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QUESTION 3: Does the International Consensus Group (ICG) agree with the Infectious Diseases Society of America (IDSA) guidelines regarding the recommended duration of antibiotic therapy in orthopaedic infection?

RECOMMENDATION: There is some disagreement between what the ICG and the IDSA recommends regarding the duration of antibiotic treatments for different infective organisms. The differences between the two organizations resides on the duration of oral antibiotic therapy following a pathogen-specific intravenous (IV) antimicrobial therapy.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 82%, Disagree: 3%, Abstain: 15% (Super Majority, Strong Consensus)

RATIONALE

The optimal length of antibiotic treatment following surgical treatment of periprosthetic joint infections (PJIs) by resection arthroplasty, one-stage exchange arthroplasty, or debridement and implant retention remains unknown. There are numerous studies related to this subject and during the last meeting of the ICG, it was felt that antibiotic treatments between two and six weeks appeared to be sufficient for patients with PJIs.

The last ICG found no conclusive evidence regarding the ideal duration of antibiotic therapy when considering treatment following resection arthroplasty due to PJIs. They found that the ideal duration of antibiotic therapy, either IV or combined with oral medications, was unknown. Cost and resistance were lower when decreasing the time of antibiotic regimens [1–6]. Most of the literature, at the time, recommended antibiotic therapy between 6 and 12 weeks, although Bernard et al. found that 1 week of an IV antibiotic regimen plus a following 5 weeks with oral regimen was sufficient to control infection. This study involved irrigation and debridement (I&D), single-stage exchange arthroplasty and two-stage exchange arthroplasties [4]. Stockley et al. used a short two weeks IV-only antibiotic therapy following I&D and placement of an antibiotic-impregnated cement spacer, and noted an 87% success rate [7]. Nevertheless, the ICG strongly recommends a course of two to six weeks of antibiotics.

The ICG then explored how the duration of antibiotic treatments could be determined, agreeing that there was not enough evidence to determine whether biomarkers or clinical symptoms could be used to monitor response to treatment.

Additionally, the ICG attempted to determine the duration for antifungal therapy in the presence of fungal PJIs. They strongly agreed upon consensus stated that systemic antifungal treatment should be initiated before resection, and continued for at least six weeks, and stopped before reimplantation, without a need (in most cases) to restart antifungal therapy. For Fluconazole, the literature had 3 to 6 weeks or more (in some studies even 26 weeks) before reimplantation, then no further treatment, or only 2 to 6 weeks more after reimplantation. For Amphotericin B, the duration was often found to be about six weeks before reimplantation [8–20].

IDSA Guidelines

The IDSA guidelines suggest no more than a 6-week course of antimicrobial therapy following resection arthroplasty for PJIs due to more virulent organisms such as *Staphylococcus aureus* [21]. The IDSA recommends two to six weeks of pathogen-specific IV antimicrobial therapy combined with 300 to 450 mg of rifampin given orally twice daily. The treatment should continue with rifampin plus a companion oral drug (ciprofloxacin (A-I), or levofloxacin (A-II), or others for a total of three months for Staphylococcal total hip arthroplasty PJI, treated with one-stage exchange or with debridement and retention of the prosthesis. The IDSA recommendation for Staphylococcal total knee arthroplasty PJI is the same, but for a total of six months when treated with debridement and prosthesis retention.

For organisms other than Staphylococci, the IDSA guidelines recommends an initial course of pathogen-specific IV therapy for four to six weeks, or highly bioavailable oral antimicrobial therapy (B-II). Chronic suppression after fluoroquinolone treatment of gram-negative bacilli was not unanimously recommended [21]. Longer courses of combination antimicrobial therapies of six months or more are recommended by the current guidelines and reports for bone infections due to rapidly growing mycobacteria (RGM) [22,23].

IDSA guidelines recommend a minimum of six weeks of antifungal therapy for fungal PJIs, but a longer course of antifungal therapy has been considered to be an essential factor for the success of fungal PJIs treated with staged reimplantation. Phelan et al. administered antifungal therapies after resection arthroplasty for six weeks to nine months in four patients who underwent two-stage reimplantations [8].

Regarding the IDSA guidelines on the treatment of osteomyelitis due to invasive Candidiasis, they recommend treatment duration from 6 to 12 months.

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QUESTION 4: Is the type, dose, route of administration and duration of antimicrobial treatment influenced by the type of infective organism causing periprosthetic joint infection (PJI)?

RECOMMENDATION: The duration, dose, route of administration and the type of antibiotic administered to patients with PJI is determined by the type of infective organism(s) isolated.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 4%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

There have been reports showing increased risks of treatment failure reported in patients with a sinus tract [1] and infections due to certain organisms such as *Staphylococcus aureus* [2], methicillin-resistant *Staphylococcus aureus* (MRSA) and gram-negative organisms [3-11] when not treated with a rifampin combination. For Staphylococcal PJIs, the Infectious Diseases Society of America (IDSA) guidelines recommend, based on expert opinion, two to six weeks of pathogen-specific intravenous (IV) antimicrobial therapy in combination with rifampin, followed by rifampin plus a companion oral drug for a total of three months [12].

The duration of antimicrobial therapy for most bacterial PJIs depends on the type of surgical procedure used to treat PJIs (debridement and retention vs. one-stage, vs. two-stage exchange, etc.) rather than the infecting microorganism itself.

One retrospective cohort study of 39 patients with PJIs undergoing single-stage exchange, of which 28 had Staphylococcal infections, demonstrated that two weeks of intravenous therapy followed by three months of oral antimicrobial therapy was sufficient

to control the infection [13]. This study was limited by its small cohort size, lack of a control group and possible confounding variables.

The optimal duration of antimicrobial therapies in two-stage exchange arthroplasty is unclear. Multiple cohort studies have demonstrated acceptable cure rates in two-stage exchange arthroplasty with the use of six weeks to three months of total antibiotic therapy (IV and oral antibiotics) [14-19].

These retrospective cohort studies included a variety of infecting organisms, including *Staphylococcal* PJIs. These studies did not report any robust evidence that outcomes were worse for any organisms. There are no prospective trials directly comparing the duration of antibiotic therapy for Staphylococcal PJIs managed with two-stage exchange arthroplasty.

A retrospective cohort analysis of 30 patients with Streptococcal PJIs demonstrated high failure rates of 45%, in patients who underwent two-stage revisions [20]. The patients were managed with 2 weeks of IV antibiotics followed by 10 weeks of oral antibiotics.