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] erthryomicin,[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) During 2003, the Food and Drug Administration (FDA) 510[k] cleared three commercial types of ALBC 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.

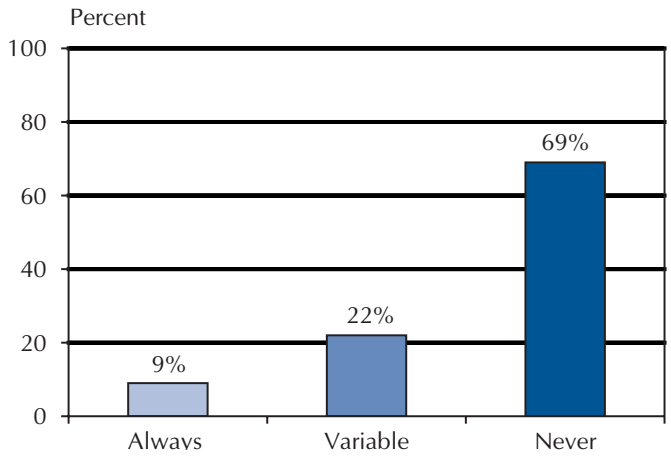


Figure 1. *Clinical use of ALBC in primary joint replacement in the United States (1995).*

Derived from: Heck, et al[12]

Table: FDA 510(k) Cleared Antibiotic Bone Cements

Cement	Manufacturer	Cement Type	Dosage per 40g of bone cement
Simplex™ P	Stryker® Howmedica Osteonics (Mahwah, NJ)	Copolymer Medium viscosity	1.0g Tobramycin
DePuy 1	DePuy Orthopaedics, Inc. (Warsaw, IN)	Homopolymer High viscosity	1.0g Gentamicin
Palacos® G	Biomet Inc. (Warsaw, IN)	Copolymer High viscosity	0.5g Gentamicin

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.

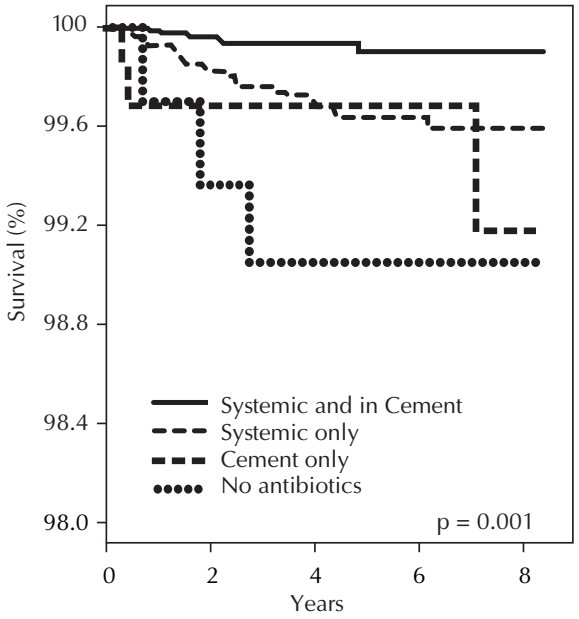


Figure 2. *Survival curves of THAs performed in Norway from 1987 to 1995 with infection as an endpoint for patients receiving different prophylaxis regimes.*

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 erythematosis
- 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]

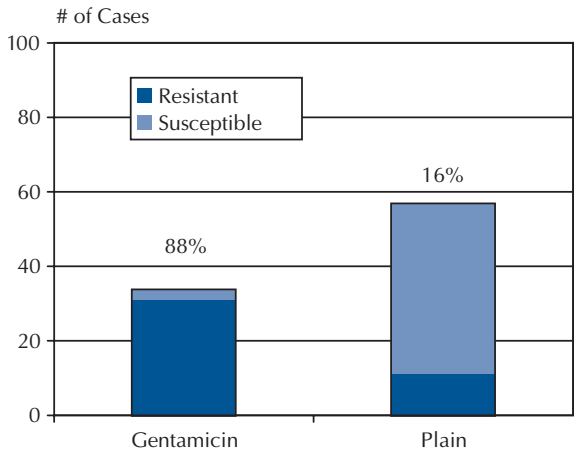


Figure 3. *Derived from: Hope et al.*[13]

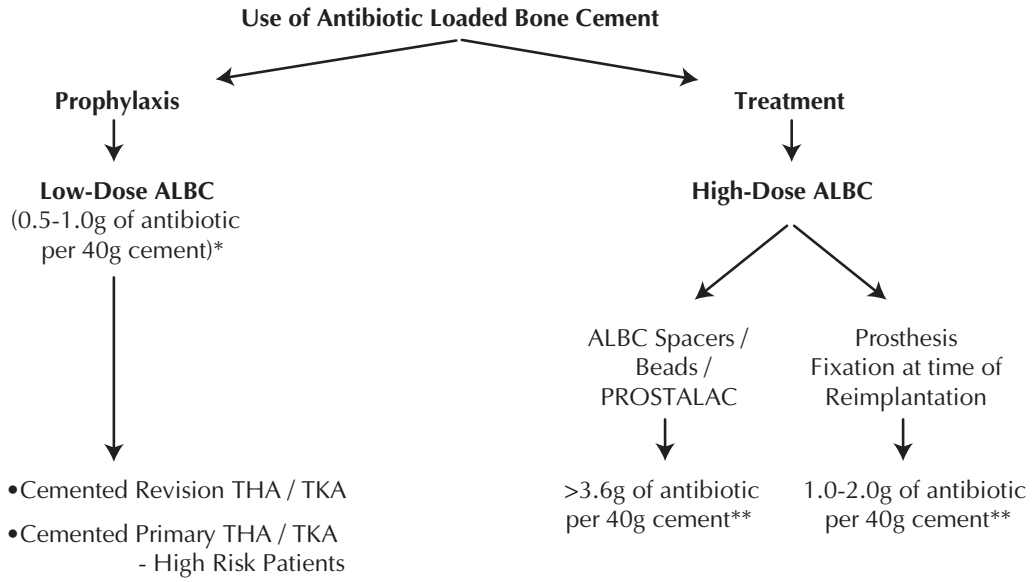
- Evidence for hypersensitivity reactions
  There is no evidence for hapten mediated hypersensitivity related to the interaction of antibiotics and bone cement. Systemic levels of antibiotic are high enough, however, to produce an allergic reaction to the antibiotic if the patient is sensitized to that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

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).

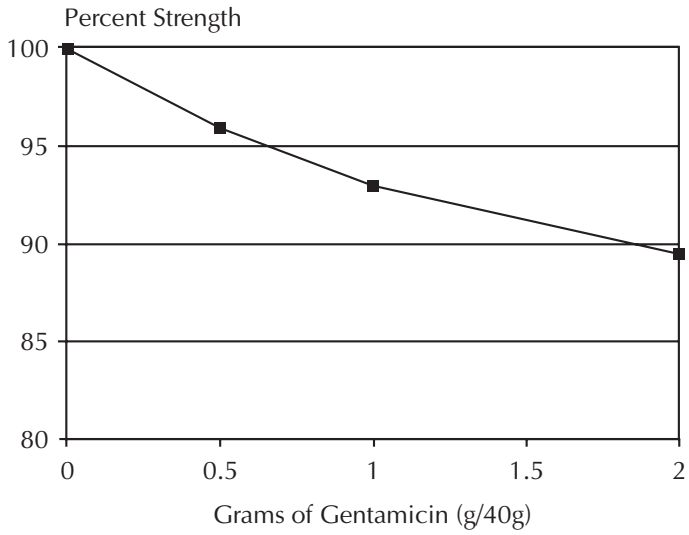


Figure 4. *The affect of industrial pre-mixed Gentamicin on % shear strength reduction of Palacos R.*

Derived from: Moran, et al.[19]

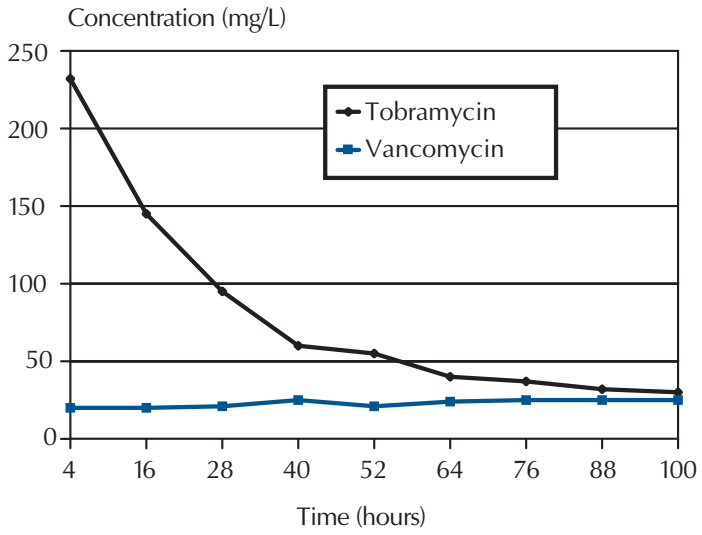


Figure 5. *Graph showing the in vivo elution of 2.4g Tobramycin and 1.0g Vancomycin from 40g of bone cement. Local antibiotic levels exceed minimum inhibitory concentrations for most susceptible pathogens.*

From: Duncan and Masri[7]

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.

REFERENCES

1. Bourne RB: Antibiotic bone cement approval: Fuss-in at the Feds. Orthopedics 25:913-914, 2002.
2. Brien WW, Salvati EA, Klein R, Brause B, Stern S: Antibiotic impregnated bone cement in total hip arthroplasty. An in vivo comparison of the elution properties of tobramycin and vancomycin. Clin Orthop 296:242-248, 1993.
3. Buchholz HW, Elson RA, Heinert K: Antibiotic-loaded acrylic cement: Current concepts. Clin Orthop 190:96-108, 1984.
4. Chiu FY, Chen CM, Lin CF, Lo WH: Cefuroxime-impregnated cement in primary total knee arthroplasty: A prospective, randomized study of three hundred and forty knees. J Bone Joint Surg 84-A:759-762, 2002.
5. Chiu FY, Lin CF, Chen CM, Lo WH, Chaung TY: Cefuroxime-impregnated cement at primary total knee arthroplasty in diabetes mellitus. A prospective, randomised study. J Bone Joint Surg 83-B:691-695, 2002.
6. Davies JP, O'Connor DO, Burke DW, Harris WH: Influence of antibiotic impregnation on the fatigue life of Simplex P and Palacos R acrylic bone cements, with and without centrifugation. J Biomed Mater Res 23:379-397, 1989.
7. Duncan CP, Masri BA: The role of antibiotic-loaded cement in the treatment of an infection after a hip replacement. Instr Course Lect 44:305-313, 1995.
8. Espehaug B, Engesaeter LB, Vollset SE, Havelin LI, Langeland N: Antibiotic prophylaxis in total hip arthroplasty. Review of 10,905 primary cemented total hip replacements reported to the Norwegian arthroplasty register, 1987 to 1995. J Bone Joint Surg 79-B:590-595, 1997.
9. Fish DN, Hoffman HM, Danzinger LH: Antibiotic-impregnated cement use in US hospitals. Am J Hosp Pharm 49: 2469-2473, 1992.
10. Hanssen AD, Osmon DR, Nelson CL: Prevention of deep periprosthetic joint infection. Instr Course Lect 46:555-567, 1997.
11. Hanssen AD, Osmon DR: The use of prophylactic antimicrobial agents during and after hip arthroplasty. Clin Orthop 369:124-138, 1999.
12. Heck D, Rosenberg A, Schink-Ascani M, Garbus S, Kiewitt T: Use of antibiotic-impregnated cement during hip and knee arthroplasty in the United States. J Arthroplasty 10:470-475, 1995.
13. Hope PG, Kristinsson KG, Norman P, Elson RA: Deep infection of cemented total hip arthroplasties caused by coagulase-negative staphylococci. J Bone Joint Surg 71-B:851-855, 1989.
14. Josefsson G, Kolmert L: Prophylaxis with systematic antibiotics versus gentamicin bone cement in total hip arthroplasty. A ten-year survey of 1,688 hips. Clin Orthop 292:210-214, 1993.
15. Joseph TN, Chen AL, Di Cesare PE: Use of antibiotic-impregnated cement in total joint arthroplasty. J Am Acad Orthop Surg 11:38-47, 2003.
16. Lynch M, Esser MP, Shelley P, Wroblewski BM: Deep infection in Charnley low-friction arthroplasty. Comparison of plain and gentamicin-loaded cement. J Bone Joint Surg 69-B:355-360, 1987.
17. McQueen MM, Hughes SP, May P, Verity L: Cefuroxime in total joint arthroplasty. Intravenous or in bone cement. J Arthroplasty 5:169-172, 1990.
18. Malchau H, Herberts P, Ahnfelt L: Prognosis of total hip replacement in Sweden. Follow-up of 92,675 operations performed 1978-1990. Acta Orthop Scand 64:497-506, 1990.
19. Moran JM, Greenwald AS, Matejczyk MB: Effect of gentamicin on shear and interface strengths of bone cement. Clin Orthop 141:96-101, 1979.
20. Murray WR: Use of antibiotic-containing bone cement. Clin Orthop 190:89-95, 1984.
21. Steinbrink K: The case for revision arthroplasty using antibiotic-loaded acrylic cement. Clin Orthop 261:19-22, 1990.
22. Sterling GJ, Crawford S, Potter JH, Koerbin G, Crawford R: The pharmacokinetics of Simplex-tobramycin bone cement. J Bone Joint Surg 85-B:646-649, 2003.
23. Trippel SB: Antibiotic-impregnated cement in total joint arthroplasty. J Bone Joint Surg 68-A:1297-1302, 1986.
24. Wahlig H, Dingeldein E, Buchholz HW, Buchholz M, Bachmann F: Pharmacokinetic study of gentamicin-loaded cement in total hip replacements. Comparative effects of varying dosage. J Bone Joint Surg 66-B:175-179, 1984.