HK 93: What antibiotics should be added to PMMA cement-spacer in patients undergoing resection arthroplasty for culture negative periprosthetic joint infection (PJI)?

David Rodriguez MD, Conor George BS, and Matthew Squire, MD, MS

Response/Recommendations:
Addition of vancomycin combined with either an aminoglycoside, Meropenem, or Piperacillin/Tazobactam to PMMA spacer is a reasonable approach for treatment of patients with culture negative periprosthetic joint infection (PJI).

Level of Evidence: Limited

Delegate Vote:

Rationale:

Periprosthetic joint infections (PJIs) continue to be the leading cause of revision hip and knee arthroplasties in the United States and Europe [1]. Around 1% of patients undergoing total hip or knee arthroplasty develop a PJI with annual treatment expected healthcare costs of around $2 billion by the year 2030 [2,3]. Also, with the numbers of revision hip and knee replacement on the rise, the even higher incidence of PJI in revision arthroplasty requires arthroplasty surgeons to focus on prevention but also in appropriate infection eradication practices [3].
Even though there is recent data documenting acceptable success with debridement and antibiotics with implant retention (DAIR) and one-stage exchange for acute and chronic PJI, two-stage revision has been considered as the gold standard for treating PJI [4-7].

Spacer antibiotic selection during two stage revision arthroplasty is guided by preoperative cultures and sensitivities. Between 5 to 42% of PJIs are culture negative (CN) infections which can pose significant challenges in terms of antibiotic selection for both cement spacer construction as well as parenteral antibiotic treatment [8,9]. Documented risk factors for CN cases include prior use of antibiotics before aspiration/procedure, inappropriate culture tools, insufficient culture period, persistent wound drainage or draining sinus, and infection with fastidious organisms or fungi [10].

Studies show that fastidious organisms such as fungi, mycobacteria, *Listeria monocytogens*, *Propionibacterium acnes*, Brucella, and *Coxiella burnetiid* are present in up to 50% of CN PJI cases [8, 33-34]. The use of advanced microbial identification techniques such as culture of specimens in blood culture vials, extended incubation times and more recently next-generation DNA sequencing may allow for more accurate detection of fastidious bacteria and fungi [35]. In addition to guiding optimal antimicrobial selection during PJI treatment, successful organism identification also enhances antimicrobial stewardship by eliminating the need for excessively broad spectrum empiric antimicrobial use.

Reported success rates for the two-stage treatment of CN PJI vary with numerous studies showing comparable and sometimes higher success rates in CN cohorts as compared to culture positive (CP) cohorts [11, 18]. Currently, no consensus exists with respect to the type or dose of antimicrobials that should be added to the spacer in the first stage of treatment. [12,13]. To improve our understanding of the optimal drug(s) and dose(s) to be placed in spacers for CN PJI, a systematic review was performed assessing PJI treatment success as a function of the antimicrobial drug(s) placed in spacers used in the two-stage treatment of CN PJI.

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we conducted a systematic search of the online bibliographic databases MEDLINE and PubMed from inception through November 2024 to identify studies evaluating success rates on culture negative PJIs undergoing two stage revision hip or knee arthroplasty. Exclusion criteria were as follows: articles not written in English language, investigations not including specific dose and type of antimicrobials added to the spacer, Shoulder, elbow, and ankle arthroplasty PJI studies, editorials, commentaries, case reports, reviews, and technique articles without patient success and/or follow-up data. Two of the authors independently screened the title and abstract of an initial number of 654 articles to apply the selection criteria. Disagreements were solved by consensus after reading the full text. We reviewed the full text of 68 articles and finally included 21 articles for analysis. For comparative analysis of the outcomes of each study, a data sheet containing the author's name, year of publication, study design, number of CN cases, spacer contents, two-stage exchange arthroplasty success rate, and average follow up was designed. The review results of the 21 included studies are summarized in Table 1 [15-35].

In the 21 studies identified for data analysis, a total of 649 patients were identified of which 41% (266 patients) had CN PJI. None of these studies reported results according to the MSIS 2019 Outcome Reporting Tool for PJI cofounding direct comparisons among them. To facilitate meaningful data analysis, our study group decided to divide and analyze five subgroups depending on the antibiotic combination and dosage within the spacer. The cohorts were as follows:

a. Cohort 1 (High dose Vancomycin/Tobramycin) – Patients that received Vancomycin 3-4g/Tobramycin 2-3.6g (n=386)

b. Cohort 2 - Patients that received Vancomycin 1-2g/Piperacillin/Tazobactam1g (n= 27)

c. Cohort 3 - Patients that received Vancomycin 1-2g/Meropenem/Imipenem 2g (n= 80)

d. Cohort 4 - Patients that received Vancomycin 1-2g only (n=40)

e. Cohort 5 - (Low dose Vancomycin/Tobramycin) – Patients that received Vancomycin 1-2/Tobramycin 80mg-1.2g (n=165)

Of the 80 patients treated with the vancomycin/carbapenem combination, there were no PJI treatment failures noted. The low dose (n=165) and high dose (n=386) vancomycin/aminoglycoside cohorts demonstrated 96.6% and 89.2% PJI treatment success rates, respectively. A chi square test to compare the success rate among these cohorts did not reveal any statistically significance differences between them (p=0.003). Our group understands the potential for selection bias of this noted significance given the different numbers in the high dose and low dose groups. In the very limited spacer cohort containing Vancomycin and Piperacillin/Tazobactam (n=27) there were no failures noted. The vancomycin only cohort (n=40) demonstrated the lowest success rate with only a 75% success rate. With the potential of CN infections being caused by multiple organisms it possible to suggest that utilizing ALBC with a single antibiotic might increase the risk of treatment failure.

Studies suggest that CN infections are not a negative prognostic factor for treatment infection eradication [14,15]. Our data support the combined use of Vancomycin combined with either an aminoglycoside, Meropenem, or Piperacillin/Tazobactam in spacers for CN PJI. While our data presented support the use of spacers containing either a low or high dose combination of Vancomycin and an aminoglycoside, prior investigations have shown that spacers containing lower doses of both vancomycin and aminoglycosides may increase the risk of PJI treatment failure as compared to spacers containing high doses of both vancomycin and aminoglycosides

[16]. With the limited data available for this systematic review, the use of spacers containing a single antibiotic in low doses are not recommended for CN PJI. In a cohort of 114 CN PJI cases, Yang et al. utilized two different spacer antimicrobial combinations. The spacer antimicrobial combination of Vancomycin, Meropenem and Amphotericin (VMA protocol) had a 100% success rate in 45 patients, illustrating the importance of covering for fungal and other fastidious organisms in CN PJI [17].

Conclusion:

Our systematic review reveals even though CN PJIs pose a significant challenge, a negative culture might not be an adverse predictor of success during two stage revision arthroplasties. The overall results of this review indicate that dual antibiotic cement spacer regimens (Vancomycin-aminoglycoside, Vancomycin-Piperacillin/Tazobactam, Vancomycin-Meropenem) provide comparable and high success rates for treatment of CN PJI and the use of these antibiotic combinations in PMMA spacers can be recommended for the treatment of CN PJI. In contrast, this systematic review suggests spacers containing only Vancomycin may have inferior treatment success rates; therefore, the use of PMMA spacers containing only vancomycin is not recommended for the treatment of CN PJI. In cases where CN PJI occurs in immunocompromised hosts, is present after failed 2-stage exchange for PJI, or is associated with the presence of a sinus tract, fastidious organisms including fungi must be suspected. It is recommended that PMMA spacers used to treat these challenging clinical scenarios contain a combination of antimicrobial drugs that provides broad-spectrum coverage against all suspected pathogens.

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