Protocol for Use of Antibiotic Loaded Bone Cement (ALBC) for Treatment of Periprosthetic Hip and Knee Joint Infections at The Minneapolis VA Medical Center

Background:

Use of high-dose antibiotic-loaded bone cement (ALBC) spacers is considered by many to be the standard of orthopaedic care in the management of periprosthetic joint infection (PJI) of the hip and knee.[1,2] High-dose ALBC requires hand mixing by the surgeon to facilitate the use of high dosages and choices of multiple antibiotics. Treatment of infected hip and knee arthroplasties with high-dose ALBC is aided by the creation of spacers of various shapes and sizes. These spacers, whether they are static or articulating (mobile), are meant to provide local delivery of antibiotics, stabilization of soft tissues, facilitation of an easier re-implantation, and improved clinical outcomes.[3] Published studies report that infection control rates may exceed 90% when combining ALBC with a two-stage exchange arthroplasty, although no randomized controlled studies exist regarding the efficacy of ALBC.[4,5]

Presently, there are no evidence-based guidelines for determining the ideal ratio of antibiotic to cement for treatment of PJI with an ALBC spacer. Although there are many antibiotics suitable for the creation of an ALBC spacer, tobramycin and vancomycin have been used most commonly based on their favorable elution properties, broad-spectrum of coverage, and availability in powder form.[6] The goal of mixing high doses of antibiotic with bone cement is to achieve sustained elution of each drug at levels that inhibit growth of the pathogenic organism(s) being treated.

Although the use of high-dose ALBC spacers is generally considered safe[7], cases of skin hypersensitivity, acute kidney injury, renal failure, hepatic failure, and even bone marrow suppression have been reported after implantation for treatment of PJI.[8,9,10,11,12,13,14,15,16,17] Most of these cases have been associated with use of high doses of aminoglycoside in the ALBC resulting in elevated serum levels (range 2 to 19.8 mcg/mL).

At the Minneapolis VAMC, treatment of patients with PJI with ALBC spacers with high-doses of vancomycin and tobramycin has been associated with postoperative acute renal failure in several cases. To improve upon the current institutional practices and to protect patients from such serious complications, a multidisciplinary task force was assembled to review the current method of treating PJI with ALBC and to make recommendations for optimization of this practice.

Considerations prior to treatment of PJI with ALBC:

1) **Use antibiotics with the following properties:**
   a. Available in powder form
   b. Wide antibacterial spectrum
   c. Elute from bone cement in high concentrations and over prolonged period
   d. Thermal stability
   e. Low or no risk for allergy
   f. Low side-effect profile (i.e. nephrotoxicity, hepatotoxicity, ototoxicity, neurotoxicity etc.)

2) **Target antimicrobial therapy to the pathogen(s). Common PJI pathogens include:**
   a. Methicillin-susceptible *Staphylococcus aureus*
   b. Methicillin-resistant *Staphylococcus aureus*
   c. Methicillin-susceptible coagulase-negative staphylococci
   d. Methicillin-resistant coagulase-negative staphylococci
   e. Enterococci
   f. *Escherichia coli*
   g. *Pseudomonas spp.*
   h. *Propionibacterium acnes*
   i. *Corynebacteria*

3) **Select dosages that are clinically appropriate, optimizing efficacy while minimizing risk of toxicity:**
   a. The total amount of antibiotic powder that may be mixed per 40 gm bag of cement for treatment of PJI
      i. Should not be > 8 grams
      ii. Should not be < 2.5 grams
   b. Standardized dosages will be used at MVAMC and total packs of cement will be limited to three 40 gm bags/case

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<u>Protocol for using ALBC to treat PJI at MN VAMC</u>:

1) **General**
   a. The combination of two antibiotics in an ALBC spacer is advisable, due to the enhanced elution of both agents and the wider antimicrobial spectrum.[17]
   b. PALACOS® is the preferred cement as it has the best antibiotic elution characteristics of any bone cement.[18]
   c. NO additional antimicrobials will be added to cement that comes premixed with antibiotic from the manufacturer under any circumstance.
   d. An ALBC spacer is routinely made from two or three 40 gm bags of cement.[18] Therefore, consideration must be given not only to the amount of antibiotic mixed into each 40 gm bag, but also to the total volume of cement/amount of antibiotic implanted. Standardized doses will be used and not more than three 40 gm bags of cement will be used per case.
   e. If a patient requires the implantation of multiple ALBC spacers in a short period of time (i.e. bilateral PJI), the doses in this protocol should be individualized to prevent unusually high total doses which could increase the risk of systemic exposure and toxicity.
   f. Tobramycin will no longer be used in high-dose ALBC spacers at MN VAMC due to high risk of systemic exposure leading to toxicity.
   g. Orders for antibiotics to be mixed into cement spacers will be entered in the medical record via a standardized order set in the Clinical Decision Support System (CDSS) to ensure appropriate documentation and safety checks. The antimicrobial orders will be entered as "delayed orders" which will be filled the night before surgery and delivered to OR by pharmacy the morning of the procedure.

2) **Antibiotic options for ALBC spacers at MN VAMC**
   a. Vancomycin: preferred primary antibiotic for all spacers based on relative safety, spectrum and consistency of elution.
      i. Safety
         - Vancomycin shows the least cytotoxic effect of all commonly used antibiotics in ALBC and is not likely to cause systemic side effects after local application.[17-18]
         - Vancomycin therapy has been associated with nephrotoxicity when administered intravenously with trough levels >20mg/L or when given concomitantly with piperacillin/tazobactam.[19] Based on systemic exposure seen in ALBC elution studies, vancomycin used in ALBC is unlikely to cause nephrotoxicity.
         - Patients on systemic intravenous vancomycin post-operatively will have serum levels followed. Patients who receive only local vancomycin in ALBC do not require additional monitoring.
      ii. Spectrum
         - Bactericidal activity against biofilm embedded staphylococci and MRSA.[20] Penetrates biofilm rapidly when high local doses are used.
         - Active against most gram-positive organisms including MSSA, MRSA, streptococcal and enterococcal isolates and most Propionibacterium and Corynebacterium isolates.
      iii. Consistency of elution
         - Vancomycin has much slower and more consistent elution characteristics relative to other antimicrobials.[21]

   b. Cefuroxime: preferred secondary/synergistic antibiotic to be used in combination with vancomycin whenever possible based on relative safety and antimicrobial spectrum[22,23,24]
      i. Safety
         - Overall well tolerated and low-risk of significant systemic exposure from doses used in ALBC.
         - Potential for cross-reactivity in patients with a history of a <u>true hypersensitivity</u> reaction to beta-lactams; do not use cefuroxime in antibiotic spacer for patients with history of hypersensitivity reaction to beta-lactams in the absence of additional information/evaluation of allergy (NOTE: it is appropriate to use cefuroxime in antibiotic spacer for patients with history of non-hypersensitivity reaction such as GI upset/diarrhea; also appropriate to use if patient has allergy to penicillin, but has tolerated first or second-generation cephalosporins in the past, etc.).
            - Consider ID consult if additional antibiotic allergy evaluation is needed.
      ii. Spectrum
         - 2nd generation cephalosporin (beta-lactam) with excellent bactericidal activity against relevant PJI pathogens including MSSA, streptococcal isolates, *E. coli*, *Proteus spp*. and *Klebsiella spp*.

   c. Aztreonam: preferred secondary/synergistic antibiotic to be used in combination with vancomycin when cefuroxime is not appropriate (based on safety and antimicrobial spectrum) i.e. patient with beta-lactam allergy (and any infecting organism) OR non-allergic patient with PJI known to be caused by *pseudomonas spp*. [25]
      i. Safety
         - Overall well tolerated and low-risk of significant systemic exposure from doses used in ALBC.
         - No cross reactivity in patients with beta-lactam allergies (i.e. okay to use in patients with history of rash/anaphylaxis to penicillin)
      ii. Spectrum
         - Monobactam with bactericidal activity against gram-negative pathogens only, including *Pseudomonas spp*.

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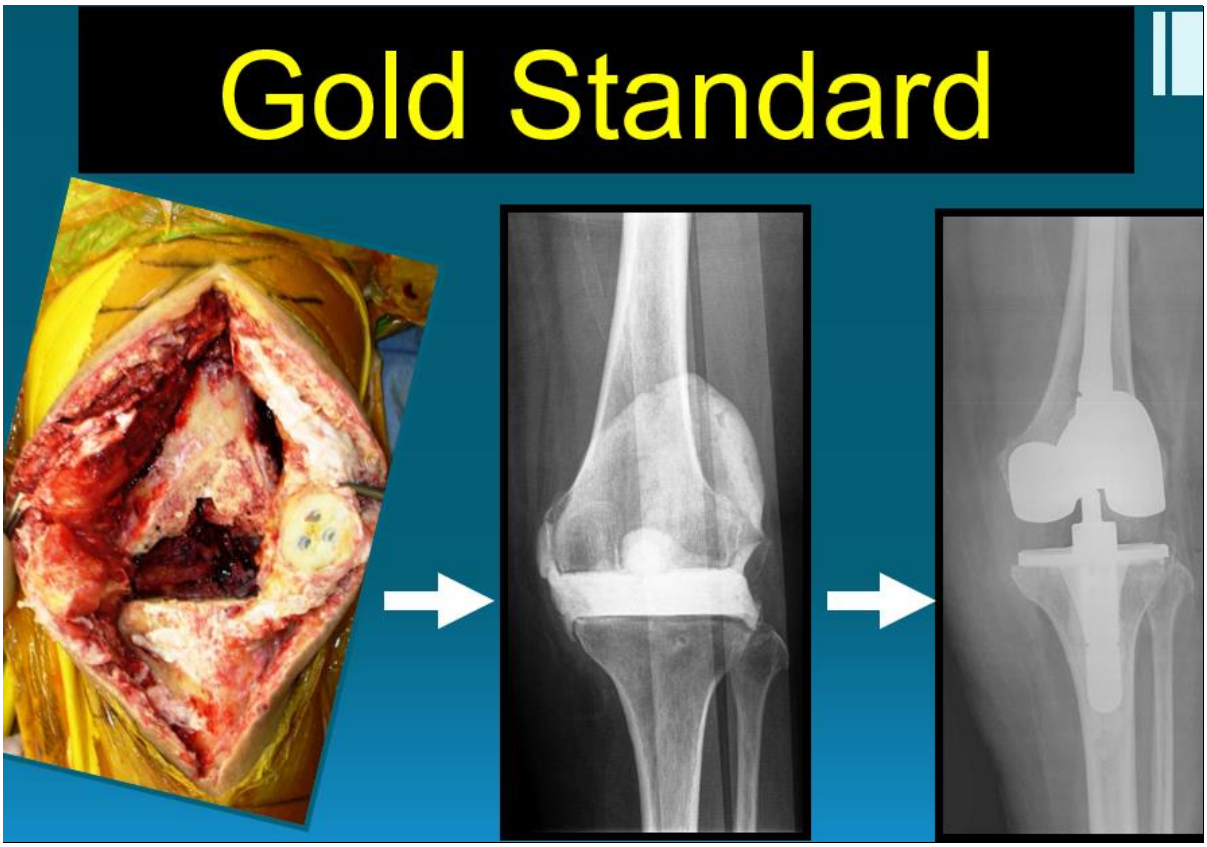
3) Protocol for ALBC spacers for treatment of PJI at MN VAMC based on pathogen & drug allergies

Patient Classification	Recommended Antibiotics and Dose Per 40 gm Bag of Cement	Maximum Total Dose Per Spacer (Based on max of three 40 gm bags of cement per case)
No hx of hypersensitivity to beta-lactams (okay if pt known to tolerate 1st or 2nd generation cephalosporins): gram-positive, non-pseudomonal gram-negative, or unknown infecting pathogen	Vancomycin 2g + cefuroxime 4.5g	6g vancomycin 13.5g cefuroxime
Hx of hypersensitivity reaction to beta-lactams and any infecting organism OR No hx of hypersensitivity to beta-lactams, but with documented pseudomonal infection	Vancomycin 2g + aztreonam 4g	6g vancomycin 12g aztreonam



Case example of resection of an infected TKA with placement of high dose ALBC spacer (Stage 1) followed by 6 weeks of intravenous antibiotic therapy and successful re-implantation TKA (Stage 2) by V.F. Sechriest II.

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