Antibiotic laden cement: Current state of the art

By Terry A. Clyburn MD, and Quanjun Cui, MD

Total joint arthroplasty (TJA) has become so successful and commonplace that excellent results are expected in all cases. Though rare, infection of TJA can be a devastating complication, resulting in an unhappy patient and a potential lawsuit. With public reporting, such infections may also tarnish the reputation of a skilled surgeon.

Antibiotic laden cement (ABLC) has been used for more than 30 years as a delivery device for antibiotics in the treatment of infected TJAs. Cement was first used as a spacer to maintain the joint space and soft-tissue tension for later reconstruction. When antibiotics were added to the cement, they were found to elute into involved tissue area, thus aiding in the eradication of infection. As use of ABLCs became more accepted, antibiotics were added to the cement when a previously infected total joint was reimplanted.

ABLC may be defined as "low dose"—containing less than 2 g of antibiotic per 40 g cement—or "high dose," with greater than 3.6 g of antibiotic per 40 g of cement. Over the years, a variety of cements, cement preparation methods, antibiotics, and doses have been used with varying outcomes.

ABLC was released for commercial distribution in the United States in May 2003, specifically for the treatment and reimplantation of infected arthroplasties. In Europe, however, ABLC has been available for many years, and the indications and scientific evidence for its use have expanded to primary arthroplasty. Use of ABLC for this purpose, however, remains controversial in the United States.

Treatment of infected TJA

ABLC is widely accepted in the treatment of infected TJAs and is effective at doses of at least 3.6 g of antibiotic per 40 g of cement. Doses as high as 6 to 8 g of antibiotic per 40 g of cement have also been proven safe and effective.[1,2] Elution of the antibiotics is enhanced when using more than one antibiotic and at higher doses. Commercially available ABLC contains just 1 g of antibiotic per 40 g of cement and is therefore not effective alone in the treatment of an infected TJA. Because of its inherent porosity, Palacos cement has been shown to be the most effective polymethylmethacrylate delivery device for ABLC.[3,4]

Modern principles of bone cement preparation do not apply in the treatment of infection. Although the addition of more than 2 g of antibiotic per 40 g of cement reduces the antibiotic's mechanical strength, this is not relevant to the treatment of infection. Vacuum mixing decreases the cement's porosity—thus reducing elution of the antibiotic—and is therefore contraindicated.

Homogeneous, commercial mixing of the antibiotic in cement results in better mechanical strength, but potentially less elution. Using a traditionally "poor mixing technique"—with "whipping" of the mixture—may, in fact, *improve* elution. Hand mixing without fully crushing the antibiotic crystals may also improve elution. Normally, cement is used only in powder form because liquid reduces mechanical strength. In this application, however, liquid may increase the elution rate of the antibiotic.

Antibiotic selection, risks

Tobramycin is the most often used and studied antibiotic added to cement worldwide, but gentamicin is more common in the United States. Both are acceptable because they are available in powder form, thermostable, and safe, with broad antimicrobial coverage and a low incidence of allergy. Gentamicin and tobramycin are the only antibiotics available in commercial ABLC. Other antibiotics that have been studied include vancomycin and cephalothin.

Toxicity, development of resistance, and allergic reactions—and, to a lesser degree, cost—are all concerns when using ABLC in the treatment of acute infection. There are no clinical reports of local or systemic toxicity with tobramycin, gentamicin, or vancomycin in ABLC. Levels of tobramycin and gentamicin in the joint may be 10 times toxic serum levels and thus may be effective even in cases of more resistant organisms. Peak serum doses of tobramycin—3.6 g of antibiotic per 40 g of cement—are well below toxic serum levels. Aminoglycosides have a profile of low immunotoxicity. There have been no reports of allergic reaction to antibiotics used in ABLC. There is concern with cephalosporins, due to known immunotoxicity, but no reports exist.

When possible, the choice of antibiotic should be specific for the causative organism. Gentamicin-loaded cement may not be appropriate for revision surgery if it was also used in the primary arthroplasty, because resistant coagulase-negative staphylococci may exist.[5] For this reason, the use and type of antibiotic used in the primary case should be recorded.

Commercially available preformed spacers are subject to FDA limitations and therefore have only low-dose levels of antibiotics, which have not been shown to be effective in the treatment of acute infection. If used, they should be implanted in conjunction with high-dose ABLC. Other options include using high-dose ABLC placed into commercially available molds for temporary implants or using ABLC to temporarily fix metal and polyethylene implants.

ABLC use in the second stage reimplantation of a previously infected total joint is approved by the FDA. Commercially available low-dose ABLC improves homogenicity of mixture of the antibiotic in the cement when compared to hand mixing, resulting in improved mechanical properties.

Treatment recommendations for known infected arthroplasty:

1. Use high-dose ABLC—at least 3.6 g of antibiotic per 40 g of cement—as a spacer in stage one of a two-stage reconstruction.[3]
2. Select the appropriate antibiotic based on the patient's antibiotic sensitivities.
3. Prepare the cement using "poor mixing technique" so as to increase porosity of the cement and improve elution of the antibiotic.
4. Choose a cement with known antibiotic elution characteristics.[3,4]
5. For reimplantation, use low-dose ABLC, continue to choose the antibiotic based on patient sensitivities, and use modern cement preparation techniques to maximize the cement's mechanical strength.

Using ABLC in primary TJA

Many studies quote the TJA infection rate to be at or less than 1 percent; total knee arthroplasties (TKA) have a higher infection rate than total hip arthroplasties (THA). The Swedish Knee Registry reports an infection rate of 1.7 percent in patients with osteoarthritis and 4.4 percent in patients with rheumatoid arthritis.[6] Patients with diabetes, patients older than age 75 years, immunocompromised patients—including those taking steroids and those with immune disorders—obese patients, and patients with hemophilia also have higher infection rates.

As the population ages, the indication for TJA expands to include these higher-risk groups, and increased rates of infection are inevitable. Patients and society expect excellent outcomes in TJA, and surgeons desire to minimize the risk of infection, which has led to the use of ABLC in primary TJA.

ABLC is effective in reducing the risk of infection in primary TJA, based on both animal and human studies. A study comparing infection rates among 340 patients with and without cefuroxime in bone cement found statistically fewer infections with ABLC ($P < 0.02$).[7] Animal studies using canine and rabbit models showed that—when compared to cement without antibiotics—ABLC reduced the rate of implant infections.[8,9]

Analysis of nearly 11,000 primary THAs in the Norwegian Arthroplasty Registry found that using both ABLC and systemic antibiotics was more effective in preventing deep hip infection than using either systemic antibiotics or ABLC alone.[10] Improving operating room ventilation and using ABLC resulted in statistically significant reductions in primary THA deep infections in a study of more than 92,000 THA procedures in the Swedish Hip Registry.[11] Gentamicin ABLC was associated with the lowest THA revision rates, and ABLC was found to be cost-effective in eliminating costly infections and reducing the need for revisions.

Some data suggest that the protective effect of ABLC is limited to the first two years.[12] A prospective randomized study of 1,688 THAs found parenteral antibiotics resulted in an infection rate of 1.6 percent compared to 0.4 percent for gentamicin in bone cement. At 10 years, there were two additional infections in the gentamicin group, which eliminated statistical significance. However, the parenteral antibiotic group had a total of 13 infections, compared to just five in the ABLS group.

The use of ABLC in primary arthroplasty is increasing. In Norway, use of ABLC in primary THAs increased from 40 percent in 1987 to 90 percent in 1998. In the United States, a 1995 survey of 1,015 surgeons specializing in adult reconstruction found that 56 percent use ABLC in their practice. Of these surgeons, more than 90 percent used it for prophylaxis in TJAs if the patients had a history of prior infection, while only 11 percent used it routinely with primary TJA.[13] Data from the National Hip Replacement Outcome Project in Britain indicates that 69 percent of surgeons use ABLC in primary THA replacements.[14]

Concerns persist for ABLC in primary TJA

Concerns regarding allergic reactions, mechanical failures, toxicity, development of resistance, and cost, however, continue to persist. To date, there have been no reports of allergy to common antibiotics in bone cement, although this may occur if the use of cephalosporins in ABLC increases. Mechanical strength of "low dose" ABLC has not been shown to be a factor either in vitro or clinically. The Swedish Registry has shown a slight increase in coagulase-negative staphylococci and a small drop in gram-negative organisms, but concluded that ABLC in primary THA is cost-effective.

Cost, however, is a factor in the United States. Each package of ABLC costs $284 to $349, and each TJA requires at least two packages. In the United States, cement is used primarily in TKAs, which have a higher risk of infection. With approximately 250,000 TKA cases per year, routine use of ABLC in primary TKA in this country would add up to a prophylaxis cost of about $75 million per year. But these costs may, in fact, be justified. At a 2 percent infection rate, the number of TKA infections each year would be 5,000. Assuming the direct cost of treatment is $50,000 per patient, total treatment costs for TKA infections would be $250 million. Although infections may never be completely eradicated, cutting the rate of infection in half would reduce the cost of treatment by $125 million. The additional indirect costs of lost productivity and long-term disability, and the potential costs of legal actions more than justify the cost of prophylaxis.

Terry A. Clyburn, MD, is a member of the AAOS Patient Safety Committee and an assistant professor specializing in hip & knee replacement at the University of Texas Medical School at Houston. He can be reached at drclyburn@jointreplacementassociates.com

Quanjun Cui, MD, is an assistant professor specializing in adult reconstruction at the University of Virginia.

References:

1. Springer BD, Lee BC, Osmon D, Haidukewych GJ, Hanssen AD, Jacofsky DJ. Systemic safety dose antibiotic loaded cement spacers after resection of an infected total knee arthroplasty. *Clin Relat Res* 427:47-51, 2004.
2. Hanssen AD, Rand JA, Osmon DR: Treatment of the infected total knee Arthroplasty with insertion of another prosthesis. The effect of antibiotic-impregnated bone cement. *Clin Orthop* 309:44, 1994.
3. Penner MJ, Duncan CP, Masri BA: The in vitro elution characteristics of antibiotic-loaded CMW and Palacos® bone cements. *J Arthroplasty* 14:209, 1999.
4. Joseph TN, Chen AL, Di Cesare PE: Use of antibiotic-impregnated cement in total joint arthroplasty, *J Am Acad Orthop Surg* 11:38, 2003.
5. Thomes B, Marray P, Bouchier-Hayes D: Development of resistant strains of Staphylococcus epidermidis on gentamicin-loaded bone cement in vivo. *J Bone Joint Surg Br* 84:758, 2002.
6. Robertsson O, Knutson K, Lewold S, et al: The Swedish knee arthroplasty register 1975-1997: an update with special emphasis of 41,223 knees operated on in 1988-1997. *Acta Orthop Scand* 72:603, 2001.
7. Chiu FY, Chen CM, Lin CF, et al: Cefuroxime-impregnated cement at primary total knee Arthroplasty in diabetes mellitus. A prospective, randomized study. *J Bone Joint Surg Am* 83:691, 2001.
8. Petty W, Spanier S, Shuster JJ. Prevention of infection after total joint replacement. Experimental canine model. *J Bone Joint Surg Am* 70, 536, 1988.
9. Nijhof MW, Dhert WJ, Fleer A, Vogerly HC, Verbout AJ. Prophylaxis of implant-related staphylococcal infections using Tobramycin-containing bone cement. *J Biomed Maeter Res* 52:754:2000.
10. Espehaug B, Engesaeter LB, Vollset SE, et al: Antibiotic prophylaxis in total hip Arthroplasty: Review of 10,905 primary cemented total hip replacements reported to the Norwegian Arthroplasty register, 1987-1995. *J Bone Joint Surg Br* 790:590, 1997.
11. 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, 1993.
12. Josefsson G, Kolmert L. Prophylaxis with systemic antibiotics versus gentamicin bone cement in total hip arthroplasty. A ten-year survey of 1,688 hips. *Clin Orthop Relat Res* 292:210, 1993.
13. Heck D, Rosenberg A, Schink-Ascani M, Garbus S, Kiewitt T. Use antibiotic-impregnated cement during hip and knee arthorplasty in the United States. *J Arthroplasty*. 10:470-5, 1995.
14. Best AJ, Fender D, Harper WM, McCaskie AW, Oliver K, Gregg PJ. Current practice in primary hip replacement: results from the National Hip Replacement Outcome Project. *Ann R Coll Surg* 80:350, 1998.
15. Bourne RB: Prophylactic use of antibiotic bone cement an emerging standard- in the affirmative. *J Arthroplasty* Vo19 No.4 Suppl 1, p69, 2004.
16. Hansen AD, Prophylactic Use of Antibiotic Bone Cement An Emerging Standard- In Opposition. *J Arthroplasty* Vol 19 No 4 Suppl 1, p.73, 2004.
17. Arciola CR, Campoccia D, Montanaro L: Effects of antibiotic resistance of *Staphylococcus* epidermidis following adhesion to polymethylmethacrylate and to silicone surfaces. *Biomaterials* 6:1495, 2002.

Tips for using ABLC in primary TJA

1. Low-dose ABLC is effective in preventing infection in primary TJA. Extensive data from Norwegian and Swedish hip registries and limited U.S. data indicate that use of low-dose (less than 2 g of antibiotic per 40 g of cement) ABLC is safe and effective in primary TJA. In the Journal of Arthroplasty (Vol 19, No.5, Suppl 1), Robert Bourne, MD, states, "The use of ABLC is becoming the standard of practice in Europe and Scandinavia, both for primary and revision knee and hip arthroplasties. Concerns with toxicity and mechanical cement weakness have not been realized with less than 2gm antibiotic/40gm cement."
2. Development of resistance is a concern. The emergence of resistant strains of organisms with the use of ABLC has been minimal, as indicated in the Swedish Registry. Arlen Hansen, MD, recommends against the routine use of vancomycin due to the emergence of vancomycin-resistant enterococcus and the need to reserve this antibiotic for resistant infections. The use and type of antibiotic should be recorded if used in the primary TJA.

3. Consider ABLC for high-risk primary TJA. Dr. Bourne states: “Antibiotics in bone cement have a more definitive role in high-risk patients such as those with compromised immune systems (i.e., rheumatoid arthritis, lupus, immunosuppression, diabetes, age older than 75, and in revision cases.)” Dr. Hansen states, “Available clinical evidence supports low-dose ABLC for prophylaxis in revisions and high-risk primary joints.”

4. Cost is a consideration. Concerns with cost-to-benefit ratio are minimal, according to the Swedish data. Projected savings appear to support this use of ABLC, but definitive data has not been

5. shown.

6. The FDA has approved the commercialization of low-dose ABLC only—specifically for use in the second stage reimplantation of a previously infected TJA. However, the dose available in these commercial preparations is inadequate for the treatment of active infection.

Pros and Cons

The Journal *of Arthroplasty* (Vol 19, No.5, Suppl 1) published “Affirmative” and “In Opposition” papers on the use of prophylactic use of ABLC.[15,16] In the “Affirmative” paper, Robert Bourne, MD, stated: “Our experience indicates that the use of antibiotic-impregnated bone cement is a potentially effective strategy in reducing the risk of deep infection following both primary and revision total joint arthroplasty.” He voiced continued concern with potential allergy, bacterial resistance, and cost.

In the “Opposition” paper, Arlen Hansen, MD, stated: “Available clinical evidence supports low-dose ABLC for prophylaxis in revisions and high-risk primary joints, but concerns of emerging drug-resistant organisms probably outweigh routine use of low-dose ABLC in uncomplicated primary arthroplasties.”