation.

Biodegradable implants—Since the initial work with PMMA, there has been a search to develop biodegradable matrix implants. A potential advantage of such implants is that the entire amount of antimicrobial is eventually released. However, care must be taken to ensure that the implants do not degrade too quickly, resulting in potentially dangerous release of a large amount of antimicrobial. Many of the formulations that have been developed are still in the research stage and are not yet being used clinically.

Polylactide-polyglycolide is a biodegradable polymer of aliphatic polyesters historically used as an absorbable suture material. It is extremely nonreactive and degrades in a predictable fashion by nonenzymatic hydrolysis of the ester bonds.[60] As with PMMA, antimicrobials can be incorporated during formation of the polymer. Consistent results have been obtained in vitro and in vivo following incorporation of clindamycin,[38] vancomycin,[38,61,62] gentamicin,[63] tobramycin,[38] ampicillin anhydrate,[64] cefazolin,[60] and ciprofloxacin[65] in polylactide-polyglycolide implants. A study[61] of rabbits with experimentally induced *Staphylococcus* osteomyelitis found that implantation of vancomycin-impregnated beads suppressed bacterial concentration by 100-fold after 4 weeks. In dogs with experimentally induced osteomyelitis,[63] implantation of gentamicin-impregnated polylactide-polyglycolide beads significantly reduced the prevalence of infection, compared with the control treatment, but results were not significantly different from those obtained with antimicrobial-impregnated PMMA beads. A study[66] of rats in which polylactide-polyglycolide implants impregnated with dideoxykanamicin B were implanted found that concentrations of antimicrobial in surrounding bone were high for 6 weeks, though antimicrobial activity was not assayed. Polylactide can be formulated with or without polyglycolide, and varying the ratio of polymers as well as the molecular weight can prolong the elution time and decrease the initial rapid release of antimicrobial.[38,61,62] Creating 2-layered beads, with the antimicrobial-polymer comprising the inner layer, also extends elution time.[62] Studies[38,63,65] comparing elution charac-

teristics of polylactide-polyglycolide versus PMMA revealed comparable antimicrobial release. An in vitro study[38] found that tobramycin and clindamycin eluted from PMMA at concentrations greater than the breakpoint susceptibility concentrations for more than 90 days, whereas they eluted from polylactide-polyglycolide beads at the same concentrations for up to 65 days, depending on the composition of beads. One benefit of polylactide-polyglycolide is that it can be formulated for a desired duration of elution, be it days or weeks.

Hydroxyapatite is a calcium phosphate ceramic.[c] Although it is biodegradable, it can also offer some mechanical support during the healing process, because it has the same composition as bones and teeth. Bone can grow into hydroxyapatite implants as they degrade, preventing the formation of dead space and maintaining stability. The material can be formed into a variety of implants but most often is used as beads, and it can be impregnated with various antimicrobials. Gentamicin,[67,68,d,e] cephalexin,[69] flomoxef,[68,70] and other antimicrobials[68,71,72] have been found to have good elution characteristics. In rabbits with experimentally induced *Staphylococcus aureus* osteomyelitis, implantation of gentamicin-impregnated hydroxyapatite beads suppressed but did not eradicate infection.[67] In a study[71] of dogs with experimentally induced osteomyelitis treated with antimicrobial-impregnated granules, hydroxyapatite was found to have been absorbed by 10 weeks. The infection appeared to be suppressed after 4 weeks, but this conclusion was made on the basis of clinical impressions, not on the basis of results of bacterial culture. Most studies of antimicrobial-impregnated hydroxyapatite beads have found that antimicrobials were released for periods ranging from 2 weeks to 90 days. Calcium phosphate composites can be manufactured in various manners, which may alter elution times. For example, use of a porous rather than dense formulation has been shown to result in a greater release of antimicrobial over a longer period in vitro.[e] Others have found that additives such as water-insoluble gel,[70] lipid,[72] or polymers[70,71,73] may decrease the initial rapid release of antimicrobial and prolong elution time. A study[67] comparing elution of gentamicin from hydroxyapatite verus PMMA found that local concentrations of gentamicin in rats with hydroxyapatite implants were 2.5 times as high and lasted 1.2 times as long. This study also reported that *S aureus* osteomyelitis was completely eradicated by 3 weeks of treatment. A separate study[54] found that cumulative in vitro elution of ceftiofur and gentamicin was greater for hydroxyapatite than for PMMA for 30 days.

A biodegradable bone cement consisting of **poly(propylene fumarate or glycol-fumarate) cross-linked with methylmethacrylate monomer (PPF-MMA)** has recently been developed.[74-76] The matrix incorporates calcium carbonate and tricalcium phosphate particulate; therefore, degradation of PPF-MMA implants appears to be compatible with physiologic bone remodeling, allowing new bone ingrowth.[76] An in vivo study[74] found that PPF-MMA implants were 15% degraded in 3 months. This gradual degradation is advantageous when the implant is meant to provide structural support. Increasing the amount of methylmethacrylate can increase the strength of the implant but also increases resistance to degradation. In vivo studies of PPF-MMA implants impregnated with vancomycin or gentamicin have shown that after 3 weeks, PPF-MMA is as effective as PMMA in suppressing or preventing experimentally induced osteomyelitis.[75] Pharmacokinetic studies with the same antimicrobials in rats found that PPF-MMA implants elute higher concentrations of antimicrobial than do PMMA implants.[74]

Other biodegradable implants made with fibrin,[77-79,f] bone,[80,81] and collagen[82-85] are also being studied. Fibrin, formed by the coagulation of fibrinogen with thrombin and calcium ions, acts as a tissue adhesive and promotes tissue regeneration.[77] The addition of antimicrobials to this mixture may prolong the clotting time of fibrin, but the effect appears to be dose dependent.[78] Fibrin-antimicrobial clots have been used in a variety of clinical situations, including filling bone defects resulting from osteomyelitis or preventing infection during revision of joint arthroplasties.[77,f]

A recent study[79] found that a fibrin-cefotaxim mixture was successful in the treatment of anal fistulas in 69 humans. An in vitro study[78] demonstrated that although remnants of the clot may remain for up to 2 weeks, the antimicrobials (including ampicillin, clindamycin, gentamicin, and tobramycin) had been completely eluted by 96 hours or earlier.

As a treatment for chronic osteomyelitis in 28 human patients,[80] cancellous bone grafts were mixed with antimicrobials selected on the basis of results of susceptibility testing and sealed into defects with fibrin glue. Clinical signs of osteomyelitis resolved in all but 1 patient, and success was partially attributed to the fact that fibrin promotes vascularization, and its presence causes the antimicrobial to be eluted at a slower prolonged rate. Demineralized bone and bone grafts, alone or mixed with gelatin and cephalothin or tobramycin, have been used to treat experimentally induced osteomyelitis in rabbits; however, antimicrobials were administered parenterally as well.[81] An advantage to this delivery system was that new bone formation was underway by 2 weeks and complete by 8 weeks. Prophylactically, fibrin-bone allografts impregnated with antimicrobial were found to prevent infection in 51 patients undergoing revision of a total hip arthroplasty.[f]

Collagen has been formed into sponges impregnated with gentamicin or amikacin.[82,83,85] In vitro studies have shown that the release is too fast for clinical use, comparable to administration of gentamicin in saline solution,[82] but in vivo studies have shown otherwise. A study[85] of rats with superficial wounds, for instance, showed a constant release of gentamicin or amikacin for 3 days and almost complete suppression of experimental *Pseudomonas* infection. A study[83] of 10 human patients with osteomyelitis indicated that local gentamicin concentrations were still high after 6 days, and the antimicrobial was completely eluted at about 2 weeks. Some collagen sponges are formulated as wound dressings that are meant to be removed, but fibrin and collagen do have the advantage of being

biodegradable. However, the rate of degradation is fast, so such implants can be used only for a short time. Commercially available gentamicin-impregnated collagen sponges are available in Europe but not in the United States. Although there have been no reports of adverse effects, there is a slight risk of immune reactions, because the implant may be derived from human or bovine sources.

Plaster of paris (or gypsum) is a calcium sulfate hemihydrate that has been used as a local antimicrobial delivery system.[59,86-90,g] It is biodegradable but takes a long time to deteriorate, usually weeks to months. Experimentally, some dogs and rabbits have had transient increases in serum calcium concentration and alkaline phosphatase activity, but no clinical abnormalities have been detected.[87,88,91] Plaster of paris has been predominantly used in orthopedic surgery, because it does not inhibit bone ingrowth. Elution characteristics vary depending on the antimicrobial that is used, but those that seem to result in elution of longer duration include fusidic acid and gentamicin.[88,90] Like many other local antimicrobial delivery systems, there is an initial rapid release of antimicrobial. An in vitro study[g] of gentamicin-impregnated plaster of paris found that 80% of the drug was released within the first 48 hours. Microbiologic assays indicated that bactericidal concentrations of the drug were present for 14 days, the length of the test period.

Glyceryl monostearate (GMS) is a newer compound that has been developed as a short-term local antimicrobial delivery system.[92,93] In vitro studies[93] with ciprofloxacin and cefazolin indicate release durations of 80 and 25 hours, respectively, into agar gel. Activity of the antimicrobials was not tested, but an in vivo study[92] of rats with subcutaneous infection, duration of release and effective activity of cefazolin was 3 days. Multiple GMS implants were placed to release a specific amount of antimicrobial over a given time. This system is geared to provide controlled but not prolonged treatment to a wound site.

Implantable pumps—Several antimicrobial delivery systems that do not involve a biodegradable or non-biodegradable matrix implant have been developed. One of the most commonly used is an implantable pump, a nondegradable system that pumps out a controlled amount of antimicrobial from a subcutaneous reservoir through a catheter inserted into the infection site. Several types of pumps are available.[15] In vivo studies[94,95] with rabbits and dogs show that high local antimicrobial concentrations can be achieved, even in cortical bone, for the duration of pump implantation. Clinical work with humans has shown good success rates with increased familiarization with the procedure.[96-98] Clinically, pumps have been used in dogs and horses to treat osteomyelitis. There is no appreciable rise in systemic antimicrobial concentrations and, therefore, no toxic effects. Placement of the pump is done in 2 stages: subcutaneous implantation of the pump followed by debridement of the wound itself and tunneling of the catheter to the site. There is a risk of infection of the pump site itself, but this can be overcome with experience in the placement technique.

Pumps are advantageous in that they allow a continuous measured outflow of drug as long as is needed. Many of the pumps are refillable. Pumps are usually used only to treat resistant infections. In these instances, it is important to obtain an adequate sample for bacterial culture and susceptibility testing and to choose an appropriate antimicrobial prior to implantation of the pump. The antimicrobial must be stable at body temperature and not interfere with the structure of the pump itself. For instance, 1 type of implantable pump[h] was shown to result in crystallization of vancomycin,[99] whereas tobramycin, gentamicin, clindamycin, and amikacin did not have any such effects over a period of 3 weeks. As with other nonbiodegradable systems, a second surgery is required to remove the pump.

Atypical delivery systems—Various atypical antimicrobial delivery systems for treatment or prevention of infection have also been developed. Many of the most common pathogens, such as *S aureus* and *Pseudomonas aeruginosa*, are capable of clinging to a surface and secreting a polysaccharide matrix, or glycocalyx, causing strong adherence and accumulation of bacteria and debris[7,8] and interfering with the host immune response[28] and the activity of antimicrobials.[100] The film is extremely difficult to eradicate once established.

Any implant, including orthopedic implants, vascular grafts, and IV catheters can be coated with antimicrobial-impregnated material to prevent formation of a biofilm. Studies of titanium implants coated with hydroxyapatite or calcium phosphate found that mechanical strength of the implants was not affected and that bone ingrowth may have been enhanced.[101] Titanium implants can also be coated by creating an oxide with phosphoric or sulfuric acid to attach an antimicrobial such as gentamicin sulfate.[102] With this porous coating, antimicrobial activity could be maintained for 2 weeks. Polylactide-polyglycolide with gentamicin has also been used to coat orthopedic implants, with elution of antimicrobial at antibacterial concentrations for 15 days in vitro.[103]

A comparison of vascular grafts with gelatin coatings soaked in rifampicin versus uncoated grafts found no significant difference in prevalence of infection,[104] but a clinical trial of grafts coated with fibrin glue and soaked in sisomicin found no clinical evidence of infection after 1 month.[105] However, there was no control group with which to compare results. A porous polyurethane matrix, polyethylene glycol, that can release ciprofloxacin for 5 days in vitro has been designed.[8] Another polyurethane surface copolymer (acrylic acid-acrylamide) impregnated with gentamicin and grafted to pacemaker leads that were implanted subcutaneously in 6 rats challenged with *S aureus* prevented infection.[106] In vitro studies with this material found that gentamicin was completely released within 3 to 6 weeks. Gentamicin-soaked collagen sponges have been implanted with leads, but simply dipping the leads in gentamicin solution was found to be more effective.[84] Studies in humans with IV catheters soaked in rifampin and minocycline show good prophylaxis, with activity lasting up to 4 weeks.[107]

There has been work in recent years with multivesicular liposomes as delivery systems, and a formulation of liposomes[i] able to contain a variety of agents is available.[108] An advantage is the slow release as liposomal layers are gradually dissolved. In addition, liposomes are sequestered by phagocytes of the reticuloendothelial system, resulting in even slower clearance.[109] Liposome foam formulated with gentamicin was found to suppress infection in rats if administered 2 to 4 days prior to challenge exposure, but the number of test subjects was low.[108] An in vivo study[109] of sponges that incorporate tobramycin-encapsulated liposomes found no significant difference in prevalence of infection, compared with open-cell polyurethane sponges containing tobramycin. Recent work with liposomes involves incorporating them with an antimicrobial into a cross-linked gelatin implant coating for implants.[110]

A select group of local antimicrobial delivery systems has been developed for the treatment of periodontal disease. Minocycline and doxycycline polymers can be delivered as a gel into the periodontal pockets and release antimicrobial over time as they dissolve.[111-113] Currently, doxycycline gel is the most commonly used formulation in veterinary medicine.[j] Metronidazole has also been formulated into a gel that hardens when it comes into contact with water.[111,113] It does degrade, but requires 2 applications 2 weeks apart. Ethylene-vinyl acetate copolymers have been formed into fibers and impregnated with tetracycline. Though effective, they can be difficult to place and require removal after 10 days.[111,113] All of these devices are effective in the treatment and prevention of periodontitis, but most are successful only in conjunction with scaling and root planing.

Advantages of Local Antimicrobial Delivery

The main advantage of local antimicrobial delivery systems is that local concentrations that well exceed the minimum inhibitory concentration can be achieved at the site of infection, even in the face of ischemic tissue. This has led to a proposal that the effective local concentrations of antimicrobials be defined by other terms, because the minimum inhibitory concentration is based on the serum concentrations needed to kill an organism. Organisms that may be resistant to achievable serum concentrations of a particular drug may be susceptible at the concentrations achieved with local delivery.

The second major advantage of local antimicrobial delivery systems is that although local concentrations of the antimicrobial may be high, serum concentrations typically are low or undetectable. This decreases the risk of adverse drug reactions, systemic toxicoses, and allergic reactions.

Implants can also be designed to deliver antimicrobials for a prolonged period, which may be particularly desirable when treating chronic infections such as chronic osteomyelitis. One study[20] found that gentamicin was still diffusing from PMMA 5 years after implantation. This is of particular benefit for soft-tissue implants such as pacemaker leads and IV catheters, for which the risk of infection increases the longer they are present.

Disadvantages of Local Antimicrobial Delivery

There are a few disadvantages to the use of local antimicrobial delivery systems. Although most are nonreactive, some may cause foreign body reactions or inhibit components of the immune response such as late complement proteins, peripheral lymphocytes, and polymorphonuclear cell function.[5,6,11,114] These effects are mild, however, and are usually manifested histologically rather than clinically, and there are no data suggesting that local delivery systems inhibit or delay wound healing.

Another potential drawback of some local antimicrobial delivery systems is their requirement of a second surgery for removal. The implants are usually well-encapsulated by early fibrous tissue by 10 to 14 days after implantation, making surgical removal difficult in some instances.[14] In addition, there are concerns that if antimicrobial concentrations fall sufficiently and become less than the minimum inhibitory concentration, antimicrobial resistance could develop. There have been no documented instances of this, however.

Conclusions

Many methods for local antimicrobial delivery are available. Such systems, however, should not be expected to take the place of proper aseptic technique, surgical debridement of contaminated wounds, and, when appropriate, parenteral use of antimicrobials. Although most surgical infections are caused by skin contaminants, it is crucial to obtain samples for bacterial culture and susceptibility testing prior to implantation of local delivery systems, especially with chronic infections. Although there are no absolute criteria for when to use or not use local antimicrobial delivery systems, a veterinarian should consider the use of these systems when treating acute extensive localized infections and deep chronic infections that are resistant to traditional surgical and medical management treatments.

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[a]Palacos bone cement, Biomet Inc, Warsaw, Ind.
[b]Simplex P Radiopaque bone cement, Howmedica Inc, Rutherford, NJ.
[c]Bone Source, Osteogenics Inc, Richardson, Tex.
[d]Tyndall D, Waller S, Cornell CN, et al. Treatment of experimental osteomyelitis using antibiotic impregnated bone graft substitute vs systematically administered antibiotics (abstr), in *Proceedings*. 38th Orthop Res Soc Meet 1992;218.
[e]Spadaro JA, DiStefano RJ, Chase SE. Evaluation of dense and porous antimicrobial hydroxyapatite materials (abstr), in *Proceedings*. 38th Orthop Res Soc Meet 1992;430.
[f]Braun A, Papp J. Revision surgery of the hip with an antibiotic impregnated fibrin bone allograft (abstr). *J Bone Joint Surg Br* 1993;75(suppl 1):10.
[g]McGarvey L, Santschi EM. Elution of gentamicin from plaster of paris-gentamicin beads (abstr), in *Proceedings*. Am Coll Vet Surg Annu Symp 1998;30.
[h]Arrow pumps, Arrow International Corp, Reading, Pa.
[i]Depo-Foam, DepoTech Corp, San Diego, Calif.
[j]Doxirobe, Pharmacia & Upjohn, Kalamazoo, Mich.

References

1. Rosenstein BD, Wilson FC, Funderburk CH. The use of bacitracin irrigation to prevent infection in postoperative skeletal wounds. *J Bone Joint Surg Am* 1989;71:427–430.

2. Buchholz HW, Elson RA, Heinert K. Antibiotic-loaded acrylic cement: current concepts. *Clin Orthop* 1984;190:96–108.

3. Trippel SB. Antibiotic-impregnated cement on total joint arthroplasty. *J Bone Joint Surg Am* 1986;68:1297–1302.

4. Calhoun JH, Mader JT. Antibiotic beads in the management of surgical infections. *Am J Surg* 1989;157:443–449.

5. Henry SL, Galloway KP. Local antibacterial therapy for the management of orthopaedic infections: pharmacokinetic considerations. *Clin Pharmacokinet* 1995;29:36–45.

6. Tobias KMS, Schneider RK, Besser TE. Use of antimicrobial-impregnated polymethyl methacrylate. *J Am Vet Med Assoc* 1996;208: 841–845.

7. Chang CC, Merritt K. Effect of *Staphylococcus epidermidis* on adherence of *Pseudomonas aeruginosa* and *Proteus mirabilis* to polymethyl methacrylate (PMMA) and gentamicin-containing PMMA. *J Orthop Res* 1991;9:284–288.

8. Kwok CS, Wan C, Hendricks S, et al. Design of infection-resistant antibiotic-releasing polymers: I. Fabrication and formulation. *J Controlled Release* 1999;62:289–299.

9. Wahlig H, Dingeldein E, Buchholz HW, et al. Pharmacokinetic study of gentamicin-loaded cement on total hip replacements: comparative effects of varying dosage. *J Bone Joint Surg Br* 1984;66:175–179.

10. Eckman JB, Henry SL, Mangino PD, et al. Wound and serum levels of tobramycin with the prophylactic use of tobramycin-impregnated polymethyl methacrylate beads in compound fractures. *Clin Orthop* 1988;237:213–215.

11. Henry SL, Seligson D, Mangino P, et al. Antibiotic-impregnated beads: part I: bead implantation versus systemic therapy. *Orthop Review* 1991;20:242–247.

12. Brien WW, Salvati EA, Klein R, et al. Antibiotic impregnated bone cement in total hip arthroplasty: an in vivo comparison of the elution properties of tobramycin and vancomycin. *Clin Orthop* 1993;296:242–248.

13. Kanellakopoulou K, Giamarellos-Bourboulis EJ. Carrier systems for the local delivery of antibiotics in bone infections. *Drugs* 2000;59:1223–1232.

14. Stabile DE, Jacobs AM. Development and application of antibiotic-loaded bone cement beads. *J Am Podiatr Med Assoc* 1990;80:354–359.

15. Dash AK, Cudworth GC. Therapeutic applications of implantable drug delivery systems. *J Pharmacol Toxicol Methods* 1998;40:1–12.

16. Chapman MW, Hadley WK. The effect of polymethyl methacrylate and antibiotic combinations on bacterial viability: an in vitro and in vivo study. *J Bone Joint Surg Am* 1976;58:76–81.

17. Quinlan W, Mehigan C. The release of antibiotics from bone cement. *Ir J Med Sci* 1978;147:425–429.

18. Fish DN, Hoffman HM, Danziger LH. Antibiotic-impregnated cement use in US hospitals. *Am J Hosp Pharm* 1992;49: 2469–2474.

19. Nelson CL, Griffin FM, Harrison BH, et al. In vitro elution characteristics of commercially and noncommercially prepared antibiotic PMMA beads. *Clin Orthop* 1992;284:303–309.

20. Aubrey DA, Jenkins NH, Morgan WP, et al. The use of gentamicin-PMMA chains in abdominal surgery: a pilot study of prophylaxis against wound infection. *Pharmatherapeutica* 1986;4: 536–540.

21. Wahlig H, Dingeldein E. Antibiotics and bone cements: experimental and clinical long-term observations. *Acta Orthop Scand* 1980;51:49–56.

22. Picknell B, Mizen L, Sutherland R. Antibacterial activity of antibiotics in acrylic bone cement. *J Bone Joint Surg Br* 1977;59:302–307.

23. Welch AB. Antibiotics in acrylic bone cement. In vitro studies. *J Biomed Mater Res* 1978;12:679–700.

24. Wininger DA, Fass RJ. Antibiotic-impregnated cement and beads for orthopedic infections. *Antimicrob Agents Chemother* 1996;40:2675–2679.

25. Kuechle DK, Landon GC, Musher DM, et al. Elution of vancomycin, daptomycin, and amikacin from acrylic bone cement. *Clin Orthop* 1991;264:302–308.

26. Elson RA, Jephcott AE, McGechie DB, et al. Antibiotic-loaded acrylic cement. *J Bone Joint Surg Br* 1977;59:200–205.

27. Hoff SF, Fitzgerald RH, Kelly PJ. The depot administration of penicillin G and gentamicin in acrylic bone cement. *J Bone Joint Surg Am* 1981;63:798–804.

28. Kendall RW, Duncan CP, Smith JA, et al. Persistence of bacteria on antibiotic loaded acrylic depots: a reason for caution. *Clin Orthop* 1996;329:273–280.

29. Schurman DJ, Trindade C, Hirshman HP, et al. Antibiotic-acrylic bone cement composites: studies of gentamicin and Palacos. *J Bone Joint Surg Am* 1978;60:978–984.

30. Walenkamp G. Small PMMA beads improve gentamicin release. *Acta Orthop Scand* 1989;60:668–669.

31. Masri BA, Duncan CP, Beauchamp CP. Long-term elution of antibiotics from bone-cement: an in vivo study using prosthesis of antibiotic-loaded acrylic cement (PROSTALAC) system. *J Arthroplasty* 1998;13:331–338.

32. Lautenschlager EP, Marshall GW, Marks KE, et al. Mechanical strength of acrylic bone cements impregnated with antibiotics. *J Biomed Mater Res* 196;10:837–845.

33. Lautenschlager EP, Jacobs JJ, Marshall GW, et al. Mechanical properties of bone cements containing large doses of antibiotic powders. *J Biomed Mater Res* 1976;10:929–938.

34. Ger E, Dall D, Miles T, et al. Bone cement and antibiotics. *S Afr Med J* 1977;51:276–279.

35. Nelson RC, Hoffman RO, Burton TA. The effect of antibiotic additions on the mechanical properties of acrylic cement. *J Biomed Mater Res* 1978;12:473–490.

36. Murray WR. Use of antibiotic-containing bone cement. *Clin Orthop* 1984;190:89–95.

37. Davies JP, O'Connor DO, Burke DW, et al. Influence of antibiotic impregnation on the fatigue life of Simplex P and Palacos R acrylic bone cements, with and without centrifugation. *J Biomed Mater Res* 1989;23:379–397.

38. Mader JT, Calhoun J, Cobos J. In vitro evaluation of antibiotic diffusion from antibiotic-impregnated biodegradable beads and polymethyl methacrylate beads. *Antimicrob Agents Chemother* 1997;41:415–418.

39. Weisman DL, Olmstead ML, Kowalski JJ. In vitro evaluation of antibiotic elution from polymethyl methacrylate (PMMA) and mechanical assessment of antibiotic-PMMA composites. *Vet Surg* 2000;29:245–251.

40. Hill J, Klenerman L, Trustey S, et al. Diffusion of antibiotics from acrylic bone-cement in vitro. *J Bone Joint Surg Br* 1977;59: 197–199.

41. Elson RA, Jephcott AE, McGechie DB, et al. Bacterial infection and acrylic cement in the rat. *J Bone Joint Surg Br* 1977;59: 452–457.

42. Wahlig H, Dingeldein E, Bergmann R, et al. The release of gentamicin from polymethyl methacrylate beads: an experimental and pharmacokinetic study. *J Bone Joint Surg Br* 1978;60:270–275.

43. Welch AB. Antibiotics in acrylic bone cement. In vivo studies. *J Biomed Mater Res* 1978;12:843–855.

44. Bayston R, Milner RDG. The sustained release of antimicrobial drugs from bone cement: an appraisal of laboratory investigations and their significance. *J Bone Joint Surg Br* 1982;64:460–464.

45. Josefsson G, Gudmundosson G, Kolmert L, et al. Prophylaxis with systemic antibiotics versus gentamicin bone cement in total hip arthroplasty: a five-year survey of 1688 hips. *Clin Orthop* 1990;253:173–178.

46. Evans RP, Nelson CL. Gentamicin-impregnated polymethacrylate beads compared with systemic antibiotic therapy in the treatment of osteomyelitis. *Clin Orthop* 1993;295:37–42.

47. Nelson CL, Evans RP, Blaha JD, et al. A comparison of gentamicin-impregnated polymethyl methacrylate bead implantation to conventional parenteral antibiotic therapy in infected total hip and knee arthroplasty. *Clin Orthop* 1993;295:96–101.

48. Ostermann PAW, Henry SL, Seligson D. The role of local antibiotic therapy in the management of compound fractures. *Clin Orthop* 1993;295:102–111.

49. Seyral P, Zannier A, Argenson JN, et al. The release in vitro of vancomycin and tobramycin from acrylic bone cement. *J Antimicrob Chemother* 1994;33:337–339.

50. Nelson CL, Hickman SG, Harrison BH. Elution characteristics of gentamicin-PMMA beads after implantation in humans. *Orthopedics* 1994;17:415–416.

51. Scott CP, Higham PA, Dumbleton JH. Effectiveness of bone cement containing tobramycin. *J Bone Joint Surg Br* 1999;81:440–443.

52. Moehring HD, Gravel C, Chapman MW, et al. Comparison of antibiotic beads and intravenous antibiotics in open fractures. *Clin Orthop* 2000;372:254–261.

53. Adams K, Couch L, Cierny G, et al. In vitro and in vivo evaluation of antibiotic diffusion from antibiotic-impregnated polymethyl methacrylate beads. *Clin Orthop* 1992;278:244–252.

54. Ethell MT, Bennett RA, Brown MP, et al. In vitro elution of gentamicin, amikacin, and ceftiofur from polymethyl methacrylate and hydroxyapatite cement. *Vet Surg* 2000;29:375–382.

55. Levin PD. The effectiveness of various antibiotics in methyl methacrylate. *J Bone Joint Surg Br* 1975;57:234–237.

56. Hughes S, Field CA, Kennedy MRK, et al. Cephalosporins in bone cement: studies in vitro and in vivo. *J Bone Joint Surg Br* 1979;61:96–100.

57. Tomczak RL, Dowdy N, Storm T, et al. Use of ceftazidime-impregnated polymethyl methacrylate beads in the treatment of *Pseudomonas* osteomyelitis. *J Foot Surg* 1989;28:542–546.

58. Rodeheaver GT, Rukstalis D, Bono M, et al. A new model of bone infection used to evaluate the efficacy of antibiotic-impregnated polymethyl methacrylate cement. *Clin Orthop* 1983;178: 303–311.

59. Bowyer GW, Cumberland N. Antibiotic release from impregnated pellets and beads. *J Trauma* 1994;36:331–335.

60. Jacob E, Cierny G, Zorn K, et al. Delayed local treatment of rabbit tibial fractures with biodegradable cefazolin microspheres. *Clin Orthop* 1997;336:278–285.

61. Calhoun JH, Mader JT. Treatment of osteomyelitis with a biodegradable antibiotic implant. *Clin Orthop* 1997;341:206–214.

62. Liu SJ, Ueng SWN, Chan EC, et al. In vitro elution of vancomycin from biodegradable beads. *J Biomed Mater Res* 1999;48:613–620.

63. Garvin KL, Miyano JA, Robinson D, et al. Polylactide/polyglycolide antibiotic implants in the treatment of osteomyelitis: a canine model. *J Bone Joint Surg Am* 1994;76:1500–1506.

64. Jacob E, Setterstrom JA, Durwood DE, et al. Evaluation of biodegradable ampicillin anhydrate microcapsules for local treatment of experimental staphylococcal osteomyelitis. *Clin Orthop* 1991;267:237–244.

65. Teupe C, Meffert R, Winckler S, et al. Ciprofloxacin-impregnated poly-L-lactic acid drug carrier: new aspects of a resorbable drug delivery system in local antimicrobial treatment of bone infections. *Arch Orthop Trauma Surg* 1992;112:33–35.

66. Wei G, Kotoura Y, Oka M, et al. A bioabsorbable delivery system for antibiotic treatment of osteomyelitis: the use of lactic acid oligomer as a carrier. *J Bone Joint Surg Br* 1991;73:246–252.

67. Korkusuz F, Uchida A, Shinto Y, et al. Experimental implant-related osteomyelitis treated by antibiotic-calcium hydroxyapatite ceramic composites. *J Bone Joint Surg Br* 1993;75:111–114.

68. ShintoY, Uchida A, Korkusuz F, et al. Calcium hydroxyapatite ceramic used as a delivery system for antibiotics. *J Bone Joint Surg Br* 1992;74:600–604.

69. Otsuka M, Matsuda Y, Kokubo T, et al. Drug release from a novel self-setting bioactive glass bone cement containing cephalexin and its physicochemical properties. *J Biomed Mater Res* 1995;29:33–38.

70. Takechi M, Miyamoto Y, Ishikawa K, et al. Effects of added antibiotics on the basic properties of anti-washout-type fast-setting calcium phosphate cement. *J Biomed Mater Res* 1998;39:308–316.

71. Eitenmuller J, Schmidt KH, Peters G, et al. Experimental and preliminary clinical experience with absorbable calcium phosphate granules containing an antibiotic or antiseptic for the local treatment of osteomyelitis. *J Hosp Infect* 1985;6(suppl):177–184.

72. Yamamura K, Iwata H, Yotsuyanagi T. Synthesis of antibiotic-loaded hydroxyapatite beads and in vitro drug release testing. *J Biomed Mater Res* 1992;26:1053–1064.

73. Ikada Y, Hyon SH, Jamshidi K. Release of antibiotic from composites of hydroxyapatite and poly(lactic acid). *J Controlled Release* 1985;2:179–186.

74. Gerhart TN, Roux RD, Horowitz G, et al. Antibiotic release from an experimental biodegradable bone cement. *J Orthop Res* 1988;6:585–592.

75. Gerhart TN, Roux RD, Hanff PA, et al. Antibiotic-loaded biodegradable bone cement for prophylaxis and treatment of experimental osteomyelitis in rats. *J Orthop Res* 1993;11:250–255.

76. Frazier DD, Lathi VK, Gerhart TN, et al. Ex vivo degradation of a poly(propylene glycol-fumarate) biodegradable particulate composite bone cement. *J Biomed Mater Res* 1997;35:383–389.

77. Braun A, Gussbacher A, Heine WD, et al. Fibrin-antibiotic complex: laboratory investigation and clinical results. In: Uhthoff HK, Stahl E, eds. *Current concepts of infections in orthopaedic surgery*. Berlin: Springer-Verlag Inc, 1985;265–294.

78. Greco F, dePalma L, Spagnolo N, et al. Fibrin-antibiotic mixtures: an in vitro study assessing the possibility of using a biologic carrier for local drug delivery. *J Biomed Mater Res* 1991;25:39–51.

79. Patrlj L, Kocman B, Martinac M, et al. Fibrin glue-antibiotic mixture in the treatment of anal fistulae: experience with 69 cases. *Dig Surg* 2000;17:77–80.

80. Lack W, Bosch P, Arbes H. Chronic osteomyelitis treated by cancellous homografts and fibrin adhesion. *J Bone Joint Surg Br* 1987;69:335–337.

81. Petri WH. Evaluation of antibiotic-supplemented bone allograft in a rabbit model. *J Oral Maxillofac Surg* 1991;49:392–396.

82. Sorenson TS, Sorenson AI, Merser S. Rapid release of gentamicin from collagen sponge: in vitro comparison with plastic beads. *Acta Orthop Scand* 1990;61:353–356.

83. Ipsen T, Jorgensen PS, Damholt V, et al. Gentamicin-collagen sponge for local applications: 10 cases of chronic osteomyelitis followed for a year. *Acta Orthop Scand* 1991;62:592–594.

84. vanWachem PB, vanLuyn MJA, deWit AW, et al. Tissue reactions to bacteria-inoculated rat lead samples. I. Effect of local gentamicin release through vicinal sponge or solution-dipping. *J Biomed Mater Res* 1997;35:217–232.

85. Grzybowski J, Kolodziej W, Trafny EA, et al. A new anti-infective collagen dressing containing antibiotics. *J Biomed Mater Res* 1997;36:163–167.

86. Miclau T, Dahners LE, Lindsey RW. In vitro pharmacokinetics of antibiotic release from locally implantable materials. *J Orthop Res* 1993;11:627–632.

87. deWet IS, Jansen C. The use of plaster of Paris to fill large defects in bone: an experimental study to determine the ultimate fate of a measured amount of plaster of Paris inserted into the bone of a living animal. *S Afr J Surg* 1973;11:1–8.

88. Mackey D, Varlet A, Debeaumont D. Antibiotic loaded plaster of Paris pellets: an in vitro study of a possible method of local antibiotic therapy in bone infection. *Clin Orthop* 1982;167: 263–268.

89. Dahners LE, Funderburk CH. Gentamicin-loaded plaster of Paris as a treatment of experimental osteomyelitis in rabbits. *Clin Orthop* 1987;219:278–282.

90. Mousset B, Benoit M-A, Delloye C, et al. Biodegradable implants for potential use in bone infection. An in vitro study of antibiotic-loaded bone calcium sulphate. *Int Orthop* 1995;19:157–161.

91. Dacquet V, Varlet A, Tandogan RN, et al. Antibiotic-impregnated plaster of Paris beads: trials with teicoplanin. *Clin Orthop* 1992;282:241–249.

92. Allababidi S, Shah JC. Kinetics and mechanism of release from glyceryl monostearate-based implants: evaluation of release in a gel simulating in vivo implantation. *J Pharm Sci* 1998;87:738–744.

93. Allababidi S, Shah JC. Efficacy and pharmacokinetics of site-specific cefazolin delivery using biodegradable implants in the prevention of post-operative wound infections. *Pharm Res* 1998; 15:325–333.

94. Perry CR, Rice S, Rittersbusch JK, et al. Local administration of antibiotics with an implantable osmotic pump. *Clin Orthop* 1985;192:284–290.

95. Budsberg SC, Brown J. Distribution of clindamycin in cortical bone during direct local infusion of the canine tibia. *J Orthop Trauma* 1994;8:383–389.

96. Perry CR, Rice S, Ritterbusch JK, et al. Antibiotic administration using and implantable drug pump in the treatment of osteomyelitis: a preliminary report. *Contemp Orthop* 1985;10:45–52.

97. Perry CR, Pearson RL. Local antibiotic delivery in the treatment of bone and joint infections. *Clin Orthop* 1991;263:215–226.

98. Perry CR, Hulsey RE, Mann FA, et al. Treatment of acutely infected arthroplasties with incision, drainage, and local antibiotics delivered via an implantable pump. *Clin Orthop* 1992;281:216–223.

99. Perry CR, Ellington LL, Becker A, et al. Antibiotic stability in an implantable pump. *J Orthop Res* 1986;4:494–498.

100. Arizono T, Oga M, Sugioka Y. Increased resistance of bacteria after adherence to polymethyl methacrylate, an in vitro study. *Acta Orthop Scand* 1992;63:661–664.

101. Maxian SH, Zawadsky JP, Dunn MG. Mechanical and histological evaluation of amorphous calcium phosphate and poorly crystallized hydroxyapatite coatings on titanium implants. *J Biomed Mater Res* 1993;27:717–728.

102. Dunn DS, Raghavan S, Volz RG. Gentamicin sulfate attachment and release from anodized Ti-6Al-4V orthopedic materials. *J Biomed Mater Res* 1993;27:895–900.

103. Price JS, Tencer AF, Arm DM, et al. Controlled release of antibiotics from coated orthopedic implants. *J Biomed Mater Res* 1996;30:281–286.

104. Braithwaite BD, Davies B, Heather BP, et al. Early results of a randomized trial of rifampicin-bonded Dacron grafts for extra-anatomic vascular reconstruction. *Br J Surg* 1998;85:1378–1381.

105. Osada T, Yammamura K, Yano K, et al. Distribution and serum concentration of sisomicin released from fibrin glue-sealed Dacron graft in the rat and human. *J Biomed Mater Res* 2000;52:53–57.

106. vanWachem PB, vanLuyn MJA, deWit AW, et al. Tissue reactions to bacteria-inoculated rat lead samples. II. Effect of local gentamicin release though surface-modified polyurethane tubing. *J Biomed Res* 1997;35:233–247.

107. Raad I, Hanna H. Intravascular catheters impregnated with antimicrobial agents: a milestone in the prevention of bloodstream infections. *Support Care Cancer* 1999;7:386–390.

108. Grayson LS, Hansbrough JF, Zapata-Sirvent R, et al. Soft tissue infection prophylaxis with gentamicin encapsulated in multivesicular liposomes: results from a prospective, randomized trial. *Crit Care Med* 1995;23:84–91.

109. Price CI, Horton JW, Baxter CR. Topical liposomal delivery of antibiotics in soft tissue infection. *J Surg Res* 1990;49:174–178.

110. DiTizio V, Karlgard C, Lilge L, et al. Localized drug delivery using crosslinked gelatin gels containing liposomes: factors influencing liposome stability and drug release. *J Biomed Mater Res* 2000; 51:96–106.

111. Killoy W. Chemical treatment of periodontitis: local delivery of antimicrobials. *Int Dent J* 1998;48(suppl 1):305–315.

112. Hayashi K, Takada K, Hirasawa M. Clinical and microbiological effects of controlled-release local delivery of minocycline on periodontitis in dogs. *Am J Vet Res* 1998;59:464–467.

113. Ciancio SG. Site specific delivery of antimicrobial agents for periodontal disease. *Gen Dent* 1999;47:172–178.

114. Petty W. The effect of methylmethacrylate on bacterial phagocytosis and killing by human polymorphonuclear leukocytes. *J Bone Joint Surg Am* 1978;60:752–757.