1.3. PREVENTION: ANTIMICROBIALS (SYSTEMIC)

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QUESTION 1: What is the most appropriate perioperative prophylactic antibiotic (agent, route and number of doses) for patients undergoing primary total joint arthroplasty (TJA) to reduce the risk of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: The most appropriate perioperative prophylactic antibiotic is a first or second-generation cephalosporin (i.e., cefazolin or cefuroxime) administered intravenously within 30 to 60 minutes prior to incision as a single- and weight-adjusted dose.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 90%, Disagree: 8%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

The optimal prophylactic antibiotic should be a bactericidal agent against the most common organisms responsible for causing SSIs/PJIs. The agent must be present within the tissues at the time of initial incision, with adequate serum concentrations above the minimum inhibitory concentration (MIC) and should be maintained during the procedure [1,2]. A first- or second-generation cephalosporin (i.e., cefazolin or cefuroxime) can be used for routine perioperative prophylaxis with excellent distribution and cost effectiveness. The American Academy of Orthopaedic Surgeons (AAOS) currently recommends the use of either of these two agents in patients undergoing any orthopaedic procedure including TJA [3]. Prophylaxis should target the most common organisms (i.e., *Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli,* and *Proteus*) while avoiding unnecessary broad-spectrum therapies [4]. Glycopeptides, such as teicoplanin and vancomycin, have also been introduced as reasonable alternatives, although they have a narrower spectrum of action with minimal activity against gram-negative bacteria [5–7].

Vancomycin is selectively used in patients, such as nursing home residents and healthcare workers, who are MRSA carriers or at high-risk of MRSA colonization. In patients with documentation or suspicion of an allergy to cephalosporins, clindamycin can also be utilized and should be administered within one hour of the surgical incision. Vancomycin should be started two hours prior to incision due to the extended infusion time [8,9]. Although alternative agents such as vancomycin have been suggested in cases of allergies to cephalosporins, these have been associated with higher rates of SSIs if used alone [10–12]. In the study by Courtney et al., the authors reported that the addition of vancomycin to the prophylactic antibiotic regimen does not decrease the rates of SSIs, when compared with cefazolin alone, and could increase the risks of adverse effects [12]. Without clear evidence, the superiority of dual-antibiotic prophylaxis in prevention of infection should be carefully considered.

Bosco et al. [13] evaluated the increasing prevalence and virulence of gram-negative pathogens as these were the causative pathogens in up to 30% of infections in total hip arthroplasty (THA). They instituted the Expanded Gram-Negative Antimicrobial Prophylaxis (EGNAP) for hip arthroplasty patients. Two groups were compared in terms of SSI rates; one group did not receive weight-based, high-dose gentamicin while the second group did. The reported rates were 1.19 vs. 0.55% after EGNAP was implemented ($p = 0.05$). On a different study, Tan et al. [14] specifically evaluated the influence of comorbidities and use of perioperative antibiotics in 1,022 patients with PJIs to determine the influence of comorbidities on organism profile. They found that no comorbidities were associated with an increased rate of gram-positive or gram-negative infections. Their results support the current recommendations of a universal antibiotic prophylaxis protocol rather than an antibiotic regimen individualized to a patient's comorbidities.

Malhas et al. [15] examined microbiological results from hip and knee revisions from 2001 to 2010. Antibiotic resistance patterns were evaluated on *Staphylococcus aureus* (SA) and coagulase-negative *Staphlococcus* (CNS) cultured from regional pan-speciality sources. A total of 72 revisions in 67 patients were included. The most common organisms were SA (36%) and CNS (35%). Resistance to methicillin was 72 for CNS vs. 20% for SA and resistance to gentamicin was 40% for CNS vs. 4% for SA. Among all regional (background pan-speciality) cultures, SA resistance to methicillin fell from 32 to 16% from 2006 to 2010 with no change in gentamicin resistance at 3%. During the same period, resistance of CNS to methicillin and gentamicin increased from 63 to 70% and 32 to 47%, respectively. The prophylaxis regimen prior to 2008 was cefuroxime, and after 2008 was gentamicin and flucloxacillin.

Other Agents

Flucloxacillin and gentamicin: Torkington et al. [16] investigated bone penetration of intravenous antibiotic prophylaxis with flucloxacillin (2 gm) and gentamicin (3 mg/kg) single doses during hip (18 patients) and knee (21 patients) arthroplasty, and their efficacy against *S. aureus* and *S. epidermidis*. This study demonstrated that the intravenous antibiotic prophylaxis combination of flucloxacillin and gentamicin achieved adequate concentrations in bone against the common causative organisms in total knee arthroplasty (TKA) and total hip arthroplasty (THA) PJIs, adding to the available evidence to support its use.

Teicoplanin: Four randomized controlled trials provided strong evidence for the use of a single dose of 400 mg of teicoplanin at induction in selected cases [17,18]. Although there is no evidence to suggest that higher doses or prolonged courses of treatments result in fewer SSIs, studies have shown that this dose may be inadequate for patients weighing over 70 kgs [19].

Sulbactam-ampicillin: Yuasa et al. [20] compared the incidence of SSIs with two doses of sulbactam-ampicillin after THA: 1.5 and 3 grams. They found a global decrease in SSIs in the 3 gm dose group from 2.91 to 1.08% ($p = 0.268$), and in deep infection from 1.2 to 0% ($p = 0.231$).

Cloxacillin vs. clindamycin: Robertson et al. compared the risks of PJIs between the use of cloxacillin and clindamycin as perioperative antibiotics in 80,018 TKAs. The risk of failure leading to revision due to PJI was higher with clindamycin compared to cloxacillin (risk ratio (RR) = 1.5, 95% confidence interval (CI): 1.2 to 2.0; $p = 0.001$). Clin-

damycin inhibits bacterial protein synthesis by binding to bacterial 50S ribosomal subunits and it may be bacteriostatic- or bactericidal-based on the organism and drug concentration. Cloxacillin is in the beta-lactam category and works by binding to specific penicillin-binding proteins located inside the bacterial cell wall which inhibit cell wall synthesis. The primary reason for using clindamycin as a perioperative prophylaxis antibiotic is a reported allergy to penicillin. Even though between 5 and 10% of hospitalized patients report allergy to penicillin, most have negative results when tested for type-I hypersensitivity [21].

Dose

Current guidelines and studies recommend giving universal antibiotic prophylaxis to all TJA patients regardless of their medical conditions or immune status [2,3,14]. We did not identify studies that showed consistent reports on prophylactic dosage. Clinical practice guidelines, based on available evidence and expert opinion, recommend increasing the single preoperative prophylactic antimicrobial agent dose for select prophylactic antimicrobial agents in overweight and obese patients. For cefazolin, recommendations are to administer 2.0 gm for patients weighing > 60-80 kg and 3.0 gm if > 120 kg. For aminoglycosides, dosing is calculated using the patient's ideal body weight plus 40% of the difference between the actual and ideal body weight. Vancomycin should be dosed at 15 mg/kg. The goal of dosing is to achieve a safe and effective tissue concentration of the drug that sufficiently exceeds the concentration needed to inhibit the growth of most colonizing skin flora at the time of surgical incision [2,7].

Angthong et al. [22] found that IV cefazolin at a dose of 2 gm produced greater intraosseous concentrations overall than a dose of 1 gm. However, the higher intraosseous concentrations did not correlate with higher inhibitory effects. A second study demonstrated that biofilm formation could develop for up to 1–2 days [12]; therefore, hypothetically, the higher dose (2 gm) of cefazolin might be more beneficial than the lower dose of 1 gm [22].

Redosing: Moderate-quality evidence suggested no benefits of intraoperative antibiotic redosing. Clinical practice guidelines, based on a review of the evidence and expert opinion, recommend prophylactic antimicrobial agent redosing in cases of prolonged procedures (when the procedure exceeds the half-life of the prophylactic antimicrobial agent or is longer than 3 to 4 hours) and in patients with major blood loss (> 1,500 ml) or extensive burns. Redosing should also be performed at intervals of 1 to 2 times the prophylactic antimicrobial agent half-life, starting at the beginning of the preoperative dose [2].

Route

The best route to deliver antibiotics prior to total joint arthroplasty is considered to be intravenous in order to reach levels above MIC. Therapeutic concentrations should be maintained for the duration of the surgical procedure. Recent publications have suggested alternate routes such as intraosseous administration, although further research is required [1]. Irrigation solutions with antibiotics have also been used with little or no evidence. Among the few available low-evidence studies, Whiteside reported his experience in 2,293 arthroplasties using an irrigation solution of normal saline with vancomycin 1,000 mg/l and polymyxin 250,000 units/L at 2 L/hour. No patients required readmission for primary infection or further antibiotic treatment [23]. However in a meta-analysis study evaluating the use of topical antibiotic in colo-rectal surgery, no benefit was identified when used in conjunction with systemic antibiotics [1]. At present, the use of topical antibiotics, in conjunction with systemic antibiotics for prophylaxis in total joint arthroplasty, remains unproven.

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