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Authors: Hangama Fayaz, Carlos A. Higuera, Igor Shubnyakov

QUESTION 4: What is the importance of two-week antibiotic holiday prior to reimplantation?

RECOMMENDATION: Unknown. There is no conclusive evidence to support the need or the ideal length of an antibiotic holiday prior to reimplantation.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 7%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

Two-stage exchange arthroplasty continues to be the preferred method of treatment for chronic periprosthetic joint infections (PJIs) in the United States and Europe. Traditionally, the procedure involves removal of all foreign material and a six-week period of ensuing antibiotic treatment. Prior to reimplantation it is customary to implement a 14-day antibiotic-free interval, known as a drug holiday, intended to allow for "emergence" of residual infection [1]. During this period serological testing and synovial aspiration are usually performed to ensure that infection is under control prior to proceeding with reimplantation. However, this widely implemented therapeutic option has remained controversial [2] because of the paucity of the systemic antibiotic treatment after six weeks, which can lead to the persistence of an infection and the development of multiple drug-resistant bacterial strains.

In addition, the accuracy of serological tests and synovial aspiration under ongoing systemic antibiotic therapy is debatable. Ghanem et al. [3] and Spangehl et al. [4] have reported that data regarding the value of serological markers and synovial aspiration between the stages have been published using heterogeneous cohorts, short follow-up periods and inconsistent antibiotic-free intervals. Meanwhile, some studies have suggested the abandonment of the systemic antibiotic pause after six weeks in favor of a continuous antibiotic administration [5,6].

Bejon [7] et al. (2010) retrospectively reported on 152 patients with periprosthetic joint infection (PJI) who were treated with two-stage revision with a success rate of 83% over a median follow-up duration of 5.7 years; this is within the reported range of success rates [7]. The reimplantation was preceded by a two-week antibiotic-free period in 88% of the cases. However, the microbiology was positive in 3 of 18 patients (16%) without a two-week antibiotic-free period compared with 18 of the 134 patients (13%) with a two-week antibiotic-free period. At reimplantation, more knee joints were culture positive than hip joints, despite being less frequently culture positive at the first-stage excision. Spacers were used in all knee joint revisions; however, they were rarely used for the hips (13%). They did not use aspiration but waited during the two-week antibiotic-free period and decided whether to perform reimplantation based on the clinical appearance. Most unexpected debridements following the first

stage were performed without discontinuing the antibiotics. They concluded that there was no evidence supporting the application of an antibiotic-free period prior to reimplantation and routine reimplantation microbiology. The authors did not find evidence to support the implementation of an antibiotic holiday.

Müllhofer [5] et al. (2018) examined 112 patients who were MusculoSkeletal Infection Society (MSIS) criteria-positive for prosthetic joint infection, including 45 patients with total hip arthroplasties (THAs) and 67 with total knee arthroplasties (TKAs). They treated all patients with a two-stage protocol using a mobile polymethal methacrylate (PMMA) spacer after a 14-day antibiotic-free interval, during which serological markers (C-reactive protein (CRP) and leucocytes) were assessed and synovial aspiration (white blood cell (WBC) count, polymorphonuclear cell (PMN) percentage and microbiological culture) was performed, and the outcomes were compared with those of their long-term follow-up (mean follow-up, 27 months; range, 24 to 36 months). They identified no reliable marker that was suggestive of the long-term persistence of an infection. CRP and leukocytes were often elevated although the infection was controlled. Normalized serum markers did not exclude the persistence of an infection during the follow-up period.

The synovial analysis of WBC count and PMN percentage did not support their well-investigated diagnostic reliability before stage one. The authors pointed out that microbiological synovial fluid analysis was often misleading because of false-positive microbiological cultures, which resulted in overtreatment. In addition, they emphasized the need for high-quality antibiotic treatment, including biofilm-active antibiotics, without any antibiotic holiday for diagnostic reasons. Moreover, they suggested that the reliability of serum markers increases if the time between the first and second stages is prolonged up to 6 months or one year, accounting for a poor functional outcome and increased psychosocial burden [3,5].

In contrast, Janz [8] et al. (2016) have reported remarkably high sensitivity (95%) with low specificity (20%) for serum CRP for predicting the persistence of the infection of resection arthroplasty hips without PMMA spacers. In their study group, the interval between the removal of an implant and the performance of the second stage was up to several months in the Girdlestone-hip group, whereas the cohorts of Müllhofer [5], Kusuma et al. [9] and Ghanem et al. [3] exhibited a standardized timeline with a diagnostic workup eight weeks after explanation.

Boelch [6] et al. (2018) retrospectively analyzed 92 aspirations before the planned joint reconstruction during the two-stage exchange with hip spacers. The PJI was diagnosed according to the Clinical Practice Guidelines by the Infectious Diseases Society of America.

The mean duration from the index surgery to the prosthesis removal was 58.75 months (median, 14.38 months). In the study, 47.8% of the prosthesis removal were primary revisions, and 57.6% patients were males. In addition, the mean age at the prosthesis removal was 67.46 years, and the mean Body Mass Index (BMI) was 29.8 kg/cm^2. An articulating (91.3%) or a resection arthroplasty spacer (8.7%) was implanted at the surgeon's preference. Spacers were molded by hand with a Steinman pin as an endoskeleton. In addition, Palacos R+G and 2 gm of vancomycin per 40 cm^3 of the batch were routinely applied. If preoperative cultures from aspiration exhibited no growth, then antibiotic therapy was initiated in combination with an aminoglycoside and a cephalosporin.

In case of bacterial detection, antibiotic therapy was modified according to a microbiologist's recommendation. In this study, the mean duration of intravenous antibiotic administration was 18.5 days, followed by a course of oral antibiotic therapy for a mean of 17.0 days.

The mean combined duration of antibiotic therapy was 34.4 days, and the mean drug holiday was 15.3 days. Precisely, 72.8% of inter-stage aspirations were performed after a drug holiday of at least 14 days. Aspiration was performed under sterile conditions. Their results implicated that neither the synovial fluid culture nor the synovial leucocyte count at the inter-stage aspiration during the two-stage exchange of the hip with a spacer was consistent as a standard approach for ruling out the persistence of the infection.

Thus, the authors preferred reconstruction or spacer exchange without any cessation of systemic antibiotic therapy, and they strongly discouraged aspiration during the two-stage exchange and instead recommended considering a high CRP before prosthesis removal and reconstruction suggestive of an increased risk of the persistence of an infection. Our literature review highlights that no single factor could be used alone when evaluating the success of two-stage arthroplasty in eliminating infection.

Thus, we must rely on a combination of clinical evaluation, imaging, serologic tests and biopsies to ascertain the timing of reimplantation. Additionally, there seems to be little evidence for deferring reimplantation until all serologic markers are normalized, which, perhaps, can lead to prolonged disability and ultimately cause soft tissue contractures and further bone loss [3].

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