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Workgroup 11:

Antibiotic Treatment and Timing of Reimplantation

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QUESTION 1: Can oral antibiotic therapy be used instead of intravenous for the initial treatment of periprosthetic joint infection (PJI) following resection?

Consensus: There is evidence to support pathogen-specific, highly bioavailable oral antibiotic therapy as a choice for the treatment of PJI.

Delegate Vote: Agree: 79%, Disagree: 11%, Abstain: 1% (Strong Consensus)

Justification:

PJI is traditionally treated with intravenous (IV) antibiotics in order to obtain the minimum inhibitory concentration in the shortest time possible. Once this goal is met and there is clinical evidence of improvement, some IV antibiotic regimens can be switched to oral regimens. There is scarce literature reporting on the use of oral (combined or single) antibiotic therapy for the treatment of PJIs without an initial IV regimen [1–5]. Most of these studies were conducted in cases where the prosthesis was retained. There is one study in which no oral or prolonged IV regimen was used after debridement and the use of an antibiotic-impregnated cement spacers led to a 87% eradication rate [6]. No literature conclusively supports the use of only oral (combined or single) antibiotic therapy prior to reimplantation. The recently-published guidelines of the Infectious Diseases Society of America (IDSA) [7] suggest that pathogen-specific, highly bioavailable oral therapy (e.g. linezolid or fluoroquinolones) may be an alternative as initial therapy for some cases of PJI. Concerns against the routine use of appropriate oral agents in the treatment of PJI largely comprise questions of patient medication compliance and the long-term use of medication therapy with less intensive efficacy and toxicity monitoring.

QUESTION 2: Is oral antibiotic therapy appropriate after an initial IV antibiotic course?

Consensus: There is evidence that pathogen-specific, highly bioavailable oral antibiotic therapy is an appropriate choice for the treatment of PJI after an initial IV antibiotic regimen.

Delegate Vote: Agree: 98%, Disagree: 1%, Abstain: 1% (Strong Consensus)

Justification:

An IV antibiotic regimen is preferred in order to obtain the ideal plasma concentration in the shortest time possible. Switching to oral regimens, if possible, lowers the financial burden on patients and payers, reduces the risks of vascular access, and increases the possibility of home-based therapy. Most studies use a protocol of 4–6 weeks of IV antibiotics followed by 2–4 weeks of an oral regimen [8–10], although some studies use the IV regimen alone. A recent study with only 14 days of an IV regimen followed by 6–8 weeks of oral therapy showed no relapse [11]. We support the use of oral antibiotic therapy after an initial course of IV antibiotics for sensitive pathogens.

QUESTION 3: What is the ideal length of antibiotic treatment following removal of the infected implant?

Consensus: There is no conclusive evidence regarding the ideal duration of antibiotic therapy. However, we recommend a period of antibiotic therapy between 2 and 6 weeks.

Delegate Vote: Agree: 93%, Disagree: 5%, Abstain: 2% (Strong Consensus)

Justification:

The ideal duration of antibiotic therapy (IV alone or combined IV and oral) is not known. Decreasing the time of antibiotic regimens reduces cost and development of resistance and complications inherent to a single or combined therapy [8–16]. Most of the literature recommends antibiotic therapy with duration between 6 and 12 weeks. A prospective non-randomized study by Bernard et al [17] concludes that 6 weeks of antibiotic treatment (with one week of an IV antibiotic regimen) was sufficient to control infection, but this study includes groups of patients treated with irrigation and debridement (I&D), single-stage exchange arthroplasty, and two-stage exchange arthroplasty. Other investigators have suggested a shorter parenteral course; Stockley et al [6] used a non-oral and non-prolonged regimen (2 weeks of IV) after debridement and placement of an antibiotic-impregnated cement spacer, with an 87% eradication rate.

QUESTION 4: How should the length of antibiotic treatment be determined? (Inflammatory markers, clinical signs, etc).

Consensus: There is no conclusive evidence on how to determine the length of antibiotic therapy. A combination of clinical signs and symptoms and biochemical markers may be employed. There is the

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need for a marker that can determine the optimal timing for reimplantation.

Delegate Vote: Agree: 96%, Disagree: 3%, Abstain: 1% (Strong Consensus)

Justification:

Improvement of clinical signs has been used as a proxy for control of infection while antibiotics are administered. Unfortunately, improved clinical signs during antibiotic therapy alone do not reliably predict eradication of infection or determine the length of antibiotic therapy. For this reason, progressive sequential decreases in the values of inflammatory markers, namely erythrocyte sedimentation rate and C-reactive protein, have been used as an adjunct along with improvement in clinical signs to determine the ideal time for termination of antibiotic therapy and for reimplantation [18–23]. In addition, no ideal cut-off value has been determined for these inflammatory markers to predict the ideal time for discontinuation of antibiotic treatment or for reimplantation [19,24]. Further large-scale studies are needed to validate and determine the parameters of use of new inflammatory markers such as pro-calcitonin [25], leukocyte esterase [26–28], IL-6, and others [29].

QUESTION 5: Should there be an antibiotic holiday period prior to reimplantation?

Consensus: There is no conclusive evidence supporting a holiday period following discontinuation of antibiotic treatment and prior to reimplantation surgery as a means of ensuring eradication of infection.

Delegate Vote: Agree: 74%, Disagree: 22%, Abstain: 4% (Strong Consensus)

Justification:

Although Bejon et al [30] did not find evidence to support the clinical utility of an antibiotic-free period, this was a retrospective analysis published before the new definition of PJI from the Musculoskeletal Infection Society workgroup [31–33] was available. In practice, improvement of clinical signs is frequently used as a proxy for infection control and effective antibiotic therapy. However, these improved clinical signs may persist only while such antibiotic therapy is in place and it is desirable to identify persistence of infection before reimplantation. For these reasons, some practitioners feel that, a holiday period of antibiotics prior to reimplantation opens the opportunity for ongoing observation, where stability or clinical improvement could indicate eradication of the infection while deterioration might indicate recurrence. No evidence conclusively supports the need for an ideal length of such a holiday period.

QUESTION 6: Does the use of rifampin in conjunction with IV antibiotic therapy following removal of the infected implant lead to a more rapid and definitive eradication of staphylococcal infection (particularly methicillin-resistant *Staphylococcus aureus* [MRSA])?

Consensus: There is no evidence to support the use of rifampin in conjunction with IV antibiotic therapy as a more adequate treatment option than either agent used alone following implant removal.

Delegate Vote: Agree: 77%, Disagree: 18%, Abstain: 5% (Strong Consensus)

Justification:

There is adequate evidence to support the use of rifampin in combination with other antibiotics for the treatment of staphylococcal PJI, especially in the setting of retained hardware [1,34,35]. Evidence supporting its use when infected hardware has been removed is less convincing. Rifampin is not to be used as monotherapy due to its low barrier for development of resistance [36]. The limitations to mandatory use of rifampin include significant drug interactions and adverse effects. Rifampin stains most bodily secretions orange, causes gastrointestinal intolerance, hepatotoxicity, and other less common adverse effects [37]. It is a significant hepatic enzyme inducer, and as such, increases the metabolism of many important and common drug classes, such as other antibiotics and antifungals, anticoagulants (including warfarin and the oral direct thrombin inhibitors), and immunosuppressants [38].

QUESTION 7: What is the optimal time to start rifampin treatment?

Consensus: There is no conclusive evidence regarding the best time to start rifampin treatment. Good oral intake and adequate administration of a primary antimicrobial agent should be well-established before starting rifampin. Potential side effects and drug interactions should be addressed prior to the start and at the conclusion of therapy.

Delegate Vote: Agree: 83%, Disagree: 11%, Abstain: 6% (Strong Consensus)

Justification:

There are no studies that address the ideal time to start rifampin therapy. Rapid emergence of rifampin resistance has occurred in the rare case where bacteremia is present [39]. Given the potential for development of resistance, it appears prudent to withhold rifampin until bacteremia has cleared and/or primary antibiotic therapy has reached adequate tissue concentrations. One study suggests, in univariate analysis that the presence of a sinus tract or prolonged wound drainage may increase the risk of rifampin resistance [40]. This association was not confirmed on multivariate analysis. As a significant hepatic enzyme inducer, it is important to account for drug interactions both at the initiation and the conclusion of rifampin therapy. Rifampin activity against any isolated pathogen should also be verified around the time of therapy initiation.

QUESTION 8: How long should antibiotic treatment be given following a single-stage exchange arthroplasty performed for PJI?

Consensus: There is no conclusive evidence regarding the ideal duration of antibiotic therapy for a single-stage exchange arthroplasty. We recommend that parenteral antibiotic be given for 2–6 weeks following single-stage exchange arthroplasty, with consideration for longer-term oral antibiotic therapy.

Delegate Vote: Agree: 87%, Disagree: 10%, Abstain: 3% (Strong Consensus)

Justification:

Single-stage exchange arthroplasty for PJI has the advantage of being only one major procedure, thus decreasing cost and the risk of complications that could arise from multiple surgeries [1,34,35]. No evidence is available regarding the ideal length of antibiotic therapy [12,41–43]. Bernard et al [17] concluded that 6 weeks of antibiotic treatment (with one week of an IV antibiotic regimen) was sufficient to control infection; however, this study included I&D and two-stage exchange arthroplasty as well. The recently published guidelines of