Local Antibiotic Therapy in Osteomyelitis

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ABSTRACT

The local delivery of antibiotics in the treatment of osteomyelitis has been used safely and effectively for decades. Multiple methods of drug delivery have been developed for the purposes of both infection treatment and prophylaxis. The mainstay of treatment in this application over the past 20 years has been non-biodegradable polymethylmethacrylate, which has the advantages of excellent elution characteristics and structural support properties. Biodegradable materials such as calcium sulfate and bone graft substitutes have been used more recently for this purpose. Other biodegradable implants, including synthetic polymers, are not yet approved for use but have demonstrated potential in laboratory investigations. Antibiotic-impregnated metal, a recent development, holds great promise in the treatment and prophylaxis of osteomyelitis in the years to come.

KEYWORDS: Antibiotic, osteomyelitis, biodegradable, elution, methylmethacrylate

The effective use of local antibiotic treatment of osteomyelitis requires a detailed understanding of the characteristics and pathophysiology of this disease. The most common pathogens responsible for osteomyelitis in humans are *Staphylococcus* species, followed by Enterobacteriaceae and *Pseudomonas* species. Osteomyelitis associated with an implant is caused by *Staphylococcus epidermidis* more than 90% of the time.[1] Diabetic foot infections are generally polymicrobial infections with mixed gram-positive and gram-negative bacteria, of both aerobic and anaerobic types.

The pathophysiology of chronic osteomyelitis is multifactorial and begins with spread of bacteria. Bacteria may reach the bone by hematogenous seeding, direct inoculation, or airborne contamination. Once in contact with bone and/or implant, bacteria have various different mechanisms to facilitate cell-cell and cell-implant adhesion. Bacteria become sessile, reduce their metabolic rate, and produce a biofilm that protects them from antimicrobials, opsonization, and phagocytosis. *Staphylococcus aureus*, for example, binds fibronectin through adhesins. Fibronectin, a glycoprotein found in connective tissue, has been shown to mediate and facilitate interaction between bacteria and foreign bodies.[2] Antibiotics act at different levels to inhibit bacterial infection. As an example, clindamycin reduces glycocalyx formation, facilitating the action of phagocytic cells and suppressing infection by glycocalyx-forming organisms.[3] Additionally, clindamycin preferentially binds to the 50S subunit of bacterial ribosomes, inhibiting bacterial protein synthesis. However, the antibiotic concentrations required to penetrate and kill bacteria enclosed in biofilm are 10 to 100 times the standard bactericidal concentration, often making systemic therapy unsafe and ineffective in such cases.[4]

Chronic bacterial infection of bone blocks cortical blood supply and leads to the formation of sequestra, pockets of necrotic cortical bone, which are avascular and difficult to treat. The sequestra are often surrounded by involucrum, new bone formed in response to the sequestra.[5] It is the presence of the sequestra in chronic osteomyelitis that mandates surgical intervention.

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Osteomyelitis; Guest Editors, Christopher J. Salgado, M.D., and Lawrence B. Colen, M.D.

Semin Plast Surg 2009;23:100–107.

DOI 10.1055/s-0029-1214162. ISSN 1535-2188.

Table 1 Commonly Used Vehicles for Local Antibiotic Delivery and Future Options

	Chemical Compound	Commercially Available?	Structural?	Types of abx That Can Be Used	Resorbable	Elution Characteristics	Speed of Resorption
Bone cement	PMMA	Palacos G (Zimmer) Simplex P (Synthes)	Yes	Hydrophilic and heat stable	No	Quick initial release; majority of release over first 4 weeks	NA
Bone graft substitute	Calcium sulfate	OsteoSet (Wright Medical)	No	Any	Yes	Similar to cement	4–8 weeks
Synthetic polymer	Multiple including polylactic acid	NA	Modifiable	Any	Yes	Can be modified indefinitely	Variable
Metal	Titanium	NA	Yes	Any	No	None; drug covalently bonded to metal	NA

Abx, antibiotics; NA, not applicable. Impregnated polymer and metal implants are not yet commercially available. Polymethylmethacrylate (PMMA) is not resorbable.

Acute infections are usually successfully treated with intravenous antibiotics. Chronicity of a bone infection can develop secondary to a variety of factors. The presence of foreign bodies and necrotic bone contributes to continued infection. In addition, properties specific to the pathogen itself, such as the ability of bacteria to remain intracellular, produce a protective film, and maintain a slow metabolic rate all impair the host's ability to eliminate infection. Patient factors including obesity and smoking, as well as systemic diseases such as diabetes and peripheral vascular disease, are also responsible for impaired host response to infection.[1]

Chronic osteomyelitis generally presents as recurrent or intermittent disease and occasionally associated late reactivation of infection. Latent periods can last decades and have been reported as long as 80 years.[6] Radiographic signs of osteomyelitis can be subtle and need to be correlated with clinical presentation. Loss of trabecular markings, elevation of the periosteum, cortical scalloping, medullary involvement, and focal osteopenia are indications of osteomyelitis on standard radiographs. Computed tomography (CT) scans may show a sequestrum with surrounding involucrum. Magnetic resonance imaging (MRI) can demonstrate a subperiosteal fluid collection as well as a Brodie abscess, a subacute or chronic metaphyseal abscess of a bone, occurring as a pus-filled cavity surrounded by a wall of dense fibrous tissue and usually found in the metaphyses of the long bones.

SURGICAL INTERVENTIONS

Surgical management of chronic osteomyelitis has changed drastically in the past 25 years with the use of flaps and vascularized bone grafts. Because of the impaired blood supply to the affected regions, as well as decreased ability of the host immune system to clear infections, surgical intervention is almost always necessary. Thorough debridement of bone in chronic osteomyelitis is essential and is often the primary factor in eliminating infection.

Such debridement often causes a large dead space that needs to be managed effectively to prevent recurrence of infection. The management of the dead space in this setting includes closed irrigation systems, local soft tissue flaps, vascularized free flaps, as well as a variety of methods for local antibiotic delivery (Table 1).

LOCAL ANTIBIOTIC THERAPY

The local use of antibiotics to prevent skeletal infections was incorporated into general practice with the development of joint arthroplasty in Europe in the 1970s. Buchholz and Engelbrecht reported in a sentinel paper that penicillin, erythromycin, and gentamicin mixed into the cement used to affix prostheses to bone was found to provide high concentrations of antibiotics for extended periods of time, facilitating the use of antibiotics in infection prophylaxis for joint arthroplasty.[7] In addition to this role, local antibiotic therapy has been instituted for treatment of arthroplasty infections, prophylaxis for open fractures, and treatment of chronic osteomyelitis. In 1979, Klemm created gentamicin-impregnated beads and used them to occupy dead space after debridement of infected bone. In more than 100 patients, a cure rate of 91.4% was achieved.[8]

Over the past three decades, numerous advantages with antibiotic-impregnated beads over systemic therapy have been recognized (Fig. 1). Placement of these beads is a simple procedure and often performed at time of initial debridement of chronic osteomyelitis or open fracture. Beads are generally prepared from commercially available cement just prior to placement in the operating room. Bead placement aids significantly in the management of large dead-space defects and bathes the hematoma and/or seroma in constantly high levels of antibiotic. Aside from the possibility of persistent drainage at the wound site, local antibiotic therapy with beads decreases the risk of complications of systemic antibiotic therapy including end-organ failure and gastrointestinal side effects. The safety of this type of treatment has been reviewed in the

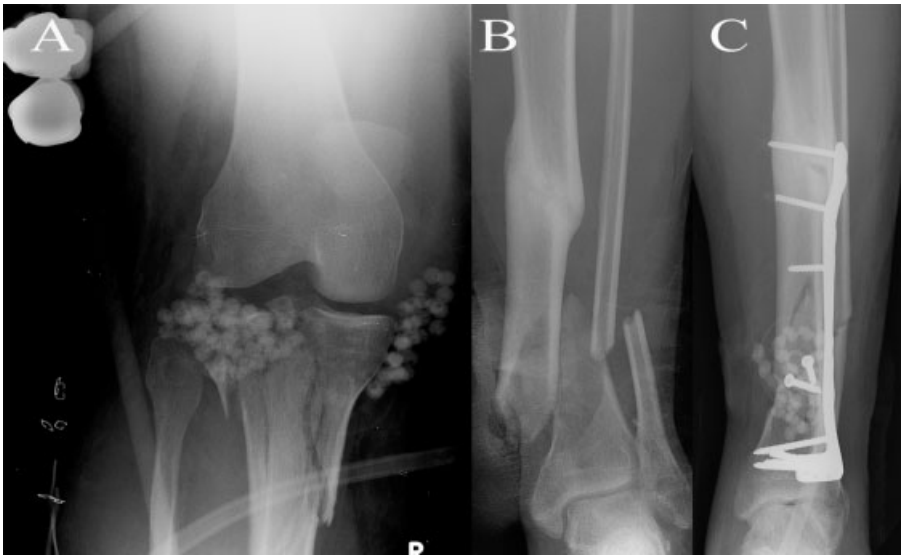

Figure 1 Examples of use of PMMA antibiotic beads in open tibia fractures. (A) Tibial plateau fracture after implantation of beads and spanning external fixation. (B) Preoperative and (C) postoperative views of open distal tibia fracture with significant bone loss treated with open reduction and internal fixation with antibiotic bead placement. The PMMA beads provide a method for antibiotic delivery as well as dead-space management but do require a future operation for removal.

joint arthroplasty literature.[9] Local antibiotic treatment is also substantially less expensive than systemic therapy, which can costs hundreds of dollars per day in an outpatient setting and much more in the hospital setting. In spite of these advantages, bead placement generally requires a second operation for removal. Multiple groups have investigated efficient methods of local antibiotic delivery with biodegradable substrates to obviate this need.[10,11]

PHYSICAL CHARACTERISTICS

The most commonly used bone cement is polymethylmethacrylate (PMMA), consisting of a powdered polymer mixed with a liquid monomer to form a solid structure. Currently, there are five antibiotic-laden PMMA bone cement products that are approved by the U.S. Food and Drug Administration (FDA). These five products include Simplex P, which contains 1 g tobramycin (Stryker Howmedica Osteonics, Mahwah, NJ); Palacos G, which contains 0.85 g gentamicin (Zimmer, Warsaw, IN); SmartSet GHV and SmartSet MHV, which contain 1 g gentamicin (Depuy Orthopaedics, Inc., Warsaw, IN), and the Prostalac prosthesis (DePuy Orthopaedics, Inc.).[4] Premixed antibiotic PMMA beads are available and widely used in Europe under the name Septopal (Biomet Merck, Dordrecht, The Netherlands) and popularized by Klemm[12] but are not currently approved in the United States.

CHOICE OF ANTIBIOTIC

Many antibiotics have been shown to maintain efficacy when mixed with PMMA. The requirements of such antibiotics are that they be heat stable and hydrophilic. The most commonly used antibiotics include gentamicin, tobramycin, and vancomycin. Gentamicin sulfate is an excellent additive to PMMA due to its broad spectrum of action, its bactericidal properties, low rate of primarily resistant pathogens, and good thermostability.[13] Vancomycin and tobramycin are both water soluble and available in powder form. Mixing of more than one antibiotic into bone cement has been shown to have a synergistic effect. Penner et al demonstrated higher elution rates in vitro when tobramycin and vancomycin were tested together compared with either one tested alone in saline baths.[14] Thus, not only does a combination of different antibiotics increase the antimicrobial spectrum, but also it would potentially lead to increased concentrations of antibiotics in the tissues.

TISSUE PENETRATION

Elution characteristics from PMMA antibiotic beads have been studied extensively and vary for each individual antibiotic. The size and shape of the bead itself has been shown to have significant differences in concentrations of antibiotics released.[15] The mechanism of elution itself has long been known to consist of leakage of antibiotic from minute cracks in the cement.[16] Alterations can be made to the cement or its solvents to increase or decrease its porosity. *Passive opportunism*, a term coined by Penner, refers to the addition of a second antibiotic that serves as a solvent for the cement, thus increasing elution of both antibiotics by increasing cement porosity.[14] Hoff et al demonstrated that the antibiotic delivery from cement beads provides significantly higher concentration levels in

desired tissue than does systemic therapy.[17] Wahlig et al tested the elution properties of gentamicin from PMMA in a buffer solution and found 600 mg/L of gentamicin per bead eluted on the first day, 120 mg/L on the 10th day, and 10 mg/L on the 80th day.[18] Normal gentamicin serum trough concentrations with systemic antibiotic therapy are near 1 mg/L, thus highlighting the efficacy of local therapy. Tobramycin, clindamycin, and vancomycin were tested by Mader et al in a similar fashion and showed elution from PMMA at high concentrations. Clindamycin and tobramycin concentrations remained above their respective breakpoint sensitivities (defined as the antibiotic concentrations at the transition point between bacterial killing and resistance) through 220 days. Vancomycin concentrations dropped below breakpoint sensitivity by day 12.[11]

Many studies have also investigated the efficacy of antibiotic delivery using PMMA in vivo. Adams et al compared elution properties of clindamycin, ticarcillin, tobramycin, ciprofloxacin, and vancomycin in 15 large mongrel dogs.[3] After creating a defect in the left tibia and inserting PMMA beads mixed with the antibiotic of choice in each animal, serum and seroma aspirates were taken intermittently for 28 days. Clindamycin proved to have the best elution profile, with the highest seroma, granulation tissue, and bone concentrations. Vancomycin demonstrated excellent bone concentrations, and tobramycin had high seroma and granulation tissue levels. Cefazolin, ciprofloxacin, and ticarcillin all failed to maintain seroma concentrations above breakpoint sensitivities for more than 14 days.

SURGICAL TECHNIQUE

Because no premixed antibiotic cement beads are commercially available in the United States, the surgeon is required to create the beads prior to placement. Generally, 40 g of cement powder is mixed with variable amounts of antibiotics. Hanssen recommends use of 3.6 g antibiotic per 40 g cement.[19] This concentration is very effective in the preparation of static spacers for joint arthroplasty but leads to structural irregularities when used to make antibiotic beads. We prefer to use no more than 2.0 g per 40 g packet of cement for the preparation of antibiotic-impregnated beads. As mentioned previously, the concentration of antibiotic in commercially available cement is substantially lower than 3.6 g per 40 g cement and the cost can be as high as 600% that of non–antibiotic-impregnated commercial cement. Therefore, the commercially available antibiotic cements are both ineffective and economically prohibitive as a lone treatment for infection. In the preparation of antibiotic-impregnated beads, our preferred technique is to mix the cement powder with the desired amount of antibiotic powder and to then add the prepackaged monomer. The components are mixed with a spatula in open air until a doughy viscosity is achieved. The resulting paste is placed into a plastic mold for beads with heavy nonabsorbable sutures. At the end of the polymerization, the suture is used to remove the beads from the plastic mold. Alternatively, the beads can be made by hand and placed on the suture manually. The sutures act as the string for the beads once dry. The polymerization reaction is highly exothermic and the process is accelerated in higher ambient temperatures. Larger volumes of antibiotic lead to a slower polymerization time. The strings of beads are then placed within the surgical wound for dead-space management and antibiotic delivery. The number of beads placed should be counted and documented in the operative report to ensure that the same number are removed at the time of surgical removal to prevent retention of foreign material.

In the treatment of infected joint replacement or in cases of segmental bone loss, a cement block can be fashioned with concentrations of up to 4 to 8 g antibiotic per 40 g pack of cement. An alternative treatment in such cases is use of cement in the case of infected joint arthroplasty as a temporary prosthesis coated with antibiotic-impregnated cement, which can continue to keep the soft tissues out to length but also maintain joint range of motion (Fig. 2).

BIODEGRADABLE MATERIALS

Despite the fact that PMMA has become the gold standard of antibiotic delivery in orthopedic infection treatment and prophylaxis, the need for a second surgical procedure for bead removal poses a significant disadvantage. The search for an antibiotic delivery device that does not require a second operation has been extensive over the past 20 years. In addition, concern has been raised over the development of antibiotic resistance due to the prolonged release of antibiotic at subtherapeutic levels.[20] PMMA has the additional undesirable quality of systemic toxicity to absorbed monomer, a factor shown to cause acute intraoperative hypotension in its use in arthroplasty. Although this has not been a significant clinical problem in the depot delivery of drug, the theoretical risk remains. Finally, whereas antibiotic-laden cement serves as an adequate substance for dead-space management, it does not participate in the bone healing process.

As a result of these shortcomings of PMMA, several alternatives to bone cement have been proposed and investigated as vehicles for antibiotic delivery. The primary area of investigation has focused on biodegradable materials. The degree of biodegradability can vary from weeks to months, allowing variable types of infections to be treated. In addition, there may be decreased need for reconstruction of tissue defects as the host soft tissue can fill in while the beads are slowly absorbed.[10] Biodegradable implants also ensure that the

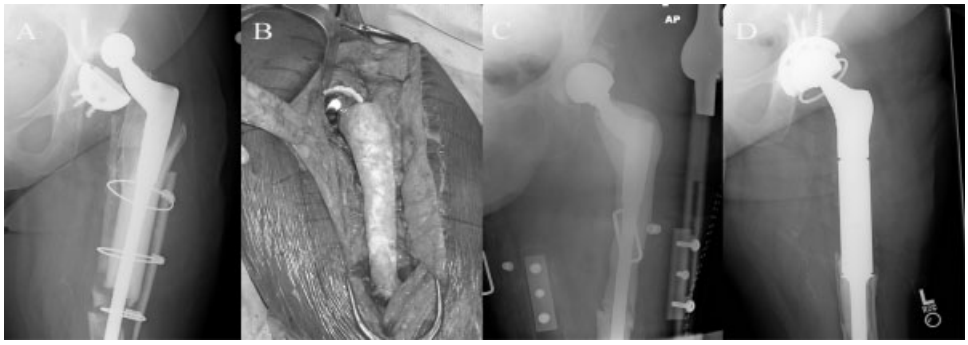

Figure 2 Use of a temporary antibiotic-impregnated prosthesis in the treatment of an infected allograft prosthetic composite total hip replacement with disassociation of the femoral and acetabular components. (A) Preoperative anteroposterior radiograph. (B) Intraoperative photograph at time of debridement. The femoral component was removed, autoclaved, and coated with antibiotic-impregnated PMMA cement and replaced as a temporary spacer prosthesis. (C) Anteroposterior radiograph after placement of the temporary prosthesis. (D) Anteroposterior radiograph after second-stage surgery 4 months later with placement of a segmental oncologic prosthesis with a constrained acetabular component.

entire desired amount of antibiotic is delivered over the course of treatment, in contrast with treatment with acrylic cements. Retention of antibiotic within PMMA is inevitable, and the drug is fully removed only with surgical removal of the non-biodegradable implant. The percentage of total delivery from acrylic cement is variable. In fact, one study found only 20% of total gentamicin was delivered during the functional period of the PMMA implant.[21]

The biodegradable substances have been divided into three main categories as described by McLaren: proteins, bone graft materials and substitutes, and synthetic polymers.[22] Grouped within proteins are a variety of substances derived from biologic tissues including collagen, gelatin, thrombin, and autologous blood clot. These tissue substrates, of which collagen has been studied most extensively, provide a scaffolding that can be used to contain the chosen antibiotic.[22] Conflicting reports exist as to the efficacy of antibiotic-impregnated collagen in the treatment of osteomyelitis. Mendel et al recently demonstrated that gentamicin with collagen substrate reduced bacterial colony counts in experimental rat osteomyelitis more significantly than did gentamicin in PMMA.[23]

Multiple bone graft substitutes have been studied in this role. Calcium sulfate and cancellous bone graft are both currently available substances that are used as defect fillers. Calcium sulfate has long been used for its low immunoreactivity, ability to be absorbed, and its structural properties (Fig. 3). One controlled study using an experimental animal model of osteomyelitis induced with *Staphylococcus aureus* and treated with calcium sulfate beads with tobramycin demonstrated no elevation of serum calcium levels, high tobramycin seroma levels, and no elevation of serum tobramycin levels.[24] Antibiotic elution from calcium phosphate is different in buffer elution trials and animal studies, with in vivo elution lasting significantly longer than the 24 hours seen in in vitro trials.[24] Silverman et al developed methods to incorporate gentamicin into the porous calcium phosphate scaffold by trapping it in clotted blood and/or bone marrow aspirate, extending antibiotic elution to 2 weeks.[25]

Synthetic polymers comprise the most recent group of biodegradable materials investigated and produced for the purpose of local antibiotic delivery. Their obvious advantages include an almost infinite number of variables that can be modified to effectively and accurately release drug quantities over a specified amount of time. Included in the list of materials tested are polylactic acid, polylactide-*co*-glycolides, polyhydroxyalkanoates, polycaprolactone, polyhydroxybutyrate-*co*-hydroxyvalerate, and cross-linked polydimethylsiloxane.[19] Polymers consisting of polylactic acid have been used as biodegradable implants in orthopedics for 30 years. Multiple studies have shown their efficacy and equivalence to metal implants in fracture fixation in the form of plates and screws. In a randomized study of displaced medial malleolar, bimalleolar, and trimalleolar ankle fractures consisting of 169 patients, polylactide screws were equal to stainless steel screws in union rates and had decreased incidence of hardware removal due to irritation.[26] One study, however, does note the possibility of advanced joint degeneration from absorbable screws.[27]

Up to now, biodegradable implants have not been approved by the FDA for use as antibiotic delivery vehicles; however, their experimental utility has been documented in the literature. Liu et al measured in vivo elution of vancomycin from poly(D,L)-lactide-*co*-glycolide (PLGA) beads in New Zealand rabbits and found seroma levels above breakpoint sensitivity past 55 days.[10] Mader et al treated rabbits with tibial osteomyelitis with debridement and PLGA beads impregnated with vancomycin and found bacterial concentrations 100 times lower than with use of debridement and systemic vancomycin alone.[11]

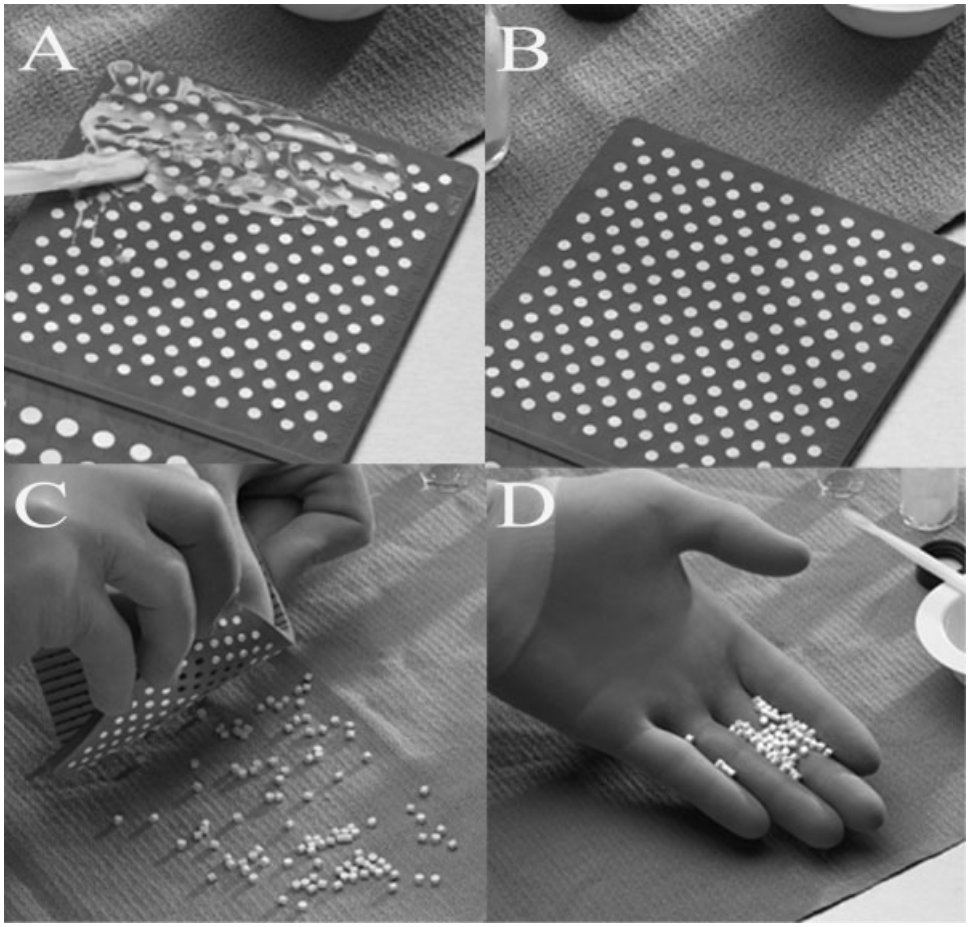

Figure 3 Method of preparation of calcium sulfate pellets with implanted antibiotics. (A) Preparation of mixture of calcium sulfate with antibiotic powder. (B) Beads after hardening in foam mold. (C) Bead removal from foam mold. (D) Beads ready for implantation. (Photographs courtesy of Wright Medical Technology, Inc., Arlington, TN.)

Exciting advances have been made recently in the engineering of synthetic polymers that will allow for complete control of length and concentration of therapy and increase the spectrum of implantable antibiotics. Huang et al used polycaprolactone (PCL) and developed ultrafine fibers, of the order nanometers in diameter, through an electrospinning technique to encapsulate gentamicin for the purpose of drug delivery. Testing in a phosphate-buffered solution showed concentrations of gentamicin at 40 mg/L after 7 days.[28]

Antibiotic-impregnated metals represent an alternative direction in the potential prevention and treatment of osteomyelitis. Parvizi et al have published a technique to covalently bind vancomycin to titanium, creating an implant with an antibiotic surface.[29,30] Such an implant does not elute antibiotics into surrounding tissues but does prevent attachment of bacteria to its surface. In one study, 105 colony-forming units of *Staphylococcus aureus* were incubated with the vancomycin-impregnated titanium implant. At 60 minutes of incubation, the investigators found an 80% reduction in colony-forming units. Long-term efficacy was validated with positive activity of the vancomycin at 1 year. Osteoblast attachment to the metal was also shown to be equal to that seen in standard implants.

ADVERSE EFFECTS ON BONE HEALING AND REGENERATION

Recent research has focused on the toxicity of high concentrations of antibiotic on tissue and bone healing. The potential for this inhibition of bone healing would greatly affect choice of antibiotic and its delivery vehicle. Eden et al tested the effects of cefazolin and vancomycin on osteosarcoma cells with in vitro concentrations between 0 and 10,000 μg/mL. Little or no effect on osteoblast replication was seen at levels under 100 μg/mL, whereas levels near 10,000 μg/mL induced cell death, with vancomycin found to be less toxic than cefazolin.[31] Further in vitro studies with ciprofloxacin, vancomycin, and tobramycin demonstrated changes in cellular morphology with exposure to antibiotics. Levels of vancomycin and tobramycin at 2000 μg/mL severely decreased cellular proliferation, and ciprofloxacin had similar effects at 100 μg/mL.[32] Clinically measured concentrations of these antibiotics are usually much

lower than these concentrations. Nelson et al noted tobramycin concentrations in rabbit wound exudates at 11.9 mg/mL when treated with calcium sulfate pellets and serum concentration of 7.82 μg/mL when treated with intravenous tobramycin.[24]

CONCLUSION

Use of local antibiotics in the treatment and prevention of osteomyelitis is safe and effective. Its advantages over systemic therapy include lower cost, lower risk of toxicity, and tremendously higher concentrations of antibiotics at the desired sites. The majority of current treatment modalities require a second procedure for removal of the antibiotic delivery device. Biodegradable devices currently under development hold promise in their ability to customize antibiotic treatment based on bacterial and patient characteristics.

ACKNOWLEDGMENTS

None of the authors has any affiliation with the above-mentioned industry entities pertaining to materials discussed in this article. No funding was received in the development of this article.

REFERENCES

1. Ciampolini J, Harding KG. Pathophysiology of chronic bacterial osteomyelitis. Why do antibiotics fail so often? Postgrad Med J 2000;76:479–483
2. Fischer B, Vaudaux P, Magnin M, et al. Novel animal model for studying the molecular mechanisms of bacterial adhesion to bone-implanted metallic devices: role of fibronectin in Staphylococcus aureus adhesion. J Orthop Res 1996;14:914–920
3. Adams K, Couch L, Cierny G, Calhoun J, Mader JT. In vitro and in vivo evaluation of antibiotic diffusion from antibiotic-impregnated polymethylmethacrylate beads. Clin Orthop Relat Res 1992;278:244–252
4. Nelson CL. The current status of material used for depot delivery of drugs. Clin Orthop Relat Res 2004;427:72–78
5. Parsons B, Strauss E. Surgical management of chronic osteomyelitis. Am J Surg 2004;188(Suppl):57–66
6. Gallie WE. First recurrence of osteomyelitis eighty years after infection. J Bone Joint Surg Br 1951;33:110–111
7. Buchholz HW, Engelbrecht H. Depot effects of various antibiotics mixed with Palacos resins. Chirurg 1970;41:511–515
8. Klemm K. Gentamicin-PMMA-beads in treating bone and soft tissue infections (author's transl). Zentralbl Chir 1979; 104:934–942
9. Springer BD, Lee GC, Osmon D, et al. Systemic safety of high-dose antibiotic-loaded cement spacers after resection of an infected total knee arthroplasty. Clin Orthop Relat Res 2004;427:47–51
10. Liu SJ, Wen-Ueng S, Lin SS, Chan EC. In vivo release of vancomycin from biodegradable beads. J Biomed Mater Res 2002;63:807–813
11. Mader JT, Calhoun J, Cobos J. In vitro evaluation of antibiotic diffusion from antibiotic-impregnated biodegradable beads and polymethylmethacrylate beads. Antimicrob Agents Chemother 1997;41:415–418
12. Klemm KW. Gentamicin-PMMA chains (Septopal chains) for the local antibiotic treatment of chronic osteomyelitis. Reconstr Surg Traumatol 1988;20:11–35
13. Klemm K. The use of antibiotic-containing bead chains in the treatment of chronic bone infections. Clin Microbiol Infect 2001;7:28–31
14. Penner MJ, Masri BA, Duncan CP. Elution characteristics of vancomycin and tobramycin combined in acrylic bone-cement. J Arthroplasty 1996;11:939–944
15. Seeley SK, Seeley JV, Telehowski P, et al. Volume and surface area study of tobramycin-polymethylmethacrylate beads. Clin Orthop Relat Res 2004;420:298–303
16. Baker AS, Greenham LW. Release of gentamicin from acrylic bone cement. Elution and diffusion studies. J Bone Joint Surg Am 1988;70:1551–1557
17. Hoff SF, Fitzgerald RH Jr, Kelly PJ. The depot administration of penicillin G and gentamicin in acrylic bone cement. J Bone Joint Surg Am 1981;63:798–804
18. Wahlig H, Dingeldein E, Bergmann R, Reuss K. The release of gentamicin from polymethylmethacrylate beads. An experimental and pharmacokinetic study. J Bone Joint Surg Br 1978;60:270–275
19. Hanssen AD. Local antibiotic delivery vehicles in the treatment of musculoskeletal infection. Clin Orthop Relat Res 2005;437:91–96
20. Neut D, van de Belt H, van Horn JR, van der Mei HC, Busscher HJ. Residual gentamicin-release from antibiotic-loaded polymethylmethacrylate beads after 5 years of implantation. Biomaterials 2003;24:1829–1831
21. Bunetel L, Sequi A, Cormier M, Percheron E, Langlais F. Release of gentamicin from acrylic bone cement. Clin Pharmacokinet 1989;17:291–297
22. McLaren AC. Alternative materials to acrylic bone cement for delivery of depot antibiotics in orthopaedic infections. Clin Orthop Relat Res 2004;427:101–106
23. Mendel V, Simanowski HJ, Scholz HC, Heymann H. Therapy with gentamicin-PMMA beads, gentamicin-collagen sponge, and cefazolin for experimental osteomyelitis due to Staphylococcus aureus in rats. Arch Orthop Trauma Surg 2005;125:363–368
24. Nelson CL, McLaren SG, Skinner RA, et al. The treatment of experimental osteomyelitis by surgical debridement and the implantation of calcium sulfate tobramycin pellets. J Orthop Res 2002;20:643–647
25. Silverman LD, Lukashova L, Herman OT, Lane JM, Boskey AL. Release of gentamicin from a tricalcium phosphate bone implant. J Orthop Res 2007;25:23–29
26. Bucholz RW, Henry S, Henley MB. Fixation with bioabsorbable screws for the treatment of fractures of the ankle. J Bone Joint Surg Am 1994;76:319–324
27. Bostman OM. Osteoarthritis of the ankle after foreign-body reaction to absorbable pins and screws: a three- to nine-year follow-up study. J Bone Joint Surg Br 1998;80:333–338
28. Huang ZM, He CL, Yang A, et al. Encapsulating drugs in biodegradable ultrafine fibers through co-axial electrospinning. J Biomed Mater Res A 2006;77:169–179
29. Antoci V Jr, Adams CS, Parvizi J, et al. Covalently attached vancomycin provides a nanoscale antibacterial surface. Clin Orthop Relat Res 2007;461:81–87

30. Parvizi J, Wickstrom E, Zeiger AR, et al. Frank Stinchfield Award. Titanium surface with biologic activity against infection. Clin Orthop Relat Res 2004;429:33–38
31. Edin ML, Miclau T, Lester GE, Lindsey RW, Dahners LE. Effect of cefazolin and vancomycin on osteoblasts in vitro. Clin Orthop Relat Res 1996;333:245–251
32. Antoci V Jr, Adams CS, Hickok NJ, et al. Antibiotics for local delivery systems cause skeletal cell toxicity in vitro. Clin Orthop Relat Res 2007;462:200–206