Antibiotic-Loaded Bone Cement for Infection Prophylaxis in Total Joint Replacement

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Current Concepts Review

Antibiotic-Loaded Bone Cement for Infection Prophylaxis in Total Joint Replacement

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- Use of antibiotic-loaded bone cement for prophylaxis against infection is not indicated for patients not at high risk for infection who are undergoing routine primary or revision joint replacement with cement.
- The mechanical and elution properties of commercially available premixed antibiotic-loaded bone-cement products are superior to those of hand-mixed preparations.
- Use of commercially available antibiotic-loaded bone-cement products has been cleared by the United States Food and Drug Administration only for use in the second stage of a two-stage total joint revision following removal of the original prosthesis and elimination of active periprosthetic infection.
- Use of antibiotic-loaded bone cement for prophylaxis against infection in the second stage of a two-stage total joint revision involves low doses of antibiotics.
- Active infection cannot be treated with commercially available antibiotic-loaded bone cement as such treatment requires higher doses of antibiotics.

Deep wound infection following total joint replacement is one of the most devastating complications facing both the physician and the patient. Antibiotic-loaded bone cement is a well-accepted adjunct for the treatment of an established infection. However, its role in the prevention of infection remains controversial because of issues regarding drug resistance, efficacy, and cost. We reviewed the pros and cons of the contemporary use of antibiotic-loaded bone cement and concluded that its use for prophylaxis should be restricted to high-risk groups that have shown a higher prevalence of deep prosthetic infection than the population as a whole. Antibiotic-loaded bone cement should be considered as a defense against direct contamination at the time of surgery, or during the postoperative period as the wound seals.

Treatment Compared with Prophylaxis (High-Dose Compared with Low-Dose Antibiotic-Loaded Bone Cement)

The use of local antibiotic delivery systems, including antibiotic-loaded bone cement, in the treatment of musculoskeletal infection is well established[1-4]. It has been shown that at least 3.6 g of antibiotic per 40 g of acrylic cement is desirable for effective elution kinetics and sustained therapeutic levels of antibiotic[5]. Doses as high as 6 to 8 g of antibiotic per 40-g batch of bone cement, when antibiotic-loaded bone cement is used in the form of beads or spacers, have been shown to be safe clinically[4]. The use of this high dose is important for the sustained elution of antibiotics at levels that are therapeutic for the pathogenic organisms being treated.

In contrast with treatment, prophylaxis requires low doses of antibiotics in the bone cement to avoid adverse mechanical effects on cement that is intended for mechanical fixation of an implant. In general, low-dose antibiotic-loaded bone cement is defined as ≤1 g of powdered antibiotic per 40 g of bone cement (Fig. 1). The mechanical characteristics of antibiotic-loaded bone cement are discussed later in detail.

Recently, six commercial low-dose antibiotic-loaded bone-cement products have been released for use following 510(k) clearance by the United States Food and Drug Administration (FDA) (Table I). These include Cobalt G-HV bone cement with 0.5 g of gentamicin per 40 g of bone cement (Biomet, Warsaw, Indiana), Palacos G bone cement with 0.5 g of gentamicin per 40 g bone cement (Biomet), DePuy 1 bone cement with 1.0 g of gentamicin per 40 g of bone cement (DePuy Orthopaedics, Warsaw, Indiana), Cemex Genta bone cement with 0.5 g of gentamicin per 40 g of bone cement (Exactech, Gainesville, Florida),

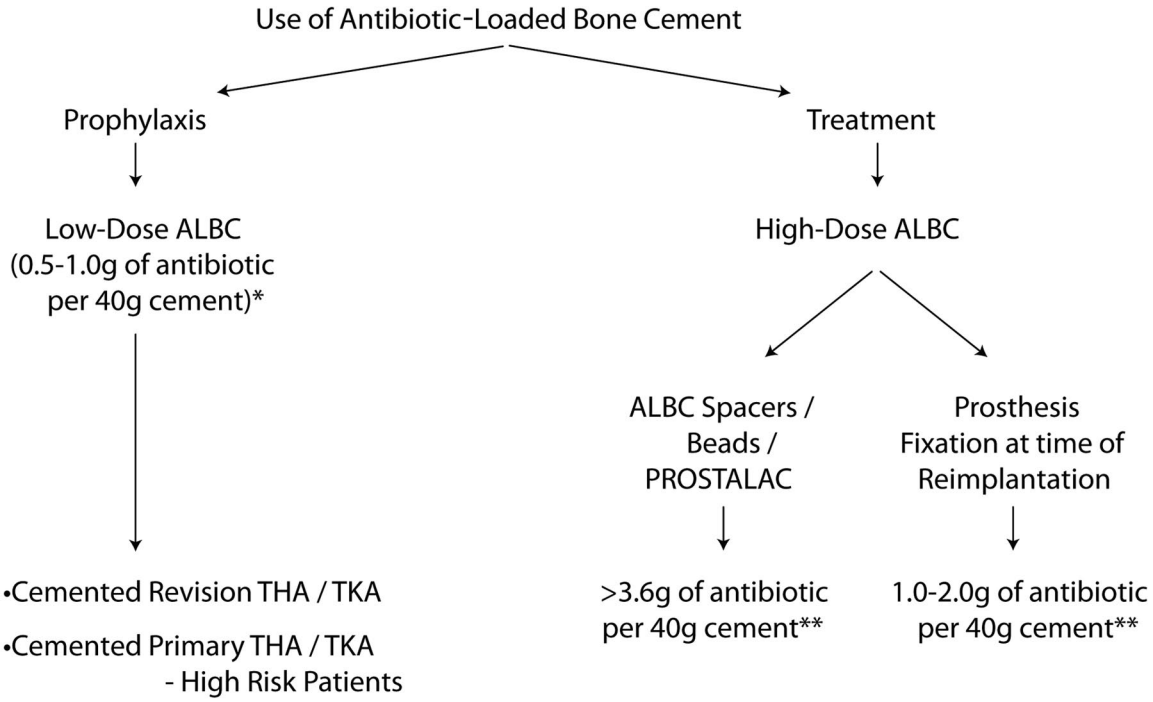

Fig. 1

Guidelines for clinical use of antibiotic-loaded bone cement (ALBC). *Antibiotics recommended for prophylaxis include gentamicin or tobramycin. Vancomycin is not indicated for prophylaxis. **The antibiotic(s) used depends on the susceptibility of the microorganisms identified or suspected.

VersaBond AB bone cement with 1.0 g of gentamicin per 40 g of bone cement (Smith and Nephew, Memphis, Tennessee), and Simplex P bone cement with 1.0 g of tobramycin per 40 g of bone cement (Stryker Orthopaedics, Mahwah, New Jersey).

It is important to note that these commercially available antibiotic-loaded bone-cement products were approved by the FDA for use in the second stage of a two-stage total joint revision following the elimination of an active infection and specifically not for the prevention of deep periprosthetic infection in patients undergoing primary or revision total joint arthroplasty. Since these are low-dose antibiotic-loaded bone-cement products, they are not appropriate for the construction of cement spacers or beads for the treatment of an established musculoskeletal infection.

Why Are Prosthetic Joints Susceptible to Bacterial Infection?

All operative procedures are vulnerable to bacterial contamination. Maathuis et al.[6] cultured samples from acetabular reamers and femoral rasps used during primary total hip arthroplasties in sixty-seven patients, and twenty patients (30%) had at least one positive culture. It is likely that other open procedures of similar duration have similar amounts of contamination, but the presence of biomaterials places patients undergoing joint replacement at increased risk for the development of deep infection.

Biomaterials have an increased susceptibility to bacterial colonization, which is multifactorial. After implantation, the host interacts with the biomaterial by forming a conditioning

TABLE I Antibiotic Bone Cements with FDA 510(k) Clearance

Product Name	Manufacturer/U.S. Distributor	Cement Type	Dosage of Antibiotic per 40 g of Bone Cement
Cobalt G-HV	Biomet (Warsaw, IN)	Copolymer high viscosity	0.5 g of gentamicin
Palacos G	Biomet (Warsaw, IN)	Copolymer high viscosity	0.5 g of gentamicin
DePuy 1	DePuy Orthopaedics (Warsaw, IN)	Homopolymer high viscosity	1.0 g of gentamicin
Cemex Genta	Exactech (Gainesville, FL)	Copolymer medium viscosity	0.5 g of gentamicin
VersaBond AB	Smith and Nephew, (Memphis, TN)	Copolymer medium viscosity	1.0 g of gentamicin
Simplex P	Stryker Orthopaedics (Mahwah, NJ)	Copolymer medium viscosity	1.0 g of tobramycin

film (a so-called biofilm) on its surface and an immune reaction toward the foreign material[7]. A self-perpetuating enlarging immunoincompetent fibroinflammatory zone develops about implants with ongoing tissue damage, which creates an increased susceptibility to infection[8]. If microorganisms are able to reach the biomaterial surface, many have the ability to adhere to it[9]. Adhesion of bacteria is mediated by the individual physicochemical surface properties of the bacteria and the biomaterial. These surface characteristics, such as polarity or surface roughness, result in variable mechanisms of bacterial attachment. There are no data to suggest that the anatomic location of the reconstructed joint (e.g., the hip as opposed to the knee) affects the propensity for infection.

In an in vitro experiment, bone cement was colonized by coagulase-negative staphylococci in greater numbers than were found on other biomaterials[10]. Increased bacterial colonization was time-dependent, and colonization was fifteen times greater than that on stainless steel and aluminum and four times greater than that on high-density polyethylene[10]. In another experiment, bioinert stainless steel, titanium alloy, bioactive sintered hydroxyapatite, and hydroxyapatite-coated titanium implants were exposed to coagulase-negative staphylococci[11]. Assays revealed that bacterial adherence to sintered hydroxyapatite was greater than that to the other three materials. It was not determined whether this effect was due to surface roughness or surface physicochemical properties.

The surface roughness of the biomaterial does appear to influence the rate of bacterial adhesion. Both smooth and sandblasted specimens of pure polymer (poly-L-lactide), a polymer composite (hydroxyapatite/poly-L-lactide), and stainless steel were exposed to *Staphylococcus aureus* and coagulase-negative staphylococci[12]. *Staphylococcus aureus* showed a preference for the metal and the polymer composite over the pure polymer, whereas coagulase-negative staphylococci showed no preference for any of these specific biomaterials. The influence of surface roughness on bacterial growth was demonstrated by increased colonization on the sandblasted specimens by both microorganisms. Collectively, these data suggest that the interactions of prosthetic implants with bacteria and host tissues are influenced by the binding of cell surface receptors and the chemistry and surface charge of the biomaterial[13].

Bacteria adherent to biomaterials can encase themselves in a hydrated biofilm matrix of polysaccharide and protein. Incubation of different bacterial strains on multiple biomaterials revealed that free-floating (planktonic) bacteria are more susceptible to antibiotics than are the same bacteria (sessile) encased within the biofilm[7]. Sessile microorganisms are highly resistant to antimicrobial agents and use multiple mechanisms to achieve that resistance[14]. Possible mechanisms include delayed penetration of the antimicrobial into the biofilm extracellular matrix, growth-rate slowing of sessile organisms, and physiologic changes brought about by interaction of the organisms with a surface[15]. These mechanisms of resistance differ from the plasmids, transposons, and mutations that confer innate resistance to (planktonic) bacteria. It also appears that some of the biofilms may be produced by the host rather than by the bacteria.

There are many areas of investigation related to the treatment of established biofilm-related infections, and the issue of treatment lies outside of the scope of this article. Prevention strategies against biofilm formation have primarily been focused on surface-modifying techniques such as antibiotic coatings on implants[16,17]. Newer lines of investigation include coating of implants with an RNAIII-inhibiting peptide (RIP), which inhibits the pathogenesis of staphylococci by disrupting bacterial cell-cell communication (so-called quorum sensing)[18]. In a vascular graft rat model, locally applied RIP completely inhibited the formation of susceptible and drug-resistant *Staphylococcus aureus* and coagulase-negative staphylococci biofilms[18].

To date, the use of antibiotic-loaded bone cement as an implant coating has been the primary and only practical method of delivering local antibiotics in the clinical setting of total joint replacement. It is not known to what extent the presence of local antibiotics delivered from antibiotic-loaded bone cement reduces infection by interfering with biofilm formation or simply by eradicating planktonic bacteria that may be adjacent to the prosthesis. It should also be noted that many infections adjacent to implants are unrelated to the formation of a biofilm. Several investigators have demonstrated that biofilm can be easily formed on antibiotic-loaded bone cement[19-21]. These reports suggest that biofilm production may be reduced but not totally eliminated in the presence of locally delivered antibiotics; this is particularly true when the antibiotic-loaded biomaterial is polymethylmethacrylate.

Bone Cement as a Drug-Delivery Vehicle

Antibiotic release from bone cement is a complex process; important variables include the type of antibiotic[5,22], the type of bone cement[23], and the mixing conditions[24-26]. Antibiotic is released from the surface of the cement and from cracks and voids in the cement[23,27]. The polymeric nature of polymethylmethacrylate allows ingress of physiologic fluids, which permits elution of incorporated antibiotic, but the relative hydrophobicity of bone cement allows only 10% of the antibiotic to elute effectively[28]. While the majority of the antibiotic release occurs in the first nine weeks, there is probably a continued low release of antibiotic through the development of cracks, with evidence that fracture of the cement mantle can liberate substantial levels of antibiotic many years after implantation[29,30].

The release time course and the amount of antibiotic that is released from the cement depend on factors inherent in the cement, such as porosity, as well as the overall surface area of the bone cement exposed to the host tissues. For example, Palacos bone cements have been observed to have higher elution levels than other types of bone cement[23,27]. This difference is attributed to the increased porosity of Palacos cements. Some antibiotics elute from bone cement better than others[22]. Most studies of this issue have evaluated high-dose antibiotic-loaded bone-cement products and have shown that mixing patterns also seem to affect patterns of elution of antibiotics[31].

For example, in a study of antibiotic elution from Simplex bone cement, with the antibiotics including cefazolin (4.5 g per 40 g of cement powder), ciprofloxacin (6 g per 40 g of powder), clindamycin (6 g per 40 g of powder), ticarcillin (12 g per 40 g of powder), tobramycin (9.8 g per 40 g of powder), and vancomycin (4 g per 40 g of powder), clindamycin, vancomycin, and tobramycin displayed good elution characteristics into surrounding bone and granulation tissue[32].

In another study, the characteristics of the elution of either 2 g of vancomycin alone or 2 g of vancomycin plus 2 g of imipenem-cilastatin from three different types of bone cement were investigated[31]. When vancomycin alone was used, a total of 7.98 mg of the antibiotic was released by CMW1 bone cement, 7.74 mg by Palacos R, and 6.76 mg by Simplex P. With the addition of imipenem-cilastatin, the total amount of vancomycin released by the three cements increased by 30.58%, 50.52%, and 50.15%, respectively. It is likely that the effect seen in these studies is related to the increased porosity of the bone cement as progressively higher amounts of powdered antibiotics are admixed.

Patterns of Use of Antibiotic-Loaded Bone Cement

In a survey of 1015 practitioners in the field of adult reconstructive surgery in the United States, only 56% used antibiotic-loaded bone cement in their practice[33]. Of the respondents who used antibiotic-loaded bone cement, >90% utilized it for additional prophylaxis during primary arthroplasty in patients with a previously infected joint and 67% used it for aseptic revisions of hip or knee replacements on a selective basis (i.e., it was used for less than one-third of the aseptic revision procedures). Eleven percent of the respondents regularly used antibiotic-loaded bone cement for routine primary total joint replacement. In contrast, data from the Scandinavian Joint Registries indicated prophylactic use of antibiotic-loaded bone cement in 95% of revision hip or knee arthroplasties[34,35]. Forty-eight percent of surgeons in Norway[35,36], compared with 85% of those in Sweden[34], were reported to use antibiotic-loaded bone cement for primary joint replacement. In the National Hip Replacement Outcome Project in Britain, 69% of the surgeon respondents used antibiotic-loaded bone cement in their primary total hip replacements, although it was not clear if this was on a selective or generalized basis[37].

It is not known to what extent the lack of FDA approval in the United States for the use of antibiotic-loaded bone cement for prophylaxis in primary total joint arthroplasty has affected these patterns of usage. Now that low-dose antibiotic-loaded bone cement has been approved as a commercially available product for the second stage of reimplantation arthroplasty, after the infection has been eradicated, it is highly possible that the use of antibiotic-loaded bone cement for prophylaxis in primary total joint arthroplasty will increase.

Potential Advantages of Routine Use of Antibiotic-Loaded Bone Cement for Prophylaxis Against Bacterial Infection

The primary basis for use of antibiotic-loaded bone cement as a prophylactic method to reduce the prevalence of deep periprosthetic infection has been the clinical experience obtained over the past three decades combined with data from several experimental studies. In a canine experiment, the use of gentamicin-loaded bone cement significantly reduced the rate of implant-related infection compared with that associated with the use of plain bone cement ($p < 0.05$)[38]. This finding was confirmed in a rabbit model in which tobramycin-loaded bone cement was compared with plain bone cement[39,40].

Gentamicin, cefuroxime, and tobramycin have been the antimicrobials most commonly admixed into bone cement in clinical studies worldwide[34,36,41-43]. In the United States, tobramycin has been used most commonly, primarily because the product is available in powdered form. Of the three antibiotics, gentamicin has been used most frequently and studied most extensively overall[44]. We are not aware of any clinical studies comparing the efficacy of one antibiotic-loaded bone cement with that of another with regard to either the type of antibiotic or the type of bone cement used. We are aware of only three prospective randomized studies that evaluated the efficacy of antibiotic-loaded bone cement for primary joint replacement[41,43,45].

In a recent prospective, randomized study of 340 primary total knee arthroplasties[41], cefuroxime-loaded cement was used for fixation in 178 knees (Group 1) and plain cement was used in 162 knees (Group 2). No deep infections occurred in Group 1, whereas a deep infection developed in five (3.1%) of the 162 knees in Group 2 ($p = 0.0238$). Further analysis revealed that all infections occurred in patients with diabetes mellitus[42]. In the group of seventy-eight patients with diabetes, forty-one received cefuroxime-loaded cement (Group 1) whereas thirty-seven were treated with plain cement (Group 2). There were no deep infections in Group 1, but an infection developed in five (14%) of the knees in Group 2 ($p = 0.021$)[42]. It is important to realize that if the high-risk patients with diabetes mellitus had been removed from the study, there would have been no infections in any patient in either Group 1 or Group 2.

In another study, of 295 patients treated with hip or knee replacement, there was no difference in results between the use of cefuroxime as an additive to the bone cement and administration of the cefuroxime intravenously[43]. The small numbers of patients in that study preclude any specific conclusions based on these data. It is likely that studies of much larger numbers of patients are required to determine a difference in infection rates in patients who are not considered to be at high risk. In a larger prospective, randomized clinical trial of 1688 hip arthroplasties[45], the group treated with systemic antibiotics had significantly more deep infections (thirteen; 1.6%) at two years postoperatively than did the group treated with gentamicin-loaded bone cement (three infections; 0.4%) ($p < 0.05$). However, at ten years, two additional infections in the group treated with gentamicin-loaded cement eliminated the significant difference in the infection rate between the two groups[45].

In what we believe was the first retrospective study of antibiotic-loaded bone cement, an infection rate of 6% in a historical control group of hip replacements performed without antibiotic-loaded cement was reduced to approximately

2% following 1655 hip replacements performed with Palacos gentamicin-loaded bone cement[46]. In another retrospective review, of 1542 total hip replacements, there was no difference in infection rate between primary total hip replacements performed with gentamicin-loaded bone cement and those performed without gentamicin-loaded bone cement[47]. However, when used in secondary operations, gentamicin-loaded bone cement provided significantly better results, with a 0.81% infection rate as compared with a rate of 3.46% following those done with plain cement[47]. This was presumably due to the occurrence of latent and unrecognized infection following some of the revision procedures.

In a large retrospective study, data on 22,170 primary total hip replacements from the Norwegian Arthroplasty Register during the period of 1987 to 2001 were analyzed[36]. Patients who received only systemic antibiotic prophylaxis (5960 total hip replacements) had a 1.8 times higher rate of infection than patients who received systemic antibiotic prophylaxis combined with gentamicin-loaded bone cement (15,676 total hip replacements) ($p = 0.01$)[36]. Another retrospective study, of 92,675 primary and revision hip arthroplasties listed in the Swedish Joint Registry, presented similar conclusions, with the use of antibiotic-loaded bone cement favored for both primary and revision hip arthroplasties[34]. The effect of antibiotic-loaded bone cement in reducing the prevalence of infection was more apparent for revision than primary replacements. It is also important to note that over the study time period, between 1978 and 1990, the infection rate decreased in all patients, with or without the use of antibiotic-loaded bone cement, because of other methods of infection control introduced over this time span[34,48].

On the basis of these retrospective studies, it appears that antibiotic-loaded bone cement is effective for prophylaxis against bacterial infection in patients treated with total joint replacement (Table II). The primary question is whether the benefits of prophylaxis with antibiotic-loaded bone cement, in the current era of joint arthroplasty with an extremely low rate of infection, are outweighed by the disadvantages associated with its routine use.

Potential Disadvantages of Routine Use of Antibiotic-Loaded Bone Cement

The primary concerns regarding antibiotic-loaded bone cement include the potential for detrimental effects on the mechanical or structural characteristics of polymethylmethacrylate when antibiotics are admixed, systemic toxicity related to high antibiotic levels eluted from the cement, allergic reactions to the specific antibiotic used, development of drug-resistant bacteria, and cost.

Mechanical Strength

The addition of >4.5 g of gentamicin powder per 40-g package of cement[49] or the addition of liquid antibiotics[50] causes a decrease in compressive strength to a level below American Society for Testing and Materials (ASTM) standards. Gentamicin in concentrations of 0.5 g, 1.0 g, and 2.0 g per 40 g of Palacos acrylic bone cement has been shown to substantially reduce the shear strength of the cement[51], a factor that will influence crack nucleation in situations of prolonged dynamic loading. Liquid gentamicin mixed into bone cement is potent and bactericidal, but the mechanical properties of this antibiotic-loaded bone cement are substantially diminished[52]. The use of high-dose antibiotics in bone-cement spacers (>2 g of antibiotic per 40 g of cement) implanted in staged revision procedures can lead to substantial cost savings to the hospital and improvement in patient care. However, the routine use of high-dose antibiotics in cement employed for fixation of prostheses is not supported by evidence. Although there are no data to show that use of low-dose antibiotic-loaded bone cement (<2 g of antibiotic per 40 g of cement) prevents infection, there is also no evidence that this practice decreases the mechanical performance of the cement[44].

Recently it has been reported that hand-mixing generic tobramycin (Pharma-Tek, Huntington, New York) into Simplex P bone cement results in a 36% decrease in the strength of the cement compared with the strength of commercially prepared tobramycin-loaded bone cement (Simplex with Tobramycin; Stryker Orthopaedics) and that of plain Simplex P cement[24]. These findings are in direct contrast with those of two previous

TABLE II Studies of the Efficacy of Antibiotic-Loaded Bone Cement for Prophylaxis in Total Joint Replacement

Study	No. of Replacements	Year of Publication	Antibiotic Used in Bone Cement	Infection Rate (%)	
				No Antibiotic-Loaded Bone Cement	Antibiotic-Loaded Bone Cement
Chiu et al.[41]	340 primary total knee	2002	Cefuroxime	3.1	0.0
Josefsson and Kolmert[45]	1688 primary total hip	1993	Gentamicin	1.6	0.4
Engesaeter et al.[36]	22,170 primary total hip	2003	Gentamicin	1	0.4
Lynch et al.[47]	1542 primary total hip	1987	Gentamicin	2.18	1.34
	1064 primary			1.72	1.65
	180 with prev.surgery on joint otherthan hip arthoplasty			4.0	1.82
	298 rev.			2.83	0.52

studies[53,54], in which the addition of gentamicin powder into Palacos R bone cement (Smith and Nephew) or either erythromycin plus colistin[37] or tobramycin powder into Simplex P bone cement[1] did not decrease the fatigue strength compared with that of the respective plain-cement controls. This was true whether or not the cement had been centrifuged.

The influence of the method of blending of gentamicin into bone cement has also been evaluated. In one study, there was no significant difference between the properties of cement in which gentamicin had been added with the use of a commercially available mechanical powder mixer and the properties of commercially mixed antibiotic-loaded bone cement[25]. The authors of that study suggested that use of this powder mixer in the operating room is more likely to produce a consistent and reproducible mixture than is manual mixing. It is important to carefully pulverize crystalline antibiotic powders when hand-mixing to minimize their effects on the mechanical properties of the bone cement.

It has been shown that, in comparison with hand-mixing, vacuum-mixing significantly increases the tensile fatigue strength of bone cement ($p < 0.0001$)[55]. When the same laboratory testing methodology was used, two of three prepackaged, 510(k)-cleared antibiotic-loaded bone cements were weaker than their plain cement counterparts[56]. In the same study, bone cement in which tobramycin had been hand-blended and vacuum-mixed (1 g of antibiotic per 40 g of cement) was weaker than its prepackaged vacuum-mixed counterpart ($p < 0.006$) as well as weaker than all of the other vacuum-mixed cements that were evaluated.

It is important to note that these in vitro studies of bone cement demonstrated a theoretical disadvantage of antibiotic-loaded bone cement. To date, clinical studies have not shown an increase in the mechanical loosening rate with the use of low-dose antibiotic-loaded bone cement.

Toxicity

To our knowledge, there have been no reports of systemic toxicity related to the use of low-dose antibiotic-loaded bone cement. The most common strategy in most studies has been to assess serum concentrations of the antibiotic to allow comparison with concentrations following intravenous administration of antibiotics. Many of the authors of these studies assessed levels associated with the use of high-dose antibiotic-loaded bone cement. For example, in a pharmacokinetic study of ten patients treated with primary total hip replacement in which vancomycin-loaded bone cement (2 g of antibiotic per 40 g of cement) had been used, blood levels were <3 μg/mL (thirty times lower than the toxic threshold), and vancomycin was undetectable in the urine after the tenth day[57].

In a recent report, specimens of blood, urine, and drainage fluid were collected for seventy-two hours postoperatively to establish the elution characteristics of low-dose Simplex-tobramycin bone cement (Howmedica, Limerick, Ireland) in ten patients who had undergone a primary total hip replacement[58]. High concentrations of tobramycin were found in the drainage fluid, with a mean level of 103 μg/L at one hour, which declined to 15.1 μg/L at forty-eight hours. The mean serum tobramycin level peaked at three hours (0.94 μg/L) and declined to 0.2 μg/L by forty-eight hours. The mean urinary tobramycin level peaked at twelve hours (57.8 μg/L) with a decline to 12.6 μg/L by twenty-four hours. These excellent local antibiotics levels, with minimal systemic absorption, suggest that use of this dose of antibiotic-loaded bone cement is an efficient and safe method of antibiotic delivery in total hip replacement. Others have found similarly safe levels with even higher doses of tobramycin[2]. The recorded systemic peak serum level of tobramycin was <3 mg/L, despite the use of up to 3.6 g of tobramycin powder per 40 g of bone cement.

While there has been no evidence of systemic toxicity, there has been considerable investigation regarding local toxicity with particular reference to osteoblast and osteocyte function. We are aware of no clinical evidence of this negative cellular effect, but results of in vitro studies raise some concern. These concerns are more relevant with high-dose antibiotic-loaded bone cement, with which local levels of antibiotics can exceed 2000 μg/mL[59]. In one study, human osteoblast-like cells derived from cancellous bone were exposed to media containing various concentrations of gentamicin (0 to 1000 μg/mL) for four days[60]. Alkaline phosphatase activity was significantly decreased ($p < 0.05$) in all cultures at gentamicin concentrations of >100 μg/mL. 3H-thymidine incorporation was also decreased ($p < 0.05$) at gentamicin concentrations of >100 μg/mL, and total DNA was decreased ($p < 0.05$) at concentrations of ≥700 μg/mL. Another study, on the effect on osteoblast-like cells of tobramycin at levels between 0 and 10,000 μg/mL, demonstrated that local levels of <200 μg/mL had no effect on osteoblast replication[61]. Tobramycin concentrations of 400 μg/mL decreased cell replication, whereas concentrations of 10,000 μg/mL caused cell death.

The effect of cefazolin and vancomycin on osteoblast-like cells has also been studied at concentrations between 0 and 10,000 μg/mL[62]. The results of this study revealed that local levels of vancomycin of <1000 μg/mL had little or no effect on osteoblast replication but concentrations of 10,000 μg/mL caused cell death. Cefazolin concentrations of 100 μg/mL had no effect on osteoblast replication, concentrations of 200 μg/mL decreased cell replication, and levels of 10,000 μg/mL caused cell death[62]. It would appear that vancomycin is less toxic to osteoblasts than cefazolin or aminoglycosides at the higher concentrations routinely achieved by current local antibiotic-delivery vehicles.

Allergic Reaction

We are not aware of any reports of allergic reactions to low or high-dose antibiotic-loaded bone cement. Thus far, however, the predominant antibiotics used in antibiotic-loaded bone cement have been gentamicin and tobramycin, which have favorable allergy profiles. Richter-Hintz et al.[63] described a patient with a type-IV hypersensitivity response to polymethylmethacrylate in which gentamicin had been added. The increase in resistance rates of bacteria isolated from infected hip joints, particularly staphylococci, has prompted investigators to pursue

the use of other antibiotics or combinations of antibiotics for prophylaxis. These investigations have primarily involved vancomycin or cephalosporins[64].

It is possible that an allergic event will occur if other antibiotics, such as the cephalosporins, are used more routinely in antibiotic-loaded bone cement. The onset of an allergic reaction in this setting might require removal of the prosthesis and all antibiotic-loaded bone cement. At present, it appears prudent for surgeons to avoid use of a particular antibiotic in bone cement if the patient has a documented allergy to that antibiotic.

Antimicrobial Resistance

The emergence of drug-resistant organisms is an ever-increasing societal concern. Much of the concern in North America has been focused on methicillin-resistant staphylococci and vancomycin-resistant enterococci. Antibiotic-loaded cement has an optimum surface for colonization, and prolonged exposure to antibiotics at subinhibitory levels allows mutational resistance to occur[21,65-69]. The surface of bone cement is a suitable substrate for bacterial growth, even in the presence of antibiotics[66]. The adhesion of bacteria onto polymethylmethacrylate induces a marked decrease in susceptibility to multiple antibiotics[70]. Interestingly, each type of bone cement has a different window of effectiveness with regard to reduction in biofilm formation that is not related to the gentamicin-release kinetics[71]. This ability of organisms to grow on antibiotic-loaded bone cement and be exposed to subinhibitory levels of antibiotics that can induce mutational resistance is a clear reason for caution regarding the widespread clinical use of antibiotic-loaded bone cement for prophylactic purposes.

In a rat model of an orthopaedic procedure contaminated with a low-dose gentamicin-sensitive inoculum of coagulase-negative staphylococci, bone cement containing either gentamicin or saline solution (control) was implanted subcutaneously[65]. Although a lower overall rate of infection was seen in the group with the gentamicin-loaded cement (73% compared with 41%), there was a significantly higher rate of gentamicin-resistant coagulase-negative staphylococcus infection in that group (78% compared with 19%, $p < 0.01$). The authors concluded that gentamicin-loaded cement might not be appropriate for revision surgery if it has been used already in previous surgery. This concern about the development of resistance has been corroborated by several clinical studies[65,72,73].

In a study of patients who had revision surgery because of presumed aseptic loosening, with most having had the primary surgery performed with gentamicin-loaded bone cement, resistant bacterial strains were grown on culture of specimens from a majority of the prostheses[74]. These recovered bacteria were resistant to gentamicin with minimal inhibitory concentrations of >512 mg/L and minimal bactericidal concentrations of >1024 mg/L.

Of ninety-one patients with a deep infection caused by coagulase-negative staphylococci, twenty-seven had multiple strains of the organism, many of which were resistant to previously used antibiotics[72]. The use of gentamicin-loaded cement in the primary arthroplasty was associated with the emergence of gentamicin-resistant coagulase-negative staphylococci in the subsequent deep infection: a gentamicin-resistant infection developed in 88% of the patients who had had gentamicin-loaded bone cement used in the primary arthroplasty as compared with only 16% of the patients who had had plain cement used in the primary arthroplasty. Seventy-two patients treated with one-stage exchange arthroplasty with use of gentamicin-loaded bone cement had an overall failure rate of 13% due to recurrence of infection. The failure rate was 21% in the patients infected with gentamicin-resistant coagulase-negative staphylococci compared with 8% in the group that was not.

In another study, coagulase-negative staphylococci were grown on culture of specimens taken from patients before and two weeks after a total hip replacement with the use of gentamicin-loaded bone cement and no systemic antibiotics[73]. Gentamicin-resistant staphylococci were only found postoperatively, in 20% of sixty-four patients. One of the primary concerns about this pattern of resistance is that the use of gentamicin-loaded cement will be ineffective for treatment and subsequent reimplantation of a new prosthesis, which will require the use of different antibiotics[65].

In a study in which forty-eight bacterial strains were recovered from cultures of specimens from twenty-six total hip replacements complicated by infection, the isolates included coagulase-negative staphylococci (seventeen), *Staphylococcus aureus* (four), *Staphylococcus hominis* (three), *Staphylococcus capitis* (two), *Staphylococcus haemolyticus* (one), *Staphylococcus sciuri* (one), Micrococcus species (one), and *Propionibacterium acnes* (nineteen)[74]. On the basis of minimum bactericidal concentrations, ciprofloxacin was the most active antimicrobial agent, followed in decreasing order by cefamandole, vancomycin, cefotaxime, gentamicin, fusidic acid, and erythromycin. The investigators concluded that performing bacterial cultures on specimens from prostheses explanted during revision total hip arthroplasty improved postoperative antibiotic therapy and should reduce the need for additional revision.

In a group of twenty-five patients with pain at the site of a prosthesis up to twenty years following primary hip or knee arthroplasty with use of gentamicin-loaded bone cement, gentamicin was detected in the joint fluid from nine of fifteen patients with a knee prosthesis and four of ten patients with a hip prosthesis[29]. The concentrations ranged from 0.06 to 0.85 mg/L, with no relationship between the gentamicin concentration and the time after the primary arthroplasty. Although most concentrations were below the levels required to inhibit susceptible pathogens, the authors concluded that gentamicin release around failing implants may lead to false-negative cultures in some patients and provide selective pressure for the emergence of resistance in patients with an infection.

The specific mechanisms that render an antibiotic ineffective against a particular bacterial strain have not been well studied in conjunction with orthopaedic biomaterials. It has been suggested that bacteria that produce a glycocalyx adhere to the biomaterial, resulting in a physiologic change in the bacteria that confers antibiotic resistance[7]. Others have sug-

gested that a possible explanation for this physiologic change is hydrophobicity of the implant material, electrostatic interactions, and/or the surface roughness of the implant material[21,71]. There is some emerging evidence that bacterial or fungal attachment to a biomaterial results in the development of antibiotic resistance. The authors of an in vitro study seeded a methicillin, gentamicin, and tobramycin-resistant strain of *Staphylococcus epidermidis* from the infected site of a knee arthroplasty onto polymethylmethacrylate disks with a resulting exposed area of 200 mm^2 (6-mm diameter)[70] . They found that coagulase-negative staphylococci that had adhered to the polymethylmethacrylate material had a significant increase in resistance to beta-lactam antibiotics (cefamandole, cefazolin, imipenem, and ampicillin) compared with non-adhered bacteria ($p < 0.005$) as demonstrated by the difference in the diameters of the growth-inhibition areas (about a 30% difference [~14 and ~20 mm, respectively]). To a lesser degree, the adhered bacteria had about a 15% increase in resistance (a ~17-mm growth-inhibition-area diameter compared with ~20-mm diameter for the non-adhered bacteria) to vancomycin, erythromycin, trimethoprim-sulfamethoxazole, and the aminoglycosides ($p < 0.0005$). The exact mechanism of this increased resistance remains unclear as bacterial contact with bone cement did not induce any phenotypic or genotypic increase in the methicillin resistance of the bacterial population[75]. It has been proposed that the protective mechanisms at work in biofilms appear to be distinct from those that are responsible for conventional antibiotic resistance[76]. In biofilms, poor antibiotic penetration, nutrient limitation and slow growth, adaptive stress responses, and formation of persister cells (those protected from all types of antimicrobial insults) are hypothesized to constitute a multilayered defense[76].

It would also appear that certain bacteria grow preferentially on certain biomaterials, with coagulase-negative staphylococci preferring attachment to bone cement and *Staphylococcus aureus* exhibiting preferential attachment to metallic surfaces[77]. Three clinical isolates of coagulase-negative staphylococci were evaluated in an in vitro study to determine their propensity for adhering to three biomaterials (stainless steel, polymethylmethacrylate, and ultra-high molecular weight polyethylene) after twenty-four hours of exposure to various concentrations of antibiotics[78]. Analysis of all three organisms revealed that ten times more surviving adherent bacteria were bound to the polymethylmethacrylate disks than to the other biomaterials. Furthermore, it is questionable whether antibiotics in the bone cement prevent bacterial attachment. In a study evaluating the inhibition of bacterial adhesion to constructs consisting of tobramycin sulfate powder (1.2 g) mixed with Palacos bone cement (40 g), the tobramycin-impregnated surfaces reduced adhesive bacterial colonization by only one log relative to control disks[79]. This suggests that tobramycin-impregnated polymethylmethacrylate may not be effective in preventing colonization of the biomaterial and may thus be a poor choice as a drug-delivery vehicle.

The difficulty is in the balancing of a potential decrease in the prevalence of deep periprosthetic infection with the potential increase in drug-resistant organisms. In a report from the Ohio State University Medical Center, the overall rate of infection decreased with the introduction and use of antibiotic-loaded bone cement; however, the prevalence of aminoglycoside-resistant bacteria, particularly in *Staphylococcus aureus* and coagulase-negative staphylococcal infections, increased[80]. Because of the considerable data suggesting the potential for the development of bacterial antibiotic resistance, antibiotic-loaded bone cement should not be used routinely for prophylaxis. Rather, it should be used for prophylaxis only when there are clear indications, such as a high-risk primary procedure or a high-risk revision arthroplasty. Although there are few studies available that can be used to clearly identify a high-risk patient undergoing total joint arthroplasty who might benefit from the routine use of antibiotic-loaded bone cement for prophylaxis, there are patient groups that have a higher risk of infection, as described below.

Vancomycin should not be used as a primary agent for prophylaxis because of the emergence of resistant organisms and the need to reserve this antibiotic for patients who require it for treatment[81].

Costs of Antibiotic-Loaded Bone Cement

Currently the increased acquisition cost of commercially available antibiotic-loaded bone-cement products is considerable. Compared with the cost of plain bone-cement products, the cost of equivalent antibiotic-loaded bone-cement products is increased anywhere from $284 to $349 (United States dollars) per 40-g packet. If the historical 11% usage of antibiotic-loaded bone cement increased to 50% of the estimated 500,000 primary total joint arthroplasties performed annually in the United States, and if two packets of cement (at a $300 increased cost per packet) were used for each joint replacement, the increase in overall health-care costs would be $117,000,000 for the 195,000 additional cases.

This estimated increased health-care cost must be balanced with the potential cost savings associated with a realized reduction in the rate of infection associated with routine use of antibiotic-loaded bone cement for prophylaxis in primary total joint replacement. At an approximately $50,000 cost for the treatment of an infection at the site of a total joint replacement, there would have to be 2340 fewer infected patients among the additional 195,000 patients for the routine use of antibiotic-loaded bone cement to be fiscally neutral. With a rather high estimated infection rate of 1.5%, a deep postoperative infection could be expected to develop in 2925 of 195,000 patients. In other words, the rate of deep periprosthetic infection would need to be reduced from this 1.5% to 0.3% to recover the costs associated with the routine use of commercially available low-dose antibiotic-loaded bone cement in primary total joint arthroplasty. Moreover, while the estimated costs for the treatment of an infection at the site of a total joint arthroplasty do not account for morbidity and mortality associated with the treatment required, the increased costs associated with the treatment of more drug-resistant organisms are unknown.

TABLE III Factors Associated with Higher Risk of Infection After Total Joint Arthroplasty[34]

Inflammatory arthropathies: rheumatoid arthritis, systemic lupus erythematosus
Disease, drug, or radiation-induced immunosuppression
Insulin-dependent (Type-I) diabetes
Previous joint infection
Malnourishment
Malignant tumor
Hemophilia

Who Is a High-Risk Patient?

For the purposes of this article, we define high-risk patient groups as those patient populations that have been shown to have a higher rate of periprosthetic joint infection than the total joint replacement population as a whole (Table III)[34]. The infection rates in several large series have been reported to be between 0.2% and 1%[82-84]. It is important to differentiate those groups that are at higher risk for early infection (i.e., infection from direct contamination at the time of the surgery as opposed to later hematogenous spread), as such groups stand to gain the most from antibiotic-loaded bone cement.

These groups can be divided into three basic subgroups: patients with a higher contamination load, patients with a history of contamination and/or infection, and patients with decreased immunity (Table IV)[85-106].

Patients with a Higher Contamination Load

Prolonged operating time: The operating time may be an important factor in the development of infection. Smabrekke et al.[87] evaluated 31,745 total hip replacements in Norway and discovered that an operating time of more than 150 minutes was associated with a higher infection rate.

Revision surgery: Revision surgery combines a usually longer operating room time (which increases the chance of contamination) with the possibility of unrecognized prior indolent infection or contamination. Blom et al.[82] examined the results of 931 primary and sixty-nine revision total knee replacements and found the prevalence of deep infection to be 1% after primary total knee replacement compared with 5.8% after revision total knee replacement.

Patients with a History of Contamination

Prior joint infection: In 1988, Jerry et al.[89] reported on a series of sixty-five patients with a history of infection of the knee joint, with or without involvement of the adjacent bone, who were treated with a primary total knee replacement at the Mayo Clinic. The rate of deep infection following the replacement was 7.7% overall and 4% in the patients who had infection of only the knee joint. In a subsequent study from the Mayo Clinic[88], involving twenty primary total knee replacements with antibiotic-loaded bone cement performed in nineteen patients with a previous knee infection, the rate of deep infection was 5%.

Patients with a Decreased Immunity

Rheumatoid arthritis: Meding et al.[105] reported a deep infection rate of 2.4% following 220 primary cruciate-retaining total knee replacements in patients who had rheumatoid arthritis. Sharma et al.[92] found an infection rate of 3.2% at a mean of 12.9 years following sixty-three total knee replacements in patients with rheumatoid arthritis. Amenabar et al.[93] reported a prevalence of deep infection of 8% in a series of twenty-five total knee replacements in patients with rheumatoid arthritis. In a study of 103 total hip replacements in seventy-five patients with rheumatoid arthritis, Creighton et al.[106] reported a 3% prevalence of deep infection at ten years. Many studies have shown that patients with rheumatoid arthritis have poorer nutritional indices, and this may make sorting out the critical variable difficult. Nonetheless, Liu et al.[94] reported that the use of cefuroxime-loaded bone cement in primary total knee replacements performed in sixty patients with rheumatoid arthritis resulted in a 0% rate of deep infection.

Diabetes mellitus: An increased risk of deep infection in patients with diabetes mellitus has been shown in at least three studies. In a randomized prospective trial, Chiu et al.[41] noted a

TABLE IV High-Risk Groups of Patients Undergoing Total Joint Replacement

Risk Group	Risk Factors	Deep Infection Rate *(%)*
Increased contamination	Revision total joint replacement	4-8[82,85,86]
Increased contamination	Operative time > 150 min	3[86,87]
History of contamination	Prior joint infection	5-9[88-91]
Decreased immunity	Rheumatoid arthritis	2.4-8[92-94,105,106]
Decreased immunity	Diabetes mellitus	3.1-7[41,95-97]
Decreased immunity	Organ transplantation	5-19[98-101]
Decreased immunity	Obesity	6[102]
Decreased immunity	Hemophilia	10-13[103,104]

deep infection rate of 3.1% in 162 knees in which plain cement had been used and a rate of 0% in 178 knees in which antibiotic-loaded bone cement had been used. Yang et al.[95] reported a deep infection rate of 5.5% in a series of 109 primary total knee replacements in eighty-six patients with diabetes mellitus. England et al.[96] found a prevalence of deep infection of 7% after fifty-nine primary total knee replacements in forty patients with diabetes mellitus. Meding et al.[97] also noted an increased prevalence of deep infection in patients with diabetes as compared with those without diabetes, but the prevalence in their series was lower than that in other studies, an observation that they attributed to the use of antibiotic-loaded bone cement. They reported on 5220 total knee replacements in which cefuroxime-loaded bone cement had been used routinely, with 363 of the procedures done in patients with diabetes mellitus, both insulin-dependent and non-insulin-dependent. The prevalence of deep infection was 1.2% in patients with diabetes and 0.7% in patients without diabetes.

Organ transplantation: Many studies have shown an increased prevalence of periprosthetic joint infection in patients with chronic immunosuppression due to organ transplantation. Murzic and McCollum[99] reported an infection rate of 10% in association with total hip replacements without cement in patients who had undergone renal transplantation. Lo et al.[100] reported a 13% infection rate in a small series of thirty patients with a renal transplant, but most of the infections occurred more than one year postoperatively. As a result of chronic pharmacologic immunosuppression, these patients are at increased risk for deep periprosthetic infection not only due to contamination at the time of surgery but also due to later hematogenous seeding. It is less clear whether antibiotic-loaded bone cement will make a difference in the infection rate in these patients. Stromboni et al.[101] reported that a deep infection developed, albeit at a mean of 6.8 years, following five of forty-eight total hip replacements that had been done in thirty-two patients with a renal transplant. They did not find a significant ($p > 0.05$) prevalence of early prosthetic infection (within the first year), however.

History of steroid injection: Kaspar and de V de Beer[107] performed a matched-pair retrospective study of forty patients who had had a total hip replacement after an intra-articular cortisone injection compared with forty patients who had had a replacement without a prior injection. A deep infection developed in four patients who had had the steroid injection and in no patient who had not had an injection. These were early infections that could also be attributed to contamination at the time of surgery.

Malnutrition: The association of preoperative nutritional deficiency and the development of postoperative infection, regardless of the type of surgery, has been known for many years[108-113]. In patients with cerebral palsy who had spine surgery, Jevsevar and Karlin[114] noted an increased infection rate when the serum albumin level was <35 g/L and the total lymphocyte count was <1500 cells/mm^3. In a study of 217 primary total hip replacements, Greene et al.[115] found that patients with a preoperative lymphocyte count of <1500 cells/mm^3 had a five times higher rate of major wound complications and those with an albumin level of <35 g/L had a seven times higher rate of wound complications. Del Savio et al.[116] showed, in a series of eighty-nine consecutive total hip replacements, that the complication rate and length of hospital stay increased for patients with a serum albumin level of <39 g/L. Marin et al.[117] found that, of 170 patients treated with a primary total hip or total knee replacement, those with a preoperative lymphocyte count of <1500 cells/mm^3 had a three times higher prevalence of healing complications. Nelson et al.[118] noted, in their multicenter study of total hip and knee replacements complicated by infection, that malnutrition was an important variable in patients with recurrence of the infection. Virtually every study also showed an increase in complications other than infection, including increased lengths of hospital stays and mortality rates, in association with malnutrition. These data suggest that, rather than performing an arthroplasty on a nutritionally depressed patient and using antibiotic-loaded bone cement, the surgeon should restore the patient's nutritional status prior to the surgery. However, it may sometimes not be possible to wait before performing implant surgery (e.g., for a patient with a femoral neck fracture), and antibiotic-loaded bone cement should be considered in such cases.

Obesity: Namba et al.[102] noted that 52% of 1813 patients treated with total knee arthroplasty and 36% of 1071 patients treated with total hip arthroplasty had a body-mass index of >30. Compared with patients with a body-mass index of <30, obese patients had 6.7 times higher odds of a deep infection developing at the site of a total knee arthroplasty and forty-two times higher odds of a deep infection developing at the site of a total hip arthroplasty. It should be noted that many of these obese patients also had diabetes, so it is difficult to sort out the critical variable.

Hemophilia: Silva and Luck[104] reported an infection rate of 13% at the time of long-term follow-up after ninety total knee replacements in sixty-eight patients with hemophilia. The ten-year rate of survival free of infection was 77%. However, nine of twelve resection arthroplasties were done because of late infection, and antibiotic-loaded bone cement would be expected to be less effective after the first six weeks. Powell et al.[103] found a rate of deep infection of 9.8% following fifty-one total knee replacements performed in patients with hemophilia between 1975 and 2002. They reported no difference in the infection rate between patients who were positive for the human immunodeficiency virus (HIV) and those who were negative for it. Many of these infections also occurred late. Thus, there is clear data showing a higher prevalence of deep periprosthetic infection after total knee replacements in patients with classic hemophilia, but there is no evidence that the use of antibiotic-loaded bone cement decreases this rate.

Choice of Antibiotic in Antibiotic-Loaded Bone Cement Used Prophylactically

The aminoglycoside antibiotics were originally selected for

use in antibiotic-loaded bone cement because of their broad bacterial coverage and their low allergy profile. Because the level of gentamicin or tobramycin in the joint is often ten times greater than safe blood levels, the efficacy of those drugs is excellent unless the organism has a specific resistance to them. Gentamicin and tobramycin are also the only antibiotics currently available in commercially premixed low-dose antibiotic-loaded bone-cement preparations. As mentioned above, however, low doses of other types of antibiotics, including several of the cephalosporins, have been hand-mixed into bone-cement preparations, and those preparations have had good success in prophylactic applications. Allergic reactions have not been reported, to our knowledge, but it is prudent for the surgeon to consider the individual patient's allergy history before selecting the antibiotic for antibiotic-loaded bone cement.

There has been considerable research on the primary bacterial contaminants in total joint surgery. Al-Maiyah et al.[119] took 627 blood-agar impressions of the gloved hands of surgical personnel during the performance of fifty total hip arthroplasties in England. Bacteria grew on culture of fifty-seven impressions (9%); 69% were coagulase-negative staphylococci, 12% were Micrococcus, 9% were diphtheroids, and 6% were *Staphylococcus aureus*. Of the coagulase-negative staphylococci, only 52% were sensitive to cefuroxime. In contrast, Ridgeway et al.[120] found *Staphylococcus aureus* in 50% of the surgical site infections (both superficial and deep) in their multiple-hospital study in England. More than half of the *Staphylococcus aureus* isolates were methicillin-resistant.

Thus, it appears that staphylococcal species are the primary bacteria toward which antibiotic-loaded bone cement would be directed. The currently available commercial gentamicin or tobramycin-loaded bone cements provide sufficient elution concentrations to be bactericidal even against methicillin-resistant organisms. Vancomycin may also be added to bone cement, but it has a lower efficacy than gentamicin or tobramycin at these concentrations. The use of vancomycin should be considered in revisions following primary arthroplasties in which gentamicin or tobramycin-loaded bone cement had been used because of the prevalence of gentamicin resistance in association with such revisions. Cephalosporins may also be considered for antibiotic-loaded bone cement that is to be used prophylactically but may not be effective against methicillin-resistant organisms.

Overview

Presently in North America, the issue of whether to use antibiotic-loaded bone cement routinely for prophylaxis against deep periprosthetic infection when performing primary or aseptic revision total joint arthroplasty is still very controversial. Currently, the only approved indication for the use of commercially available low-dose antibiotic-loaded bone cement is in the second stage of a revision, following removal of the prosthesis and all cement and other implanted material as well as eradication of the infection.

The use of high-dose antibiotic-loaded bone cement, with a variety of different antibiotic combinations, for the treatment of an established musculoskeletal infection still requires hand-mixing of the appropriate antibiotics as determined on the basis of culture results and sensitivity testing of the pathogenic microorganisms. This requires the physician to use antibiotic-loaded bone cement in a non-FDA-approved clinician-directed application. Similarly, the use of low-dose antibiotic-loaded bone cement for prophylaxis in patients undergoing primary or aseptic revision total joint arthroplasty also is a non-FDA-approved clinician-directed application. Because of concerns regarding resistance and cost, the routine use of low-dose antibiotic-loaded bone cement in aseptic joint arthroplasty cannot be recommended. On the basis of available data, it seems reasonable to suggest that low-dose antibiotic-loaded bone cement be considered a reasonable method of prophylaxis for certain high-risk patients undergoing primary or revision total joint arthroplasty.

Many questions remain unanswered, and these require additional study. They include the selection of the best antibiotic for antibiotic-loaded bone cement that is used for prophylaxis, whether the increased costs associated with the use of commercially available antibiotic-loaded bone cement are justified by a substantial reduction in the rate of deep infection, whether commercially available antibiotic-loaded bone cement is mechanically superior to less expensive hand-mixed antibiotic-loaded bone cement in the clinical setting, and whether an increased use of low-dose antibiotic-loaded bone cement will result in an increased prevalence of drug-resistant microorganisms.

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