al. followed two cohorts of patients following a two-stage revision knee arthroplasty. Twenty-eight patients had a mean of 33 days of oral antibiotics (range, 28-43 days) following the reimplantation procedure and 38 patients received between 24 and 72 hours of post-operative intravenous antibiotics as standard prophylaxis. Patients were followed over a 12-month period and evaluated for reinfection. They found that the risk of reinfection with extended oral antibiotics was 4% compared with 16% in the control cohort that received routine perioperative antibiotics [8]. The single patient who was reinfected in the oral prophylaxis cohort was found to be infected with methicillin-resistant *Staphylococcus aureus*, which was present at the time of the original component removal. In contrast, a variety of low virulence organisms were the cause of reinfection in the group that received short-term prophylactic antibiotics intravenously. In a study by the same group that examined patients treated for periprosthetic hip infections, Johnson et al. found a 13.6% rate of reinfection in the perioperative antibiotic group compared to 0% reinfection in those patients treated with oral antibiotics for 14 days following a two-stage exchange [9].

There is presently one randomized controlled trial that reported the use of prolonged prophylactic oral antibiotics following reimplantation [10]. This multi-institutional study randomized patients to receive three months of oral antibiotics or standard prophylactic intravenous antibiotics only for up to 72 hours. This study included a total of 107 patients who were undergoing a two-stage revision hip or knee arthroplasty for a periprosthetic infection that met the MusculoSkeletal Infection Society (MSIS) criteria at the first stage and with negative cultures at the second stage. The rate of reinfection was 19% in the control group compared to 5% in the treatment group ($p = 0.0162$). Eight of the nine infections in the control group and one of the three in the extended oral antibiotic group were infections associated with a new organism. In the antibiotic cohort, three patients had to stop their antibiotic due to adverse reactions such as gastrointestinal upset and nausea. Three additional patients had minor adverse reactions such as rash or yeast infection; however, they continued to take the oral antibiotic despite these side effects.

Based on the available literature, there is moderate evidence to suggest that relatively short (three months) courses of oral antibiotic, following reimplantation after a two-stage exchange may reduce early failure with reinfection. All studies evaluating the role of antibiotic suppression have been short term and longer follow-up of the same cohort is needed as the one randomized trial did not report a full two years of follow-up for all enrolled patients. In addition, it is important to note that there were some issues with the administration of antibiotics and some patients had to discontinue the antibiotic. Administration of antibiotics under any circumstances needs to be weighed against its harm to the patient in terms of adverse effects and harm to society in terms of cost and its potential to cause emergence of resistant organisms.

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QUESTION 3: When is the optimal time to change intravenous (IV) antibiotic(s) to an oral agent(s) after a resection arthroplasty as part of two-stage exchange?

RECOMMENDATION: There is evidence to support pathogen-specific, highly bioavailable oral antibiotic therapy as an appropriate choice after resection arthroplasty in a two-stage treatment of periprosthetic joint infections (PJIs) after an initial IV antibiotic period of at least 5-7 days.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 83%, Disagree: 14%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Resection arthroplasty with a two-stage exchange is utilized in the management of PJIs in patients who are not candidates for a one-stage exchange, are medically able to undergo multiple surgeries and in whom the surgeon believes that replantation arthroplasty is possible [1]. An important part of the exchange arthroplasty includes administration of systemic antimicrobial therapy. The optimal time and the mode of administration of systemic antimicrobials has been the subject of numerous studies, with no definitive recommendations available.

Several studies recommend 4-6 weeks of pathogen-specific IV or highly bioavailable per oral (PO) antimicrobial therapy for patients with PJIs who have undergone two-stage exchange arthroplasty [1–3].

PJIs are usually treated with IV antibiotics in order to obtain the ideal plasma concentration in the shortest time possible. IV therapy requires an intravenous vascular access line that can be associated with infections and thromboembolic diseases [4]. Changing to PO therapy is less invasive for patients, lowers the financial burden and reduces hospital stay. Because of the aforementioned attributes of oral antibiotics, there has been an interest in identifying patients who may be candidates for administration of oral antibiotics.

Currently, there are no high-quality studies comparing different periods of initial IV regimens. An initial short course of IV therapy can reduce bacterial bioburden and minimize the risk of emergence of antimicrobial resistance [5–7]. Changing to PO therapy to complete the course of treatment has been shown to be effective. Darley et al. showed that 10-14 days of IV antibiotic therapy followed by 6-8 weeks of PO therapy was successful in 17 patients who underwent two-stage resection arthroplasty for management of prosthetic hip infections [8]. Ciriviri et al. and Ascione et al. showed high success rates with a similar approach [9,10]. Studies have also shown success with 5-7 days of IV therapy followed by PO therapy [11–13]. A fall in C-reactive protein (CRP) value was used to guide the timing for change in one study [14]. Observational studies using only shortened IV antibiotic courses in patients with antibiotic cement spacers have also reported success [15,16]. Of note, in examining the treatment of chronic osteomyelitis in adults, a Cochrane review of 5 small trials of 180 participants with bone or joint infection showed no benefit to IV therapy as compared to PO therapy [17].

Prospective, randomized clinical trials examining the role of PO antibiotic therapy for bone and joint infection are needed. The recently published results from the OVIVA (oral versus intravenous antibiotic treatment for bone and joint infections) trial was an important contribution. This study was a parallel group, randomized (1:1), un-blinded, non-inferiority trial conducted in 30 hospitals in the United Kingdom comparing PO to IV antibiotic treatments for bone and joint infections. Both arms had six weeks of either PO or IV antibiotics, and those selected for the PO arm had seven days or less of IV antibiotics at the start of treatment. A pilot of 228 participants that concluded in 2013 supported extension to the multicenter trial. The final analysis of 1,015 participants concluded that PO antibiotic therapy was non-inferior to IV therapy when used during the first 6 weeks in the treatment of bone and joint infections, as assessed by treatment failure within 1 year of randomization [18]. The study included 302 participants who underwent resection arthroplasty or implant removal. Additionally, a prospective study looking at extended PO antibiotics after second-stage (reimplantation surgery) showed a decreased rate of reinfection [19].

Given the availability of highly bioavailable PO antibiotic agents with good tissue penetration, the strategy of a shortened initial IV antibiotic course followed by pathogen-specific PO therapy should be considered following resection arthroplasty as part of two-stage exchanges. Additional prospective studies comparing outcomes to extended IV therapy should help clarify the optimal timing for transition. However, based on the available evidence it appears that oral administration of an antimicrobial, at least after a short period of IV treatment, is a viable option in treatment of some patients with PJIs and should be considered.

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