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QUESTION 2: What are the appropriate weight-adjusted prophylactic antibiotic dosages?

RECOMMENDATION: The recommended weight-adjusted doses of antimicrobials for prophylaxis of hip and knee arthroplasty in adults are shown in Table 1.

TABLE 1. Recommended weight-adjusted doses of antimicrobials for prophylaxis of hip and knee arthroplasty in adults

Antimicrobial	Recommended Dose	Re-dosing Interval
Cefazolin	2 gm (consider 3 gm if patient weight ≥ 120 kg*)	4 hours
Vancomycin	15-20 mg/kg*	Not applicable
Clindamycin	600-900 mg#	6 hours

*Actual body weight.
#No recommended adjustment for weight.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

We performed a systematic review in order to examine the literature and determine appropriate weight-adjusted prophylactic antibiotic doses for the prevention of infections after hip and knee arthroplasties. The nature of the question and the lack of high-quality evidence did not allow a formal systematic review. We searched for larger comparative studies or systematic reviews where different doses of antibiotics or different antibiotics are being compared or smaller prospective pharmacokinetic/tissue penetration studies where antibiotics doses are recorded. We included studies examining systemic (not local) antimicrobials and where the antimicrobial was given for a primary or revision hip or knee arthroplasty procedure and no other procedures (e.g., dental procedure) with a prosthetic joint *in situ*.

Perioperative antimicrobial prophylaxis for patients undergoing orthopaedic procedures is routinely administered and is believed to be one of the most important steps for prevention of surgical site infections/periprosthetic joint infections (SSIs/PJIs). Cephalosporins are believed to be the most effective prophylactic agents for patients undergoing orthopaedic procedures as they have excellent bone penetration, bioavailability and a relatively extended half-life. However, in patients with allergies, a range of antimicrobials may be utilized that includes vancomycin and clindamycin.

The American Society of Health-System Pharmacists (ASHP) clinical practice guidelines provide important information regarding antimicrobial prophylaxis in surgery [1]. Doses of antimicrobials commonly used for surgical prophylaxis can be found in these guidelines. No high-quality randomized trials are investigating the safety or efficacy in preventing surgical infections of different doses of prophylactic systemic antimicrobials for surgery, including joint arthroplasty. The first International Consensus Meeting in 2013 recommended that perioperative antimicrobial prophylaxis be weight-based. These recommendations were based on the notion that the dose of antibiotic administered directly influences the serum levels of the given antimicrobial with inadequate serum levels of the antimicrobial being considered detrimental.

Serum and tissue concentrations of antimicrobials given at standard doses may not be adequate in obese patients due to various factors [2]. Pharmacokinetic studies have shown that tissue levels of cefazolin below the minimal inhibitory concentration (MIC) of common pathogenic organisms are found in body tissues near the end of surgery with a 1 gm dose [3,4]. In one small, prospective study on obese patients, a 2 gram dose of cefazolin was associated with a lower surgical site infection rates than a 1 gm dose [4]. A 2 gm dose likely achieves appropriate local surgical tissue levels, including in bone, in normal size patients [5]. However, in one study with morbidly obese patients, a 2 gm dose was associated with levels below pathogen MICs of cefazolin [6]. Given the finding of these studies, as well as the low cost and favorable safety profile of cefazolin, weight-based dosing of prophylactic cefazolin has been recommended as part of the ASHP clinical practice guideline for antimicrobial prophylaxis in surgery [1]. In this guideline, 2 gm of cefazolin is recommended as a standard dose and 3 gm for patients weighing 120 kgs or greater. Subsequent small studies [7,8], including a small randomized controlled trial [9], have compared tissue levels of 2 gm with 3 gm of cefazolin in obese women undergoing caesarean section. These have shown higher tissue levels in patients receiving 3 gm; however, 2 gm doses generally exceeded the MIC of common pathogens. Given the lack of evidence showing a clear benefit in tissue penetrations or reduced infection rates, we recommend that a 2 gm dose of cefazolin is appropriate for most patients; however, given the limited toxicity, a 3 gm dose can be considered in patients ^{3} 120kg as per ASHP guidelines.

There is some evidence to suggest that vancomycin may be more likely to achieve therapeutic serum levels with weight-based dosing of 15 to 20 mg/kg compared with a standard dose (often 1 gm) when given for surgical prophylaxis without an increased risk of renal impairment. Patients receiving appropriate weight-based dosing may have a lower rate of methicillin-resistant *Staphylococcus aureus* (MRSA) infection, however, there is no evidence suggesting an overall lower rate of infection [10–12]. In addition, weight-based dosing rather than a fixed 1 gm dose has been recommended for total joint arthroplasty [10,11]. Kheir et al. reported that a fixed 1 gm dose was administered in 94% of total joint arthroplasties with 64% (1105/1726) of these patients being underdosed. Furthermore, the authors found that weight-based dosing achieved higher levels of vancomycin at all points during surgery without increasing nephrotoxicity and acute kidney injury [10].

There are no studies comparing clinical or pharmacokinetic outcomes with different doses of clindamycin for surgical prophylaxis. Older pharmacokinetic studies show a good penetration of clindamycin into surgical tissues including bone [13–15]. Based on serum levels after intravenous administration, this suggests that commonly used doses of 600 mg or 900 mg should exceed the MIC of most relevant pathogens [1,15].

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QUESTION 3: Is one dose of preoperative antibiotic adequate for patients undergoing total joint arthroplasty (TJA)?

RECOMMENDATION: Despite the current guidelines from the Centers for Disease Control and Prevention (CDC) advocating for a single dose of perioperative antibiotics, these studies are underpowered and primarily in specialties outside orthopaedics. From the limited evidence available, it appears that a single perioperative dose of antibiotics, compared to multiple doses, does not increase the rate of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs). A randomized prospective study in patients undergoing elective arthroplasty is underway that should answer this question definitively.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 7%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Perioperative antibiotic prophylaxis remains an important strategy for minimizing one of the most devastating complications following TJAs, PJIs [1,2]. All current guidelines recommend the use of perioperative antibiotics [3–7] (Table 1). For arthroplasty, the costs and morbidities associated with PJIs have led to abundant research to reduce the rate of postoperative infections. To this end, perioperative antibiotics are widely used; however, hospital protocols vary from a single preoperative dose to several days of postoperative prophylaxis. Many surgeons administer antibiotics for a total of 24 hours as this is the maximum time period recommended by several current guidelines. However, there was a recent change in the guidelines provided by the World Health Organization (WHO) and CDC. They recommend against the administration of antibiotics in the postoperative period and that only a single preoperative antibiotic be administered, largely due to fears of increased bacterial resistance and side effects of unnecessarily prolonged antibiotics [4,5]. The 2017 CDC Guidelines issued this statement as a strong recommendation with high-quality evidence. However, the limited literature in arthroplasty cannot support this recommendation.

A recent systematic review and meta-analysis by Thornely et al. explored whether or not a single preoperative antibiotic dose is adequate for arthroplasty patients [8]. Their review returned four randomized controlled trials (RCTs) [9–12] with a total of 4,036 patients. In patients receiving postoperative prophylaxis, the infection rate was 3.1% (63/2055), compared to the rate (2.3%) of a single preoperative dose (45/1981). They concluded that postoperative antibiotics did not reduce the rates of infections; however, they reported that the quality of evidence was very low. Among the available RCTs, three include teicoplanin as a single dose treatment, which is currently unavailable in the United States [10,13,14]. Heydemann et al. randomized 211 patients to a single dose vs. 48 hours of nafcillin or cefazolin; no deep infections were seen in either cohort [9]. Ritter et al. compared a single preoperative dose of cefuroxime to 24 hours of postoperative prophylaxis in a small RCT of 196 patients, and found no postoperative infections in either group [11]. Lastly, Wymenga et al., in a multicenter RCT of 3,013 patients, compared a single preoperative dose of cefuroxime to a group receiving 3 total doses and found no significant differences in infections between groups. These