

HK 91: What factors should be considered when deciding on the dose and type of antimicrobials to be added to PMMA spacers?

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Response/Recommendations:

The most important factor determining the type of antimicrobials to be added to cement spacers is the nature of the infective organism(s) and antibiotic sensitivity. Other factors that also influence the type and dose of antimicrobials added to cement spacer includes heat stability of the drugs, renal function of the patient, and the type of cement being used, as elution of antimicrobials varies markedly depending on cement type.

Level of Evidence: Limited

Delegate Vote:

Rationale:

Management of chronic periprosthetic joint infections (PJIs) following hip and knee arthroplasty commonly consists of a 2-stage revision arthroplasty with antibiotic-loaded bone cement spacer (ALCS) and organism-specific intravenous (IV) or oral antibiotics [1]. PJI microbial profile and drug susceptibilities are major factors guiding antimicrobial selection and dosing for ALCS. After implant removal, placement of an ALCS containing organism specific antibiotics has been shown to effectively eradicate infection between 80-95% of the time [2-5]. Host factors must also be considered when deciding on ALCS antibiotic type and dosing. In particular, surgeons must be aware of reasons for prior failed PJI treatment, immunocompromised hosts, presence of sinus tracts, patient allergies, and preexisting medical conditions such as renal failure. Tailoring ALCS antimicrobial drugs and dosages to these different patient issues is imperative to optimize PJI treatment success and avoid major adverse medical events [6].

We performed a systematic review of English language literature according to PRISMA guidelines revealed 1,261 publication titles between 1994 and present including mentions of PJI treatment and antibiotic spacers. Exclusion criteria for this systematic review were: shoulder, ankle, and elbow investigations, non-human studies, ex-vivo investigations, patient cohorts less than 10, technique articles, review articles, and opinion articles. Inclusion criteria for this systematic review were investigations detailing 2-stage PJI treatment utilizing an ALCS, patient cohort that received ALCS loaded with consistent drug(s) and dosage(s), spacer drug dosages clearly stated and quantified as grams antibiotics per 40g pack of bone cement, PJI treatment success rate present in text, average patient cohort follow-up of 1 year or greater. After exclusions, 273 publications were identified for full text review. After review, further exclusions were done given data parameters and a final number of 58 studies (containing 60 distinct patient cohorts) were included for analysis of ALCS drugs and dosages as well as PJI treatment success rates.

The 58 studies spanned 1994-2024 and the average PJI treatment success rates for all investigations was 85% (range 56%-100%). The average duration of follow up was 45.8 months (range 12 months to 120 months). The publications identified by this review contained 21 studies dealing with only THA spacers, 28 dealing with only TKA spacers, and 19 in which a

combination of THA and TKA spacers were studied. A total of 4379 patients were identified that were treated with 2-stage exchange that utilized an ALCS.

Each of these studies detailed the antibiotic(s) contained in the spacer and quantified the amount of each antibiotic put in a 40g pack of cement which allowed the calculation of total antibiotic per pack (TAPP). The amount of antibiotic placed in the ALCS varied widely amongst the different investigations with TAPP values ranging from 1.0-8.8g (mean 4.5g, STDEV 2.1g). The ALCS were constructed with 2 antibiotics in 41 investigations (43 distinct patient cohorts) with average TAPP value of 5.13g (range 2.0-8.8g), 1 antibiotic with an average TAPP value of 2.2g (range 1.0-4.8g) in 13 investigations, and 3 different antibiotics with an average TAPP value of 4.1g (range 3.0-7.5g) in the remaining 4 studies. The drugs included in the different ALCS, listed from most frequent to least frequent, were Vancomycin (50 studies), Tobramycin, (36 studies), Gentamycin (13 studies), Erythromycin-Colistin (3 studies), Piperacillin/Tazobactam (3 studies), Ceftazidime (2 studies), as well as Meropenem, Clindamycin, and Cefotaxime (1 study, each). Within the selected investigations, 69% of ALCS contained the dual antibiotic combinations of either Vancomycin and Tobramycin (30 studies) or Vancomycin and Gentamycin (10 studies) which is consistent with historic data demonstrating synergistic antibacterial activity and enhanced antibiotic elution as a result of these antibiotic combinations [7,8].

To facilitate statistical analysis, the TAPP values of all ALCS were divided into 3 separate groups: $TAPP \leq 2g$ (10 studies with 495 patients), $2g < TAPP \leq 4g$ (12 studies with 543 patients), and $TAPP > 4g$ (36 studies with 3341 patients). Kruskal Wallis ANOVA was then used to determine if there were differences in the PJI treatment success rates between these three groups. Additionally, the cohorts were divided into two groups with one group whose ALCS included both an aminoglycoside and Vancomycin (40 studies and 3342 patients) and one group whose ALCS did not contain the combination of an aminoglycoside and Vancomycin (18 studies and 1037 patients). Two-tailed Students t-test was used to compare these groups. Lastly, the cohorts were divided such that one group had an ALCS containing only one drug (13 studies, 612 patients) and the other group had an ALCS containing two or more drugs (45 studies, 3767 patients). Two-tailed Students t-test was used to compare these groups.

Kruskal Wallis ANOVA assessing the different TAPP groups revealed no statistically significant difference between the success rates of the $TAPP \leq 2g$, $2g < TAPP \leq 4g$, and $TAPP > 4g$ groups ($p=0.92$). Students t-test revealed no significant difference between the success rates of the ALCS group containing both Vancomycin and an aminoglycoside versus the ALCS group containing different drugs ($p=0.12$). Lastly, Students t-test revealed that the success rate of ALCS containing only one drug did not statistically differ from that of the success rate of ALCS containing more than one drug ($p=.09$).

While not specifically addressed by this systematic review, many of the assessed investigations documented the challenges posed by culture negative (CN) PJI and the variable treatment outcomes of this entity [9]. Currently there are no concrete recommendations regarding the best antimicrobial drugs and their doses to be included in spacers for the treatment of CN PJI; however, broad-spectrum antibiotic coverage with activity against resistant, fastidious, Gram-positive, Gram-negative, and potentially fungal organisms is recommended [10]. For these situations, loading of an ALCS with Vancomycin (typically effective against MRSA) combined with aminoglycosides (activity against Gram negative organisms including *Pseudomonas aeruginosa*) or a 3rd/ 4th generation Cephalosporin (effective against gentamicin-resistant bacteria) and in select cases Amphotericin or Voriconazole should be considered [11].

Acute kidney injury (AKI) following ALCS placement has been increasingly recognized as an avoidable medical complication caused by systemic absorption of nephrotoxic antibiotics that are released by spacers. The incidence of nephrotoxicity following ALCS placement varies significantly, with reported rates ranging from 0% to 45% depending on the patient population and antibiotic regimen used [12]. Springer et al., highlighting the risks associated with the choice and concentration of antibiotics used in spacers, reported that ALCS containing more than 3.6g of nephrotoxic drugs per 40g bag of cement can precipitate AKI [13]. Dagneaux et al. (2021) found that AKI following spacer placement occurred in 14% of patients with normal renal function but increased to 45% in patients with pre-existing chronic kidney disease (CKD) [14]. In particular, the use of high dose of aminoglycosides, has been noted to increase the odds of AKI by approximately six times, especially when utilizing >4.8g per cement batch [14,15].

To mitigate these risks, some institutions have recommended using broad-spectrum and less nephrotoxic antibiotics such as Daptomycin, Cefotaxime, Meropenem, or Piperacillin-Tazobactam, instead of aminoglycosides in ALCS [16,17]. Park et al. demonstrated infection control in 32 of 36 patients (89%) treated with a combination of 4.5 g Piperacillin/Tazobactam and 2 g Vancomycin per 40g bone cement pack [18]. Additionally, the substitution of Vancomycin with Daptomycin in high-risk CKD patients has also been suggested to reduce renal complications, as Daptomycin is less likely to cause creatinine elevation postoperatively [16]. Therefore, to minimize the risk of AKI associated with ALCS placement, it is recommended that antibiotic loading of the spacer should be adjusted on a patient by patient basis according to pre-existing renal function and regular renal monitoring be performed following spacer placement.

Lastly, case reports of drug allergies and severe reactions as a result of systemic absorption of antibiotics released by antibiotic spacers have been documented. Vancomycin, the most common drug in this systematic review to be included in spacers, can lead to allergic reactions such as severe rash and more serious skin and systemic manifestations. Harper and Incavo [19] documented severe drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome following the use of ALCS for PJI treatment. Williams et al. reported on a patient who experienced a diffuse desquamating rash following exposure to vancomycin-impregnated bone cement [20]. Occasionally, systemic or cutaneous reactions to antibiotics released by an ALCS may be so severe that spacer removal is required. Thus, clinicians must be vigilant in monitoring for signs of allergic reactions or systemic toxicity, especially in patients receiving spacers with higher doses of antibiotics or who have experienced prior reactions to antibiotics contained within the spacer. [13-15].

Conclusion:

The main factor affecting ALCS antibiotic selection should be the susceptibility profile of the infecting organism(s) causing PJI. While this systematic review can find no statistically significant differences in success rates based on antibiotic type or dosages placed within PMMA spacers, host factors such as renal function and allergy history must be accounted for when selecting antibiotics and their doses to be included in ALCS. The risk of nephrotoxicity, particularly with high-dose aminoglycosides within a spacer, has raised concerns, prompting some institutions to explore alternative antibiotics with reduced renal risks. Ultimately, personalized antibiotic selection, renal based dosing adjustments, and close monitoring of patient renal function are essential for maximizing PJI treatment success and minimizing associated medical complications.

References:

- [1] Fitzgerald SJ, Hanssen AD. Surgical techniques for staged revision of the chronically infected total knee arthroplasty. *Surg Technol Int*. 2011 Dec;21:204-11.
- [2] Berend KR, Lombardi AV Jr, Morris MJ, Bergeson AG, Adams JB, Sneller MA. Two-stage treatment of hip periprosthetic joint infection is associated with a high rate of infection control but high mortality. *Clin Orthop Relat Res*. 2013 Feb;471(2):510-8.
- [3] Chalmers BP, Mabry TM, Abdel MP, Berry DJ, Hanssen AD, Perry KI. Two-Stage Revision Total Hip Arthroplasty With a Specific Articulating Antibiotic Spacer Design: Reliable Periprosthetic Joint Infection Eradication and Functional Improvement. *J Arthroplasty*. 2018 Dec;33(12):3746-3753.
- [4] Zmistowski B, Fedorka CJ, Sheehan E, Deirmengian G, Austin MS, Parvizi J. Prosthetic joint infection caused by gram-negative organisms. *J Arthroplasty*. 2011 Sep;26(6 Suppl):104-8.
- [5] Gooding CR, Masri BA, Duncan CP, Greidanus NV, Garbuz DS. Durable infection control and function with the PROSTALAC spacer in two-stage revision for infected knee arthroplasty. *Clin Orthop Relat Res*. 2011 Apr;469(4):985-93.
- [6] Edelstein AI, Okroj KT, Rogers T, Della Valle CJ, Sporer SM. Nephrotoxicity After the Treatment of Periprosthetic Joint Infection With Antibiotic-Loaded Cement Spacers. *J Arthroplasty*. 2018 Jul;33(7):2225-2229.
- [7] Samelis PV, Papagrigorakis E, Sameli E, Mavrogenis A, Savvidou O, Koulouvaris P. Current Concepts on the Application, Pharmacokinetics and Complications of Antibiotic-Loaded Cement Spacers in the Treatment of Prosthetic Joint Infections. *Cureus*. 2022 Jan 5;14(1):e20968
- [8] Slane J, Gietman B, Squire M. Antibiotic elution from acrylic bone cement loaded with high doses of tobramycin and vancomycin. *J Orthop Res*. 2018 Apr;36(4):1078-1085.
- [9] Tsai SW, Mu W, Parvizi J. Culture-negative periprosthetic joint infections: Do we have an issue? *J Clin Orthop Trauma*. 2024 May 10;52:102430.
- [10] Anagnostakos, K. Therapeutic Use of Antibiotic-loaded Bone Cement in the Treatment of Hip and Knee Joint Infections. *J. Bone Jt. Infect*. 2017, 2, 29–37.
- [11] Yang C, Wang J, Yin Z, Wang Q, Zhang X, Jiang Y, Shen H. A sophisticated antibiotic-loading protocol in articulating cement spacers for the treatment of prosthetic joint infection: A retrospective cohort study. *Bone Joint Res*. 2019 Dec 3;8(11):526-534.
- [12] Rogers BA, Middleton FR, Shearwood-Porter N, Kinch S, Roques A, Bradley NW, Browne M. Does cyclical loading affect the elution of antibiotics from articulating cement knee spacers? *J Bone Joint Surg Br*. 2011 Jul;93(7):914-20.
- [13] Springer BD, Lee GC, Osmon D, Haidukewych GJ, Hanssen AD, Jacofsky DJ. Systemic safety of high-dose antibiotic-loaded cement spacers after resection of an infected total knee arthroplasty. *Clin Orthop Relat Res*. 2004 Oct;427:47-51.
- [14] Dagneaux L, Limberg AK, Osmon DR, Leung N, Berry DJ, Abdel MP. Renal Toxicity Associated With Resection and Spacer Insertion for Chronic Hip PJI. *J Arthroplasty*. 2021 Sep;36(9):3289-3293.
- [15] Menge TJ, Koethe JR, Jenkins CA, Wright PW, Shinar AA, Miller GG, Holt GE. Acute kidney injury after placement of an antibiotic-impregnated cement spacer during revision total knee arthroplasty. *J Arthroplasty*. 2012 Jun;27(6):1221-7.e1-2.
- [16] Holubar M, Meng L, Alegria W, Deresinski S. Bacteremia due to methicillin-resistant *Staphylococcus aureus*: an update on new therapeutic approaches. *Infect Dis Clin North Am*. 2020;34(4):849-861.

- [17] Chang Y, Chen WC, Hsieh PH, Chen DW, Lee MS, Shih HN, Ueng SW. In vitro activities of daptomycin-, vancomycin-, and teicoplanin-loaded polymethylmethacrylate against methicillin-susceptible, methicillin-resistant, and vancomycin-intermediate strains of *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2011 Dec;55(12):5480-4.
- [18] Park SJ, Song EK, Seon JK, Yoon TR, Park GH. Comparison of static and mobile antibiotic-impregnated cement spacers for the treatment of infected total knee arthroplasty. *Int Orthop*. 2010 Dec;34(8):1181-6.
- [19] Harper KD, Incavo SJ. Drug reaction with eosinophilia and systemic symptoms syndrome after total knee arthroplasty infection and placement of antibiotic spacer. *Arthroplast Today*. 2019 May 22;5(2):148-151.
- [20] Williams B, Hanson A, Sha B. Diffuse Desquamating Rash Following Exposure to Vancomycin-Impregnated Bone Cement. *Ann Pharmacother*. 2014 Aug;48(8):1061-1065.