Infection of orthopedic implants and the use of antibiotic-loaded bone cements

A review

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Submitted 00-05-01. Accepted 01-06-25

ABSTRACT – Infections by bacteria are a serious complication following orthopedic implant surgery, that can usually only be cured by removing the implant, since the biofilm mode of growth of infecting bacteria on an implant surface protects the organisms from the host immune system and antibiotic therapy. Over the past few decades, attempts have been made to prevent and cure orthopedic implant infections by incorporating antibiotics in polymethylmethacrylate bone cements, in primary and revision surgery. However, the clinical efficacy of antibiotic-releasing bone cements is not accepted by all and the long-term exposure to low doses from antibiotic-releasing bone cements in patients is strongly related to the emerging threat of antibiotic resistance in medicine today. In this article, we start by reviewing the mechanisms governing the formation of an infectious biofilm on orthopedic implant materials, the release mechanisms and properties of clinically-used, antibiotic-loaded bone cements. The clinical efficacy of antibiotic-loaded bone cements is evaluated analyzing separatedly the prophylactic and therapeutic uses of these products.

Polymethylmethacrylate (PMMA) was one of the first materials produced by the chemical industry to be used as a biomaterial. The first applications of PMMA were mostly in dentistry (Munson and Heron 1941, Bauer 1949), where it is still the commonest material for dentures. In orthopedic surgery, Scales and Herschell (1945) and the Judet brothers (1950) made a hip endoprosthesis of PMMA to treat coxarthrosis. Charnley (1970) introduced PMMA bone cement to stabilize metallic hip implants and transfer mechanical loads between the implant and bone. Nowadays, despite several refinements (Hasenwinkel et al. 1999), bone cements are still based on PMMA.

The use of polymethylmethacrylate, like other biomaterials in man, entails the risk of attracting infectious microorganisms (Gristina 1987). Biomaterial-associated infections pose great surgical problems, since removal is not always easy, and patients suffer severe discomfort. Such infections are not uncommon in orthopedic surgery, where infection rates range from 1% to 3%, despite the use of intraoperative systemic antibiotic prophylactics, strict hygienic protocols, and special sterile enclosure with laminar flow (Antti-Poika et al. 1990, Harris and Sledge 1990). The overall annual costs of orthopedic implant-associated infections in the United States range between 150 and 200 million USD (Sculo 1993) and about 3 times as much in various parts of the world. Buchholz and Engelbrecht (1970) incorporated antibiotics in PMMA bone cements to reduce the infection rates in orthopedic surgery, assuming that the antibiotic will gradually be released to give higher local concentrations than can be achieved by systemic therapy. Nowadays, antibiotic-loaded bone cements are used for primary and revision surgery, while antibiotic-loaded PMMA beads are part of a more comprehensive treatment of infection and supplement other—mostly surgical—interventions. Antibiotic-loaded PMMA spacers are used in multistage revision of infected implants, where they have not only an antimicrobial effect,

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but also prevent contraction of ligaments and of scar tissue from grow into the joint space.

Biomaterial-associated infections are difficult to cure with antibiotics and, in many caes, replacement of a prosthesis is the only remedy, because the biofilm mode of growth protects the infectious organisms against the host immune system and other environmental attacks, such as from antibiotics (Costerton et al. 1987). Consequently, microorganisms adhere and grow on antibiotic-loaded bone cements and are exposed over long periods to drugs, such as gentamicin, erythromicin or vancomycin incorporated in the cements and they eventually become resistant. In orthopedic surgery, Staphylococcus aureus, Staphylococcus epidermidis, Pseudomonas or other Gram-negative rods are thought to be mainly responsible for implant-associated infections. Initially, all clinical isolates of S. aureus were sensitive to gentamicin (Barber and Waterworth 1966, Hoeprich 1969, Jordan and Hoeprich 1977), but hardly a decade after the introduction of this antibiotic in general medicine and its incorporation in bone cements, outbreaks of infections in hospitals caused by gentamicin-resistant strains of S. aureus were reported (Speller et al. 1976, Wyatt et al. 1977, McGowan et al. 1979). Therefore, the use of antibiotic-loaded bone cements in orthopedic surgery may partly cause antibiotic resistance among infectious organisms (Sanzen and Walder 1988, Hope et al. 1989, Tunney et al. 1998a, Van de Belt et al.1999), although it must be emphasized that concerns about inducing antibiotic resistance among microorganisms apply not only to orthopedics, but now even to all medical disciplines (Neu 1992, MacGowan et al. 1998, Wilcox 1998).

In this review we first summarize current views on the formation of an infectious biofilm on biomaterial implants, with special emphasis on orthopedic implants, and the mechanisms by which infectious organisms adhere to an implant surface. Then, we review the prophylactic and therapeutic use of antibiotic-loaded bone cements in orthopedic surgery, including possible release mechanisms and clinical efficacy. The biomechanical effects of incorporating antibiotics in bone cements (Lautenschlager and Marschall 1976, Marks et al. 1976, Bargar et al. 1986, Davies et al. 1989, Fritsch 1996) are considered outside the scope of this review.

Formation of biofilm

Microorganisms have a strong tendency to cause surfaces to form a micro-ecosystem in which various microbial strains and species grow in a slime-enclosed biofilm. In man, the most troublesome biofilms are implant-associated and examples are numerous, including: artificial hearts, contact lenses, vascular grafts, intravenous and urinary catheters, internal fixation devices, voice and joint prostheses. In orthopedic surgery, the number of patients with an internal fixation device or artificial joint has grown rapidly to more than 4.4 million people in the United States with at least one internal fixation device and more than 1.3 million with an artificial joint (Praemer et al. 1992). In the next section, we describe the process of biofilm formation, including mechanisms of microbial adhesion to biomaterials and biomaterial surface properties that govern microbial adhesion, all with special emphasis on orthopedic applications.

Steps in biofilm formation

All biofilms originate in the same sequence of events as shown in Figure 1 (Van Loosdrecth et al. 1990). In nearly all clinical uses of biomaterials, the biomaterial surfaces are first covered with a so-called "conditioning film". This consists of adsorbed macromolecules from the biological environment in which the biomaterial is placed (Figure 1a). Dental restorative materials adsorb salivary proteins, contact lenses adsorb proteins and lipid components from tear fluid, while blood-contacting biomaterials adsorb various plasma proteins before the first microorganism appears. The process of conditioning film formation occurs within seconds of exposure to a biological environment. Orthopedic biomaterials, like PMMA, are mostly in contact with bone and come into direct contact with blood. Therefore plasma proteins can form a conditioning film.

This means that microorganisms adhere to an adsorbed conditioning film and seldom to a bare biomaterial surface. They can reach this surface via various transport mechanisms, such as diffusion, convection or sedimentation (Figure 1b). In the oral cavity, microorganisms are transported to teeth or biomaterial surfaces through these processes. Orthopedic implants can become infected

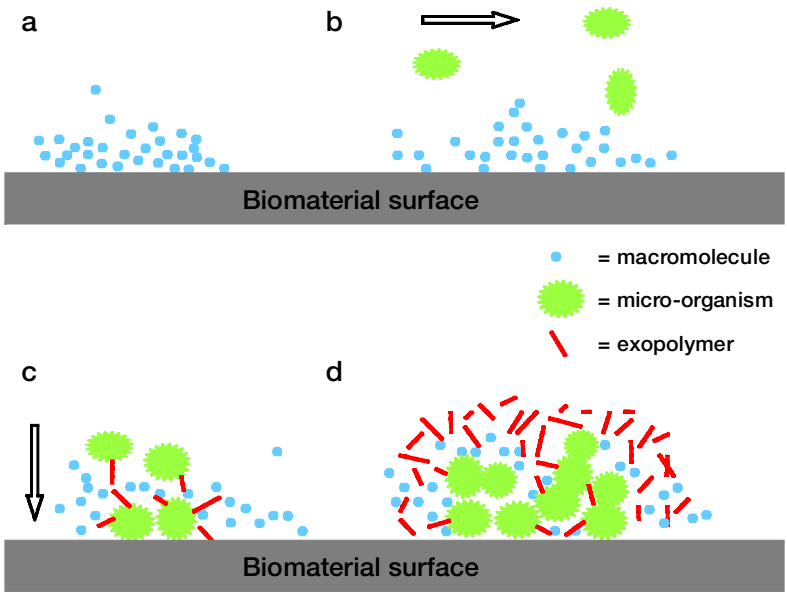

Figure 1. Sequential steps in the formation of biofilms on a biomaterial surface, including.
a. Formation of a conditioning film.
b. Microbial mass transport.
c. Initial microbial adhesion and anchoring through exopolymer production.
d. Growth of adhering microorganisms.

by direct contamination during surgery, but most infections are not surgical (Schmalzried et al. 1992). Moreover, Schmalzried et al. showed that as the follow-up period of patients increased, the incidence of infections of hematogenous origin increased concomitantly. In many cases, after urogenital tract infections or dental treatment, microorganisms are transported by the blood stream to find their way to the conditioning film on the implant surface ("convective mass transport", see Figure 1), causing late hematogenous infections (Stinchfield et al. 1980, Lindquist and Slätis 1985). Recently, LaPorte et al. (1999) concluded that infection of total hip arthroplasties after dental treatment is commoner than hitherto suspected.

The initial adhesion of microorganisms is reversible and depends on the overall physico-chemical characteristics of the microbial cell surface, the biomaterial surface and the biological bathing fluid. This reversible adhesion process of microorganisms may become irreversible through exopolymer production, causing firm anchoring (Figure 1c). The exopolymers surrounding adhering microorganisms embed the biofilm to form a so-called "glycocalix" (Figure 1d; Neu et al. 1992). This term was coined by Gristina and Costerton (1985) and refers to the accumulation of glycoproteins in the outer lining of the biomaterial. Apart from anchoring the biofilm, it protects against environmental attacks and antibiotics (Nickel et al. 1985, Brown et al. 1988, Goulet et al. 1988, Sugarman and Young 1989, Isaklar et al. 1996). Most biomaterial-associated infections in orthopedics, when cultured in routine hospital laboratories, appear to be monomicrobial, but urinary and oral infections can become polymicrobial by co-adhesion of other strains and species to an existing biofilm (Walterspiel et al. 1986, Neu et al. 1992). Growth of the adhering organisms is the main mechanism of multiplication in a biofilm and eventually leads to the formation of a thick film. In this context, "thick" refers to the thickness of the original biofilm to which new layers are being added and into which bacteria find room to multiply. As a final step in biofilm formation, organisms on the periphery of the expanding biofilm may detach or separate. This plays a large part in the pathogenesis of septic processes. In this respect, the initially adhering microorganisms play a pivotal role linking the entire biofilm mass to the biomaterial implant (Neu and Marschall 1990, Busscher et al. 1996).

Surface properties affecting microbial adhesion

Microbial adhesion, as a step in biofilm formation, mainly consists of an interaction between two surfaces in a biological bathing fluid. The properties of the interacting microbial and substratum surfaces are thus crucial to the interaction and an infection-resistant surface favors tissue adhesion

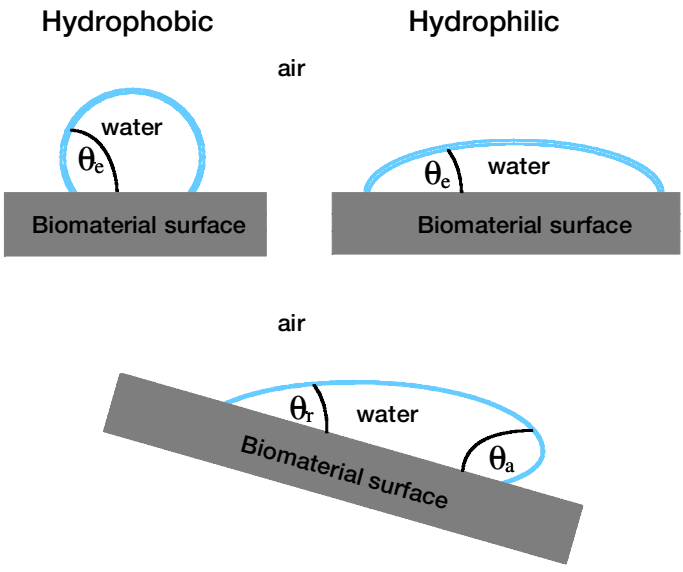

Figure 2. A liquid droplet on the biomaterial surface spreads poorly to form a high contact angle ("hydrophobic" surface), or spreads well on a hydrophilic surface (top). An advancing liquid front usually gives a different contact angle than a stable or receding liquid front (bottom).

(Gristina 1987), although especially after wear, inflammatory reactions may occur even without a microbial infection (Kozinn et al. 1986).

Initial microbial adhesion to inert substrata is caused by the combination of attractive Lifshitz-Van der Waals forces, attractive or repulsive acid-base and electrostatic interactions, the latter having the most repulsive effect (Rutter and Vincent 1980, Tadros 1980, Van Oss 1990). Lifshitz-Van der Waals attraction forces are long-range and attraction begins when the distance between the interacting surfaces is about 50–100 nm. Acid-base interactions can be attractive or repulsive, depending on the chemistry of the microbial and substratum surfaces, while electrostatic interactions are generally repulsive, because natural and synthetic surfaces are nearly always negatively charged.

The ability of surfaces to exert Lifshitz-Van der Waals forces is reflected by the contact angle with liquids on these surfaces. Figure 2 (top) shows the contact-angle equilibrium of a liquid droplet on a biomaterial (PMMA) surface. When a water droplet spreads poorly over a surface to form a high contact angle, the surface is said to be "hydrophobic", while if water spreads, the contact angle is low and the surface is called "hydrophilic". The hydrophobicity of biomaterial surfaces dictates which proteins adsorb from biological bathing fluids, like saliva, tear fluid, urine or plasma and the conformation in which these proteins adsorb. Therewith, hydrophobicity controls microbial adhesion to conditioning films. Hydrophobic biomaterials in the human oral cavity (Quirynen et al. 1988) and in the oropharynx (Everaert et al. 1997) have been found to attract less biofilm than hydrophilic biomaterials (Busscher et al. 1990). The hydrophobicity of biomaterials used in orthopaedic surgery varies (Table 1).

In a physiological environment, electrostatic interactions are usually small due to the high ionic strength of physiological bathing fluids. Frequently, it is attempted to create more negatively charged biomaterials surfaces, as these would repel infectious, negatively charged micro-organisms. Recently, it has been shown, however, that growth of infectious organisms is slower on positively charged biomaterials surfaces, either as a direct result of the antimicrobial positively charged groups or because adhesion is too strong to allow cell division (Gottenbos et al. 2001). These observations may offer new pathways for the design of infection-resistant biomaterials.

Roughness is another important surface feature with regards to biofilm formation, especially in orthopaedics. Parts of bone cements are cured against the bone and metallic implant, after which polymerisation shrinkage occurs, leaving a cement surface consisting of an imprint of the opposing surfaces. Consequently, bone cement in the clinical environment is inevitably rough. Although

Table 1. The hydrophobicity of various biomaterials used in orthopedics according to their water contact angles, including advancing and receding contact angles (see also Figure 2) and the surface roughness of various gentamicin-loaded acrylic bone cements pressed against glass (unpublished)

Bone cement	Contact angle (degrees)	Advancing–receding angles (degrees)	Surface roughness (μm)
Titanium alloy	35–45	Nd	Nd
Ceramic	40–50	Nd	Nd
Stainless steel	65–75	Nd	Nd
Cobalt alloy	70–80	Nd	Nd
Polyethylene	95–100	Nd	Nd
PMMA	70–80	Nd	Nd
CMW1	70	85–45	0.33
CMW3	75	79–53	0.30
CMW Endurance	75	76–51	0.20
CMW 2000	73	81–51	0.16
Palacos	76	79–53	0.29
Palamed	80	80–46	0.49

Nd Not determined

it is under debate whether microbial adhesion to smooth surfaces is more or less extensive than on rough surfaces, a rough surface offers more protection sites for growth of adhering organisms (Verran and Maryan 1997, Taylor et al. 1998) and several studies have indicated that biofilms develop faster on rough surfaces (Quirynen and Bollen 1995).

Causative organisms in orthopedic implant infections

In orthopedics, biofilm-centred infection can be caused by a great number of organisms. With routine hospital laboratory cultures mostly one causative organism is found on infected implants, but using more extensive culture techniques, infections seem to be polymicrobial (Gristina and Costerton 1985, Tunney et al. 1998b). During the past decades, a change in causative strains has taken place. In the early seventies, coagulase-negative staphylococci, Propionibacterium, anaerobic peptococci and streptococci were uncommon pathogens, but nowadays these organisms are known to cause several infections (Charnley 1972, Gristina and Kolkin 1983, Gristina and Costerton 1985). Yet, bacteria isolated from orthopaedic infections are most frequently S. epidermidis and S. aureus, while aerobic Gram-negative bacteria cause 10–20% of all deep infections, and anaerobic bacteria are responsible for another 10% (Fitzgerald et al. 1995). The different physical and chemical properties of biomaterials surfaces make that bacteria show a specific variation in adherence. S. epidermidis is frequently involved in infection of polymeric biomaterials (Gristina 1987), whereas S. aureus is mostly involved in infection of metallic implants, or when dead bone acts as substratum. Possibly, different substratum surfaces offer different degrees of protection of the specific adhering micro-organism to antibiotics, as suggested by Naylor et al. (1990) comparing vancomycin, nafcillin, gentamicin, and daptomycin resistance of three different coagulase-negative, slime-producing bacteria on PMMA and metallic implants.

Antibiotic-loaded bone cements

Antibiotic-loaded bone cements essentially consist of a PMMA matrix, an antibiotic and radiopacifiers (see Table 2). Buchholz and Engelbrecht (1970) simply mixed Palacos bone cement with gentamicin. At that time, the release mechanism of the gentamicin was largely unknown. In this section we give an overview of the different constituents in antibiotic-loaded PMMA bone cements used in clinical practice and their potential influence on antibiotic release.

The polymer matrix

The constituents in different clinically used PMMA bone cement brands are chemically relatively similar and differences are confined to the relative amounts of copolymer, monomer, antibiotic, and radiopacifiers (see Table 2). The cement powders consist of PMMA beads; the size of these beads varies between 5 and 80 μm and the beads are which can usually be easily seen on electron micrographs of bone cement samples (Figure 3). Polymerization of monomeric, liquid methylmethacrylate (MMA) is an exothermic reaction initiated by the decomposition of a catalyst (benzoyl peroxide) producing free radicals that set off additional polymerization of the MMA. All monomer must react, since monomer residues may cause chemical necrosis of the bone (Paul and Bargar 1998), although some residual monomer always remains

Table 2. Composition of the commonest antibiotic-loaded acrylic cements used in orthopedics, expressed as a percentage of the total powder and liquid components (% w/w), respectively, as given by the manufacturer[a]

Components	CMW1	CMW3	CMW End.	Simplex	Palacos
Powder					
Polymethylmethacrylate	84.73	83.88	64.53	14.83	82.66
Methylmethacrylate/methacrylate/styrene			19.70	74.13	
Gentamicin sulfate	4.22	4.22	4.22		2.04
Colistimethate sodium				0.59	
Erythromycin				1.23	
Barium sulfate	9.10	10.00	9.75	9.88	
Zirconium dioxide					14.81
Benzoyl peroxide	1.95	1.90	1.80		0.49
Liquid					
Methylmethacrylate	98.23	96.54	98.01	97.50	97.84
N,N-dimethyl-P-toluidine	0.81	2.49	1.98	2.40	2.12

[a] Other constituents, such as ascorbic acid, ethanol, chlorophyll, and hydroquinone are not included.

in cements. It leaches out with time regardless of the type of cement being used. CMW bone cements contain more of the catalyst benzoyl peroxide than Palacos, which causes autocatalyzation and a larger rise in temperature during polymerization with the risk of inducing thermal necrosis of the bone. In commonly used PMMA bone cements, an accelerator is added to the monomer (N,N,dimethyl-p-toluidine). Sulfix 60 applies a new accelerator, 4-dimethylamino-phenethylalcohol (DMAPE), to increase the polymerization rate, presumably giving better mechanical properties (Fritsch 1996). Due to the increase in temperature during polymerization, air bubbles develop that can or can not escape the polymerizing mass, depending on the polymerization rate and viscosity of the cement. If these air bubbles can not escape, a porous cement results (see Figure 4). To prolong the lifetime of the pure monomer and inhibit spontaneous polymerization because of exposure to heat or light during storage, hydroquinone is included as a stabilizer. Radiopacifiers, like barium sulfate or zirconium dioxide particles of various sizes, ranging between 1 and 5 μm, are added to facilitate X-ray contrast. These particles can be clearly seen on electron micrographs (Figure 5). In most cement brands, PMMA-methylacrylate co-polymer is used, but Simplex uses the PMMA-styrene co-polymer and Sulfix 6 contains a PMMA-butylmethacrylate co-polymer. Although the above-described differences may seem minor, they greatly influence the polymer matrix of a bone cement and the release of antibiotics from it.

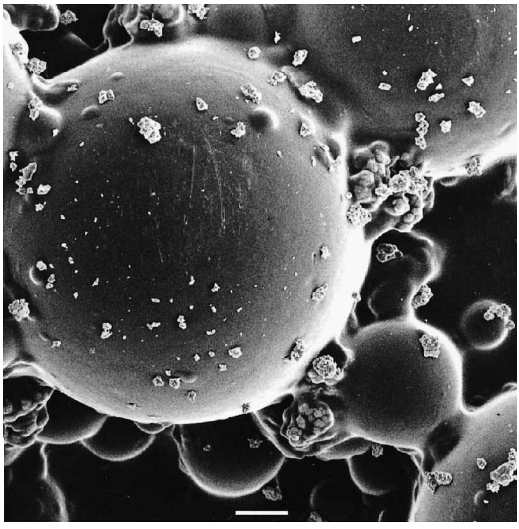

Figure 3. Scanning electron micrographs showing the matrix of Palamed bone cement, with variously-sized polymer beads. Bar represents 10 μm.

Bulk and surface properties

The bulk properties of bone cements are affected by entrapment of air in the polymer matrix and the possibility for air to escape the matrix. Air entrapment results from air bubbles surrounding the polymer powder, inclusion of air during wetting of the powder, spatulation and transfer to the cement gun. Small voids start during monomeric boiling (Wixson et al. 1987). These large and small

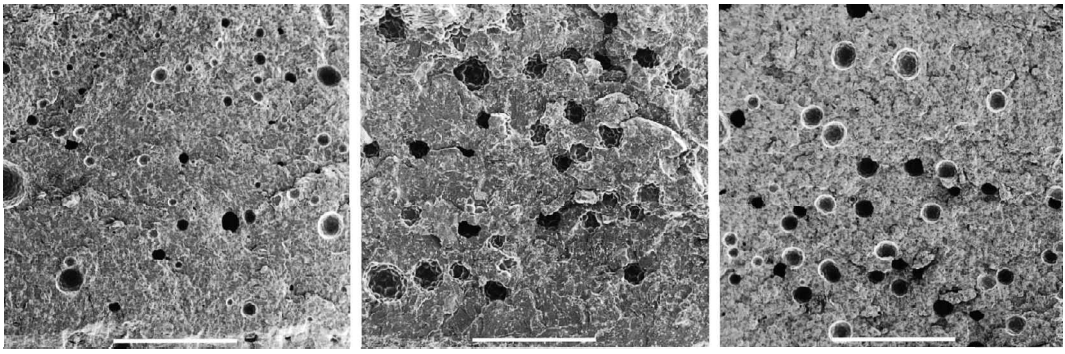

Figure 4. Scanning electron micrographs showing the surface of various freshly broken cement samples: CMW (left), Palamed (middle), and Palacos (right). Bar represents 1 mm.

voids are jointly responsible for the final porosity of the polymer matrix, which is of critical importance to the mechanical properties of the cement, because ideally, bone cement should have a fully polymerized matrix, free of any voids that mainly act as stress risers (Topoleski et al. 1990, James et al. 1992, Wixson 1992). New mixing methods have been introduced to reduce the porosity of bone cements, like vacuum mixing. During vacuum mixing, the PMMA powder is added to the MMA monomer liquid in a mixing chamber and manually stirred under a vacuum (Lidgren et al. 1984). Vacuum mixing reduces porosity to below 2.5%. To minimize the porosity, a low pressure of at least 0.47 bar is required, while an entirely air-free cement can be prepared at a pressure of 0.07 bar (Alkire et al. 1987, Wang et al. 1996).

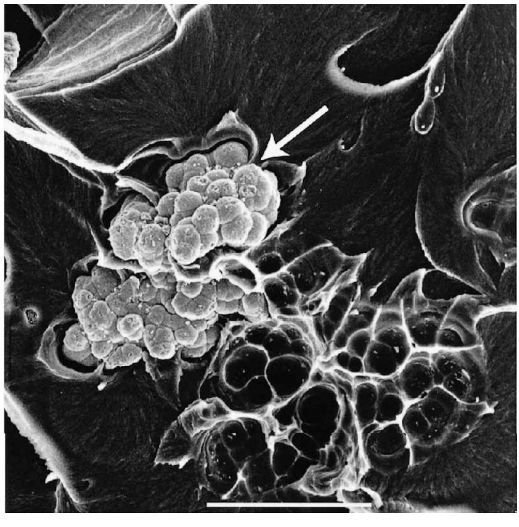

Figure 5. Scanning electron micrograph showing zirconium dioxide particle (arrow) embedded in Palacos bone cement. Bar represents 10 μm.

The final porosity of bone cements depends not only on the method of preparation, but also on the viscosity of the cement that can be regulated by varying the relative amounts of polymer and copolymer. High viscosity cements, like Palacos, possess a higher porosity than low viscosity ones, like CMW3, because of the greater difficulties encountered by entrapped air bubbles to escape the polymer matrix. To overcome this problem, prechilling of the monomer has been recomended, which slows the chemical process and causes less monomer to evaporate leading to better handling characteristics and less inclusion of air (Hansen and Jensen 1990). A certain bulk porosity of antibiotic-loaded bone cements may be needed, however, to facilitate release of antibiotics (Kuechle et al. 1991).

The surface properties of bone cements dictate the interaction of the cement with the actual implant, tissue, bone cells and potentially infecting microorganisms. Optimal biocompatibility is a race for the surface between tissue integration and infecting organisms (Gristina 1987), which possess conflicting requirements for a biomaterial surface, because although bio-adhesivity is needed bio-adhesivity is also essential. Bone cements are moderately hydrophobic materials, as judged by their water contact angles. Table 1 also lists water contact angles on PMMA and a variety of bone cements which incorporate antibiotics. Typically, water contact angles range from 70 to 80 degrees, with little, if any, effect on antibiotic loading, suggesting the absence of an antibiotic on the bone cement surface. This has been confirmed by sur-

face analytical techniques, like X-ray photoelectron spectroscopy, an extremely sensitive method (Andrade 1985).

Surface roughness and chemical heterogeneity cause a difference between the contact angle of an advancing (Θ_a) and receding (Θ_r) liquid front (Figure 2). Table 1 shows differences in advancing and receding water contact angles of up to 40 degrees on antibiotic-loaded bone cements, indicating a rough and chemically heterogeneous surface. The roughness of bone cement surfaces is also shown in Table 1, as obtained with a macroscopic stylus tracing instrument. Although surface roughness depends on the finishing procedure used, the findings clearly indicate that with an identical finishing procedure, various brands have surfaces with a different roughness. It seems likely that polymer beads and radiopacifiers, the sizes and relative prevalence of which are typical of different brands, interfere with surface finish, since the particulate matter may become embedded on top of newly polymerized material also at the surface.

The antibiotics

Antibiotics for incorporation in bone cements should have a broad antibacterial spectrum, including Gram-positive and Gram-negative pathogens, sufficient bactericidal activity, high specific antibacterial potency, low rate of primary resistant pathogens, minimal development of resistance during therapy, low protein binding, low sensitizing potential, marked water solubility facilitating its release from the bone cement, and last, but not least, chemical and thermal stability (Wahlig and Dingeldein 1980). Over the years various antibiotics have been evaluated in in vitro studies regarding their suitability for incorporation in bone cements (Table 3). In general, they show that aminoglycosides, especially gentamicin, are suitable antibiotics from a bacteriological and physicochemical point of view.

Mechanisms of antibiotic release from bone cements

It is generally accepted that antibiotics incorporated in PMMA bone cements are released to some extent, but the mechanism by which these drugs are released is still debated. Several observations indicate that antibiotic release is a surface phenomenon (Masri et al. 1995). Bone cement samples less than 100 μm release all antibiotics included, while release from thicker samples release occurrs independent of volume (Schurman et al. 1978). In line with the view that antibiotic release from bone cements is a surface phenomenon, studies using methylene blue and gentamicin diffusion through or into acrylic bone cement discs show that the bulk is essentially impermeable (Baker and Greeham 1988). All in vitro studies (Picknell et al. 1977, Hoff et al. 1981, Chohfi et al. 1998, Penner et al. 1999, Van de Belt et al. 2000a) indicate that only 5–8% of the antibiotic incorporated in an acrylic matrix is eventually released after a long time, although the duration of testing, differences in refreshing intervals, sample geometry, temperature, pH, detection assay strongly affect the amount released. In vivo studies also confirm that only a minor portion (5–18%) of gentamicin incorporated in bone cements is eluted (Törholm et al. 1983, Bunetel et al. 1989).

There is no consensus that antibiotic release is an exclusive surface phenomenon and theories favoring a bulk diffusion model have been proposed as well (Flynn 1974, Bayston and Milner 1982). The diffusion model relies heavily on the availability of pores and connecting capillaries in bone cement, through which fluids can penetrate an dissolve the antibiotics that slowly diffuse outwards. Recently, we suggested that initial release during the first hours after exposure of antibiotic-loaded bone cement to a fluid is mainly a surface phenomenon, while sustained release over several days is a bulk diffusion phenomenon (Van de Belt et al. 2000b).

Antibiotic-loaded cement and biofilm formation

Although in vitro studies suggest that antibiotics are released from acrylic bone cements, it is of some concern that various in vitro studies show adherence and growth of bacteria on antibiotic-loaded bone cement. After 30 min, equal numbers of S. aureus and Proteus mirabiles adhered to unloaded and gentamicin-loaded PMMA bone cement, but after 24 hours, fewer bacteria were found on gentamicin-loaded cement (Chang and Merritt 1992). Similarly, S. epidermidis adhered and grew on tobramicin-impregnated cement discs (Oga et al. 1992) due to the protection provided by the biofilm mode of

Table 3. Survey of studies on the release of antibiotics from various bone cements, together with conclusions drawn and references

Antibiotics	Cement	Conclusions	Reference
Gentamicin/penicillin/erythromicin	Palacos	sufficient release in all	Buchholz and Engelbrecht 1970
Gentamicin	Palacos	in vitro, sufficient release after 1 year	Wahlig and Buchholz 1972
Penicillin/methicillin/erythromycin/lincomycin/nafcillin/polymyxin/colistimate	Simplex	no difference in vitro activity	Chapman and Hadley 1976
Gentamicin	CMW/Simplex/Palacos	higher and longer release from Palacos	Holm and Vejlsgaard 1976
Gentamicin/oxacillin/cephazolin	Simplex/Palacos	all three release more from Palacos	Marks et al. 1976
Sodium fusidate/gentamicin	Palacos/Simplex/CMW	higher and longer release from Palacos	Elson et al. 1977
Fusidin/clindamycin/gentamicin	Simplex	longer antibacterial effect for clindamycin	Hill et al. 1977
Penicillin/gentamicin	Palacos/Simplex	penicillin eluted better from Palacos/gentamicin eluted equally well from Palacos and Simplex	Hoff et al. 1981
Gentamicin sulfate/ sodium fusidate/diethanolamine	Palacos/CMW	release of gentamicin from Palacos longer than from CMW, but opposite was found for sodium fusidate	Bayston and Milner 1982
Cefriaxone/coumermycin/sulfampicionmethoxazole/trimethoprim/cephalothin/vancomycin/fusidic acid/gentamicin/rifampicin/vancomycin	Palacos/CMW1	cefriaxone/trimethoprim/rifampicin/vancomycin not inhibitory within short time	Beeching et al. 1986
Vancomycin/amikacin/daptomycin	Palacos/Simplex/Zimmer low viscosity and dough type	sufficient release from all cements, but vancomycin and amikacin released better from Palacos	Kuechle et al.1991
Tobramycin/vancomycin	Palacos/Simplex	higher levels of both released from Palacos	Kendall et al. 1996
Vancomycin/tobramycin	Palacos	combining two antibiotics improves the elution of both	Penner et al. 1996
Tobramycin/vancomycin	Simplex/Palacos	tobramycin release better than vancomycin release, Palacos better than Simplex	Greene et al. 1998
Vancomycin	Cerafix	Good pharmacokinetics and mechanical properties	Chohfi et al. 1998

growth (Kendall et al. 1996). Recently, we reported that S. aureus biofilm formation was reduced on different gentamicin-loaded bone cements, as compared to unloaded cements only during a short period, which depends on the initial antibiotic release that burst out of the cement (Van de Belt et al. 2000b). However, the growth of bacteria adhering to antibiotic-loaded bone cements must be evaluated critically to assess their clinical efficacy.

Clinical use of antibiotic-loaded bone cement

Nowadays, 90% of all orthopedic surgeons in the USA use antibiotic-loaded bone cements to fix of implants (Heck et al. 1995), although they have to prepare these cements in the operating room; in Western Europe, commercial antibiotic-loaded bone cements are available (Wininger and Fass, 1996). The prophylactic use of antibiotic-loaded bone cements for the primary fixation of implants must be clearly distinguished from its therapeutic

Table 4. Prospective and retrospective studies comparing infection rates after systemic administration of antibiotics (cementation with unloaded bone cements) versus local antibiotic administration with antibiotic-loaded bone cement as infection prophylaxis in primary implant fixation

Number of patients	Study design	Infection rate (%) antibiotic loaded/unloaded cement		Follow-up (years)	Reference
667	Retrospective	0.6	4.1	4–5	Thierse 1978
800	Prospective	0.0	0.0	2	Pfarr and Burri 1979
445	Prospective	1.1	5.9	3–6	Wannske and Tscherne 1979
1688	Prospective	0.8	1.9	5	Josefsson 1988
4825	Retrospective	0.9	0.8	8	Espehaug et al. 1997

use in revision. Beads and spacers made of antibiotic-loaded bone cements to cure infections before reimplantation are another temporary application of these biomaterials. In the following sections, we critically discuss the clinical efficacy of these different applications of antibiotic-loaded bone cement.

Prophylactic use of antibiotic-loaded bone cement

The clinical efficacy of the use of antibiotic-loaded bone cements for primary implant fixation is difficult to assess in clinical studies, because many numbers of patients are needed and no double-blinded randomized studies are available for drawing any statistically reliable conclusions. Table 4 summarizes prospective and retrospective studies comparing systemic administration of antibiotics (cementation with an unloaded bone cement) versus local antibiotic administration via an antibiotic-loaded bone cement, as prophylaxis against infections in the primary fixation of implants. Thus, few studies have been done to ascertain possible protective effects of the use of antibiotic-loaded bone cements. The retrospective study by Thierse (1978) involving only 667 patients shows a significant positive effect of the use of these bone cements, but it is contradicted by a study with a sevenfold larger group of patients (Espehaug et al. 1997). Two prospective studies provided significant support for incorporation of antibiotics in bone cement, but a third prospective study, which alternated cement with and without gentamicin, found no infection in either group (Pfarr and Burri 1979). The prospective study (Josefsson et al. 1990) involving 9 centers raises several fundamental questions about methods: different protocols were used for systemic administration of antibiotics, infections were diagnosed with different criteria for infections and different protective laminar flows were employed in the different centers. Consequently, we conclude that the clinical efficacy of antibiotic-loaded bone cements for primary fixation of orthopedic implants remains to be proved.

Sanzen and Walder (1988) addressed the induction of antibiotic resistance by using antibiotic-loaded bone cements and cultured swabs from the anterior nares of patients before and 2 weeks after a total hip replacement. No gentamicin-resistant strains were found preoperatively, while postoperative gentamicin-resistant strains were cultured from 13 patients (20%). 10 of these 13 patients had a replacement with gentamicin-loaded bone cement. In another study (Hope et al. 1989), nine tenths of the patients with an infected hip, in which the primary arthroplasty had been done using gentamicin-loaded bone cement, at least one infecting staphylococcal strain resistant to gentamicin was harvested. The long-term low concentrations of antibiotics around an implant fixed with an antibiotic-loaded bone cement may well lead to the occurrence of antibiotic-resistant strains (Tunney et al. 1998a, Van de Belt et al. 1999).

Prophylactic use of antibiotic-loaded cement also leads to the release of antibiotics still trapped in the bone cement by fragments created during revision which then kill infectious organisms and lead to misdiagnoses (Powles et al. 1998). Therefore, the correct use of antibiotic-loaded bone cements for primary orthopedic implant fixation, advocated as cost-effective prophylactics against deep infections to reduce the number of revision operations needed (Persson et al. 1999), may be about to backfire.

Therapeutic use of antibiotic-loaded bone cement

Effective treatment of infected implants requires removal of the implant and eradication of the microbial biofilm. Consequently, for successful reimplantation, high concentrations of antibiotics are needed in a localized area to cure the infection. Antibiotic-loaded cements for fixation in revision surgery, beads and spacers, are used in one or multi-stage revision operations to supplement surgical debridement, systemic high doses of antibiotics in early infections, and excision arthroplasty, one or multi-stage revision, or arthrodesis in late infections (Goulet et al. 1988, Hamblen 1988). However, the risks of secondary infection in the presence of a foreign body, i.e., the cement beads themselves, and the emergence of bacterial resistance have been underestimated (Wininger and Fass, 1996).

Buchholz first used antibiotic-loaded bone cements in revision surgery and reported an increase in the rate of success to 77% with a single exchange and to 90% with multi-stage revision (Buchholz et al. 1981). In a review concerning the treatment of periprosthetic infections by using gentamicin-loaded bone cement, Garvin et al. (1994) compared the success rate of reimplantation with or without gentamicin-loaded cement and distinguished between one-stage and two-stage revision. One-stage revision after periprosthetic infection using gentamicin-loaded and unloaded cement gave success rates of 81% and 71%, respectively. In two-stage revision, the gentamicin group showed a higher success rate in revision without antibiotic-loaded bone cement (Garvin et al. 1994, Salvati et al. 1986). To describe a patient population large enough to draw meaningful conclusions, these studies included a review of retrospective data obtained from various hospitals, involving different surgeons and protocols, various types of prostheses and follow-up periods etc. Consequently, nothing can be said about the true clinical significance.

In two-stage revision, the use of temporary spacers and beads has proved to be effective (Wahlig and Dingeldein 1983, Walenkamp et al. 1998a,b, Booth and Lotke 1989, Blaha et al. 1990, Duncan and Beauchamp 1993, Nelson et al. 1993, Klemm 1993, Calton et al. 1997). This use of beads and spacers made of antibiotic-loaded bone cements is less worrisome than its use for bone cements, because beads and spacers are removed after a certain time, and subinhibitory doses of antibiotics do not occur over extended periods.

Conclusions and future prospects

The following conclusions can be drawn from this review:

1. Biomaterial-associated infections, one of the most serious and difficult complications to treat, often lead to surgical removal of the implant. Prophylaxis is especially important because the biofilm mode of growth protects the infecting organisms against host-defenses and antibiotic therapy.

2. Various biomaterials used in orthopedic surgery show different susceptibilities to infection, because adhesion and growth of infecting bacteria are controlled by biomaterial surface properties, like hydrophobicity, charge, and roughness.

3. The pharmacokinetics of antibiotic release from acrylic bone cements are inadequate, with release kinetics contributing to the development of antibiotic-resistant microbial strains.

4. The clinical efficacy of the prophylactic use of antibiotic-loaded bone cements for primary fixation purposes remains to be determined, while the efficacy of the therapeutic use of antibiotic-loaded bone cements in revision surgery has not been convincingly shown.

In future, the use of biomaterials in medicine and orthopedics, in particular, will increase with ageing populations world-wide and growing demands for a higher quality of life. Research on the development of biomaterial surfaces with antimicrobial properties has increased to an annual expenditure of about USD 430 million (Lysaght et al. 1998) and involves, inter alia, surface texturing, modification of wettability and protein coatings, all with the aim of favoring tissue integration as compared to microbial adhesion and infection (An et al. 1996). The development of biodegradable biomaterials will also be of value in orthopedic surgery and biodegradable antibiotic-loaded beads have already been manufactured (Liu et al. 1999). The release of antibiotics from these beads can be controlled by adjusting various parameters the process, while as

an additional benefit of these beads no second operation is needed for their removal. Another recent development in antibiotic-loaded bone cements involves loading the cements containing gentamicin with a second antibiotic, most notably clindamycin (CoPal, Merck Darmstadt). Careful evaluation of such products is needed, however, because combinations of drugs can show synergistic (Kuechle et al. 1991) or inhibitory (Klekamp et al. 1999) effects on release, while cross-resistance between different antibiotics exists as well.

One or more of the authors has received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this article.

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