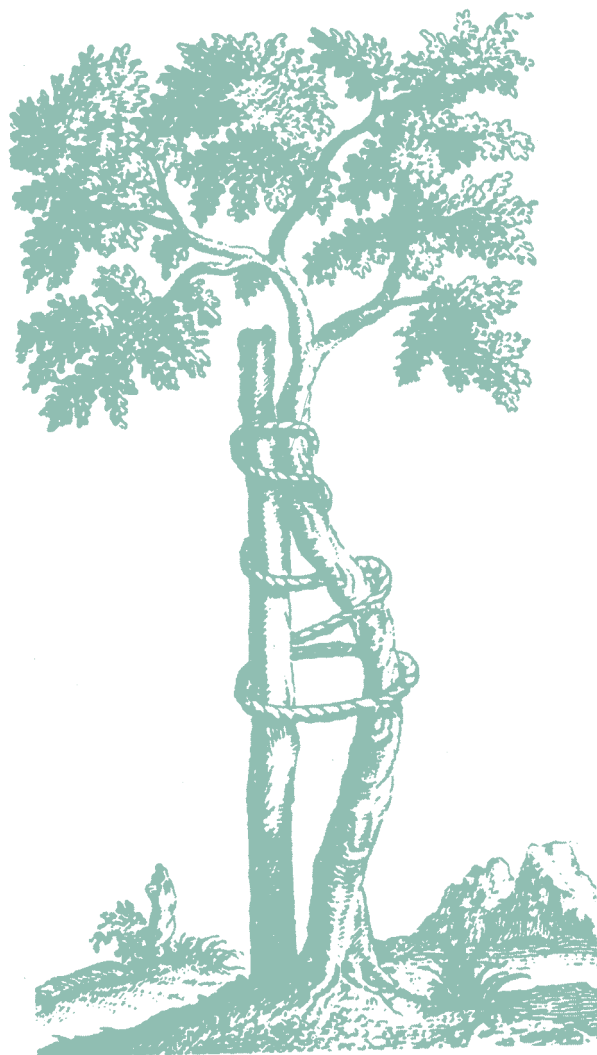

ANTIBIOTIC-LOADED BONE CEMENT IN ASEPTIC TOTAL JOINT REPLACEMENT: *WHYS, WHEREFORES & CAVEATS*



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INTRODUCTION

Deep wound infection following joint replacement is one of the most devastating complications facing both the physician and patient. The use of antibiotic-loaded bone cement (ALBC) is a well-accepted adjunct for treatment of an established infection. However, its use for prophylaxis in the prevention of infection remains controversial in North America.

Since the 1970's, the use of ALBC in Europe has been extremely widespread as a method of prophylaxis in both primary and aseptic revision joint replacement surgery.³ This exhibit presents available data which supports the efficacy of ALBC as a method of infection prevention in joint replacement.

CURRENT PRACTICES

In Europe, the most commonly included antibiotic in ALBC is Gentamicin.^{7,8,14,16} Dosages of 0.5 to 1.0g per 40g of bone cement have been shown to be clinically safe when prepared as a premixed industrial product.²⁴ Heretofore, Tobramycin has been the most commonly used antibiotic in the United States, accounting for 70% of ALBC use in a survey of hospital pharmacists.⁹ This is due to its availability as a sterilized powder that surgeons can add to bone cement in the operating room, and also has a bactericidal profile similar to Gentamicin.^{9,12} Many other antibiotics have been used including cefazolin,⁹ cefuroxime,^{4,5,17} erythromycin,²⁰ and penicillin.²³ While other antibiotics, such as lincomycin and tetracycline, are heat labile and deactivated by the polymerization process.¹⁰ However, all of these antibiotic inclusions in bone cement are "off label" uses in the US. There are no current guidelines for ALBC use for prophylaxis in arthroplasty procedures and clinical use has been variable. (Figure 1) Through 2004, the Food and Drug Administration (FDA) has cleared through the 510[k] process five commercial ALBC products for use in the second stage of a two-stage revision where the initial infection has been cleared (Table), but to date has not done so for primary prophylaxis application.

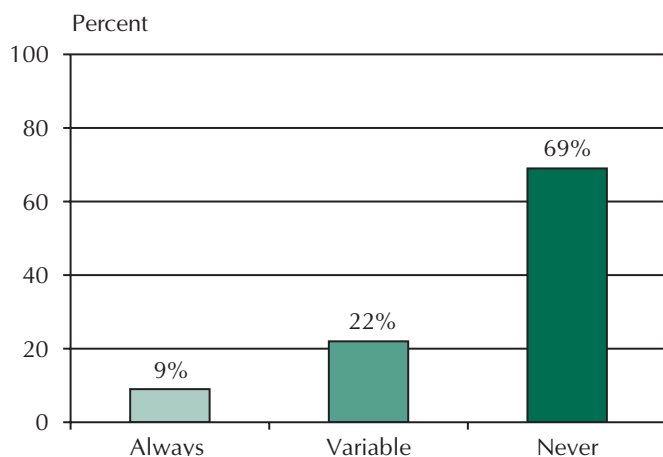


Figure 1. Clinical use of ALBC in primary joint replacement in the United States (1995).

Derived from: Heck, et al²

Table: FDA 510[k] Cleared Antibiotic Bone Cements

Cement	Manufacturer / US Distributor	Cement Type	Dosage per 40g of bone cement
Palacos® G	Biomet Inc. (Warsaw, IN)	Copolymer High viscosity	0.5g Gentamicin
DePuy 1	DePuy Orthopaedics, Inc. (Warsaw, IN)	Homopolymer High viscosity	1.0g Gentamicin
Cemex® Genta	Exactech, Inc. (Gainesville, FL)	Copolymer Medium Viscosity	0.5g Gentamicin
VersaBond™ AB	Smith + Nephew, Inc. (Memphis, TN)	Copolymer Medium viscosity	1.0g Gentamicin
Simplex™ P	Stryker® Orthopaedics (Mahwah, NJ)	Copolymer Medium viscosity	1.0g Tobramycin

EXISTING EVIDENCE

There are a number of studies that have evaluated the use of ALBC as a method of prophylaxis in the clinical setting.^{3-5,7,14,16,17} In a report from the Swedish Registry, 92,675 patients undergoing primary, cemented total hip arthroplasty (THA), the use of ALBC was a significant factor in the reduction of deep infection ($p < 0.001$).¹⁸ An additional study detailed from the Norwegian Registry reports the results of 10,905 primary, cemented THAs performed for osteoarthritis of the hip.⁸ Adjustments for gender, age, brand of cement, prosthesis, type of operating theatre, and operating time were made. The lowest rate of revision for infection was found among patients receiving ALBC plus systemic antibiotics, whereas the revision rate for patients receiving systemic antibiotics only was 4.3 times greater ($p=0.001$). In patients with ALBC only it was 6.3 times greater ($p=0.003$); and in those who did not receive any antibiotics it was 11.5 times greater ($p=0.002$).⁸ (Figure 2) This study clearly differentiates the significance of antibiotic inclusion as a means of infection prevention in THA.

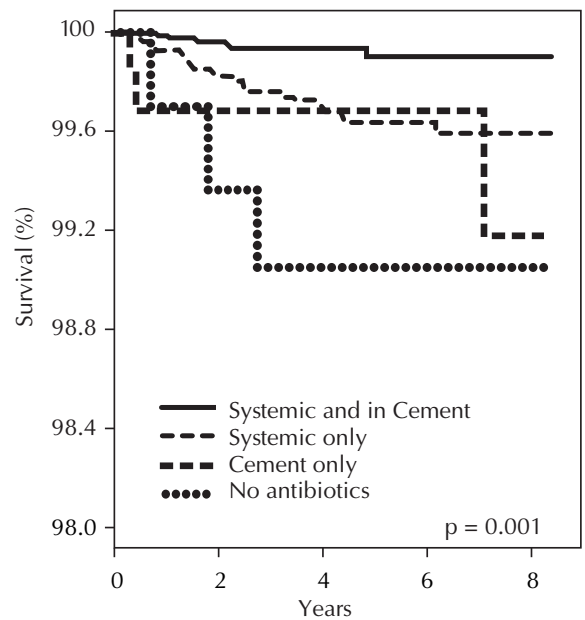


Figure 2. Survival curves of THAs performed in Norway from 1987 to 1995 with infection as an endpoint for patients receiving different prophylaxis regimens.

From: Espehaug, et al.⁸

HIGH RISK PATIENTS

Patients with medical co-morbidities or a requirement for immunosuppressive medications are considered to be at higher risk for the onset of postoperative deep infection.^{4,10,11} It seems logical that these high-risk patients undergoing primary joint replacement are considered to be candidates for the use of ALBC as an additional method of antibiotic prophylaxis. The case has also been made for the use of ALBC in revision joint arthroplasty for all patients irrespective of their underlying medical risks.²¹

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

CAVEATS

The question is whether or not ALBC should be used as a method of infection prevention in all primary or revision arthroplasties or whether its use should be restricted to the high-risk patient. The primary reasons for avoiding the indiscriminate use of ALBC include:

CAVEATS (Cont'd)

- **Emergence of antibiotic-resistant bacteria**

Although there has been little evidence for emerging resistance, one report is concerning.¹³ In a study of 91 infected hip replacements caused by coagulase negative staphylococci, 31 of 34 (88%) patients who had the original hip arthroplasty performed with Gentamicin-bone cement had an organism resistant to Gentamicin. In the patients who had not received Gentamicin-bone cement, only 9 of 57 (16%) patients had an organism resistant to Gentamicin (Figure 3).¹³

- **Evidence for hypersensitivity reactions**

There is no evidence for hapten mediated hypersensitivity related to the interaction of antibiotics and bone cement. Systemic levels of antibiotic are high enough, however, to produce an allergic reaction to the antibiotic if the patient is sensitized to that antibiotic.

- **Nephrotoxicity/Ototoxicity**

There are scant reports defining patient toxicity following ALBC use. One comparative clinical study employing 0.5g Vancomycin and 1.2g Tobramycin ALBC, suggests a minimal potential for toxicity.² However, this could be dosage and antibiotic dependent.

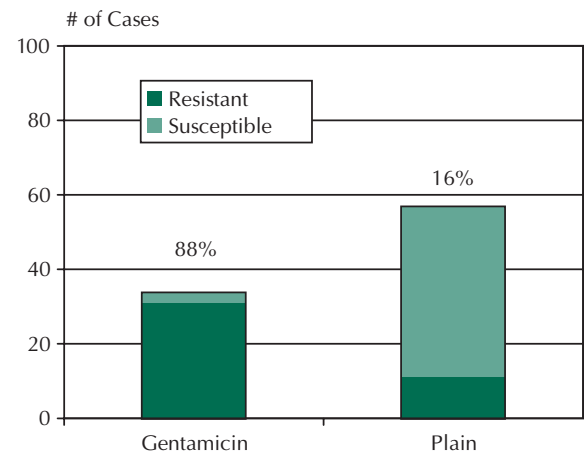
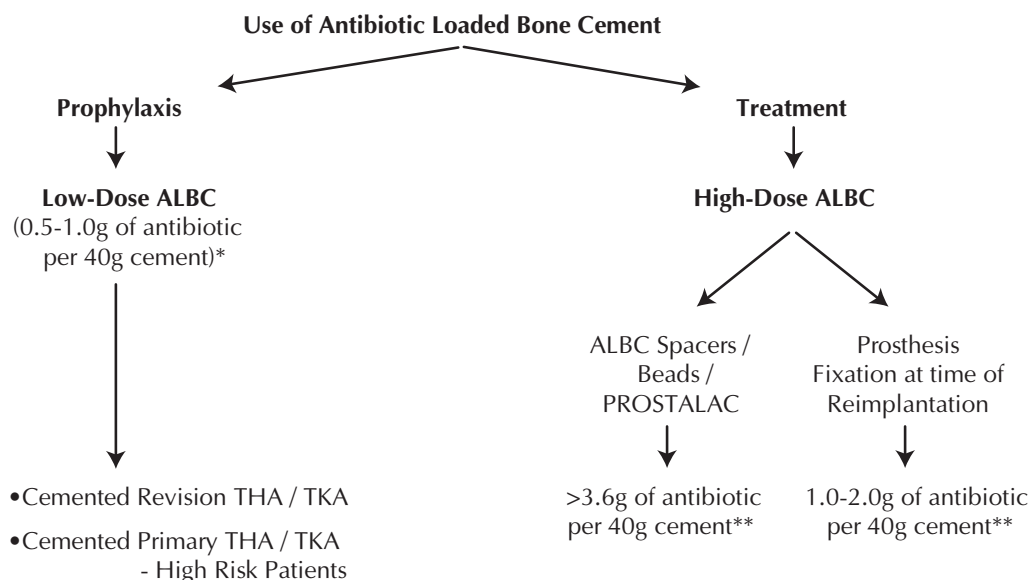


Figure 3. Derived from: Hope et al.¹³

Additionally, the American Academy of Orthopaedic Surgeons Committee on Infections has issued an advisory statement on limiting the use of Vancomycin-impregnated cement in only those situations of established infection. Evidence suggests that it is contributory to the development of antibiotic-resistant bacteria.

GUIDELINES FOR CLINICAL USE

Whether the ALBC is a pre-mixed industrial product or hand mixed at the time of surgery, the following represents a proposed algorithm of use for both prophylactic and treatment situations.



* Recommended antibiotics used for prophylaxis include gentamicin or tobramycin. Vancomycin is not indicated for prophylaxis.

** Antibiotic(s) used is dependent upon susceptibility of microorganisms identified or suspected.

INFLUENCES OF HAND MIXING

Orthopaedic surgeons may still choose to hand mix antibiotics into bone cement at the time of surgery to accommodate the appropriate concentration and antibiotic for the presenting situation. However, the antibiotics and bone cements used vary causing the quality of the resultant ALBC to be variable.^{6,7,19,22} The disadvantages of this approach include the potential poor mechanical mix of antibiotic powder into the cement and a subsequent deleterious effect on elution kinetics.¹ (Figures 4 and 5).

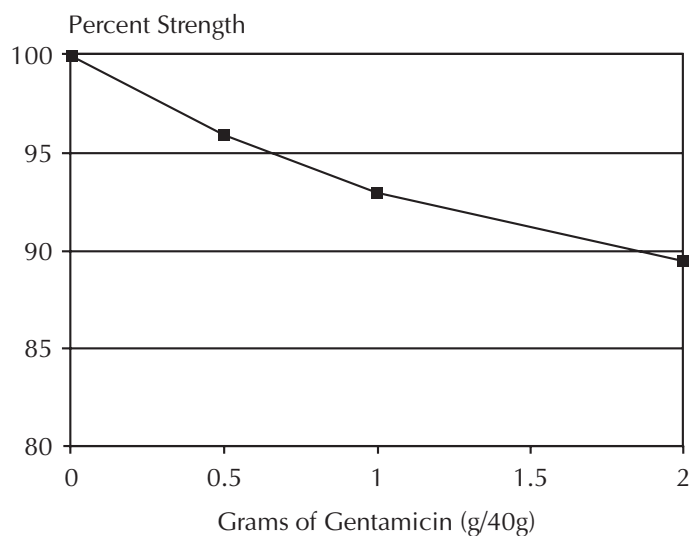


Figure 4. The affect of industrial pre-mixed Gentamicin on % shear strength reduction of Palacos R.

Derived from: Moran, et al.¹⁹

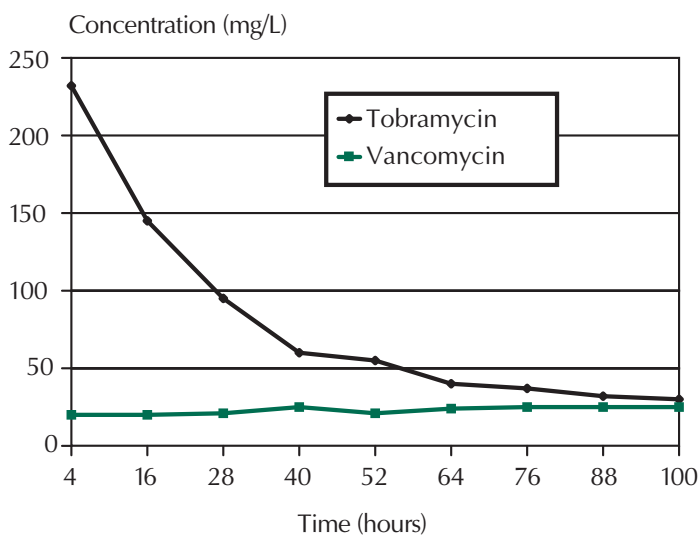


Figure 5. Graph showing the in vivo elution of 2.4g Tobramycin and 1.0g Vancomycin from 40g of bone cement. Local antibiotic levels exceed minimum inhibitory concentrations for most susceptible pathogens.

From: Duncan and Masri⁷

EPILOGUE

- The use of ALBC as a means of prophylaxis in reducing the infection rate following arthroplasty has merit based on the clinical studies available.
- Recently in the United States, several orthopaedic companies have received FDA 510[k] clearance of their pre-mixed ALBC products for use in the second stage of a two-stage revision procedure where the initial infection has been cleared. However, the use of ALBC for prophylaxis in primary joint arthroplasty procedures remains an “off-label” use.
- Because of potential side effects for developing antibiotic-resistant bacteria, allergenicity, and toxicity, it may not be appropriate to use ALBC in all primary joint replacement patients. Vancomycin is one whose prophylactic administration should be limited to established infections.
- An algorithm for ALBC use for both prophylaxis and treatment in primary and revision arthroplasty situations has been proposed.
- ALBC used for infection prophylaxis in joint arthroplasty should employ a ratio of 0.5-1.0g of antibiotic per 40g of bone cement, which provides high tissue levels without compromising material properties.

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