Hip and Knee Section, Prevention, Antimicrobials (Systemic)

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Hip and Knee Section, Prevention, Antimicrobials (Systemic): Proceedings of International Consensus on Orthopedic Infections

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Question 1: What is the most appropriate perioperative prophylactic antibiotic (agent, route, and number of doses) in patients undergoing primary total joint arthroplasty 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 before 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 surgical site infections/periprosthetic joint infections (SSIs/PJIs). It 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 currently recommends the use of either of these 2 agents in patients undergoing any orthopedic procedure including total joint arthroplasty (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 who are methicillin-resistant *S aureus* carriers or at high risk of methicillin-resistant *S aureus* colonization, such as nursing home residents and health-

care workers. In patients with documentation or suspicion of an allergy to cephalosporins, clindamycin can also be utilized and should be administered within 1 hour of the surgical incision. Vancomycin should be started 2 hours before 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 [12], 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. 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 for hip arthroplasty patients. Two groups were compared in terms of SSI rates; 1 group did not receive weight-based high-dose gentamicin while the second group did. The reported rates were 1.19 vs. 0.55% after expanded gram-negative antimicrobial prophylaxis was implemented ($P = .05$). 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 *S aureus* and coagulase-negative *Staphylococcus* (CNS) cultured from regional pan-specialty sources. A total of 72 revisions in 67 patients were included. The most common organisms were *S aureus* (36%) and CNS (35%). Resistance to methicillin was 72% for CNS vs 20% for *S aureus* and resistance to gentamicin was 40% for CNS vs 4% for *S aureus*. Among all regional (background pan-specialty) cultures, *S aureus* 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 regime before 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 grams) 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 and THA PJIs, adding to the available evidence to support its use.

Teicoplanin

Four randomized controlled trials provide 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 kg [19].

Sulbactam-Ampicillin

Yuasa et al [20] compared the incidence of SSIs with 2 doses of sulbactam-ampicillin after THA: 1.5 and 3 g. They found a global decrease in SSIs in the 3-g dose group from 2.91% to 1.08% ($P = .268$) and in deep infection from 1.2% to 0% ($P = .231$).

Cloxacillin vs Clindamycin

Robertson et al compared the risks of PJIs between cloxacillin and clindamycin used as perioperative antibiotics in 80,018 total knee arthroplasties. The risk of failure leading to revision due to PJI was higher with clindamycin compared to cloxacillin (risk ratio = 1.5, 95% confidence interval [CI]: 1.2-2.0; $P = .001$). Clindamycin 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 inhibiting cell wall synthesis. The primary reason for using clindamycin as perioperative prophylaxis antibiotic is a reported allergy to penicillin. Even though between 5% and 10% of hospitalized patients report allergy to penicillin [21], most of these 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 g for patients weighing >60-80 kg and 3.0 g 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 intravenous cefazolin at a dose of 2 g produced greater intraosseous concentrations overall than at a dose of 1g. 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 g) of cefazolin might be more beneficial than the lower dose of 1 g [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 (>1500 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 before TJA is considered to be intravenous to reach levels above minimum inhibitory concentration. 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 1000 mg/L and polymyxin 250,000 units/L at 2 L/h. 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 colorectal 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 TJA remains unproven.

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.

Level of Evidence: Moderate

Delegate Vote: Agree: 92%, Disagree: 4%, Abstain: 4% (Super Majority, Strong Consensus)

Rationale:

We performed a systematic review 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 in which different doses of antibiotics or different antibiotics are being compared or smaller prospective pharmacokinetic/tissue penetration studies in which 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 (eg, dental procedure) with a prosthetic joint in situ.

Perioperative antimicrobial prophylaxis for patients undergoing orthopedic procedures is routinely administered and is believed to be one of the most important steps for prevention of surgical site infections and/or periprosthetic joint infections. Cephalosporins are believed to be the most effective prophylactic agents for patients undergoing orthopedic procedures as they have excellent bone penetration, bioavailability, and a relatively extended half-life.

Table 1
Recommended Weight-Adjusted Doses of Antimicrobials for Prophylaxis of Hip and Knee Arthroplasty in Adults.

Antimicrobial	Recommended Dose	Redosing Interval
Cefazolin	2 g (consider 3 g if patient weight is ≥120 kg[a])	4 h
Vancomycin	15-20 mg/kg[a]	Not applicable
Clindamycin	600-900 mg[b]	6 h

[a] Actual body weight.
[b] No recommended adjustment for weight.

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 [24]. 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 for obese patients because of various factors [25]. Pharmacokinetic studies have shown that tissue levels of cefazolin below the minimum inhibitory concentration (MIC) of common pathogenic organisms are found in body tissues near the end of surgery with a 1-g dose [26,27]. In one small, prospective study on obese patients, a 2-g dose of cefazolin was associated with a lower surgical site infection rates than a 1-g dose [27]. A 2-g dose likely achieves appropriate local surgical tissue levels, including in bone, in normal size patients [28]. However, in one study with morbidly obese patients, a 2-g dose was associated with levels below pathogenic MICs of cefazolin [29]. 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 [24]. In this guideline, 2 g of cefazolin is recommended as a standard dose and 3 g for patients weighing 120 kg or greater. Subsequent small studies [30,31], including a small randomized controlled trial [32], have compared tissue levels of 2 g with 3 g of cefazolin in obese women undergoing caesarean section. These have shown higher tissue levels in patients receiving 3 g; however, 2 g 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 g dose of cefazolin is appropriate for most patients; however, given the limited toxicity, a 3 g dose can be considered in patients ≥120 kg as per the 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 1g) 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* infection; however, there is no evidence suggesting an overall lower rate of infection [7,33,34]. In addition, weight-based dosing rather than a fixed 1g dose has been recommended for total joint arthroplasty [7,33]. Kheir et al reported that a fixed 1-g 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 [7].

There are no studies comparing clinical or pharmacokinetic outcomes with different doses of clindamycin for surgical prophylaxis. Older pharmacokinetic studies show good penetration of clindamycin into surgical tissues, including bone [35–37]. 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 [24,37].

Question 3: Is one dose of preoperative antibiotic adequate for patients undergoing total joint arthroplasty?

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 orthopedics. From the limited evidence available, it appears that a single perioperative dose of antibiotics, compared to multiple doses, does not increase the rates 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: 1% (Super Majority, Strong Consensus)

Rationale:

Perioperative antibiotic prophylaxis remains an important strategy for minimizing one of the most devastating complications after total joint arthroplasty, periprosthetic joint infections (PJIs) [38,39]. All current guidelines recommend the use of perioperative antibiotics [40–44] (Table 2). For arthroplasty, the costs and morbidities associated with prosthetic joint infections have led to abundant research to reduce the rate of postoperative infections. To this end, perioperative antibiotics are widely used; however, hospital protocols are variable 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 of the current guidelines. However, there was a change in the guidelines as the recent World Health Organization and Centers for Disease Control and Prevention (CDC) guidelines 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 [41,42]. 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 [47] explored whether a single preoperative antibiotic dose is adequate for arthroplasty patients. Their review returned 4 randomized controlled trials (RCTs) [45,46,48,49] with a total of 4036 patients. In patients receiving postoperative prophylaxis, the infection rate was 3.1% (63/2055), compared with a single preoperative dose, 2.3% (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, 3 include teicoplanin as a single-dose treatment, which is currently unavailable in the United States [45,50,51]. Heydemann et al randomized 211 patients to single dose vs. 48 hours of nafcillin or cefazolin, and no deep infections were seen in either cohort [48]. 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 [46]. Finally, Wymenga et al, in a multicenter RCT of 3013 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 authors, however, recognize that their sample sizes were too small to detect a difference given the infrequency of PJIs and recommended continued use of postoperative prophylaxis until larger studies could be performed [49]. Other literature has been retrospective in nature, including reviews by Tang et al [52] and van Kasteren et al [53], each of which had <2000 patients, and found no differences in infection rates between groups. The largest retrospective review by Engesaeter et al showed significantly higher revision rate with single dose compared with 4 doses given on the day of surgery. The higher revision rate was partially caused by infections [54]. While the majority of studies are underpowered, a retrospective study by Tan et al demonstrated no differences in 90-day or 1-year PJIs in 4523 patients that received a single dose of antibiotics compared to 16,159 patients that received 24 hours of antibiotics. Throughout all preoperative risk groups, however, patients with 24 hours of antibiotics demonstrated a trend toward a higher rate of acute renal failure.

It is important to recognize the different antibiotics used in each study noted previously, as well as the small sample sizes. Furthermore, the meta-analysis performed by the CDC includes predominantly surgical interventions of the trunk without hardware retention (including vascular surgery, cardiothoracic surgery, general surgery, as well as ear, nose, and throat). For surgeries of the extremity with retained implants, however, the evidence is more limited and consists of small RCTs or retrospective reviews without sufficient power to detect a statistical difference [50,51,55–62]. Among them, Gatell et al did find a significant reduction in the rates of infections compared with a single preoperative dose for patients with retained metal implants [61]. These studies were also performed predominantly in the 1990s and early 2000s, and modern antibiotics may have a different result. Given the devastating outcomes of prosthetic joint infections for patients, we neither agree nor disagree with the CDC recommendations that antibiotics should not be provided postoperatively until sufficiently powered evidence can be provided through a multicenter RCT that is adequately powered and is considering the low event rate of infection in total joint arthroplasty. While future studies may show that there are no differences in single vs multiple doses of

Table 2
Guidelines for Perioperative Antibiotic Prophylaxis.

Recommendation From Guidelines	Organization										
	BOA 2012	AAOS 2014	SAOA 2016	ACS 2016	SCIP 2011	IHI 2012	ASHP 2013	SIGN 2014	WHO 2016	CDC 2017	NICE 2017
Appropriate antibiotic selection	√	√	√	√	√	√	√	√	√	√	√
Administration within 1 h before surgical incision	√	√	√	√	√	√	√	√	√	√	√
Discontinuation after incision closure	–	–	–	No	–	–	–	–	√	√	–
Discontinuation within 24 h	Debatable	√	√	Unknown	√	√	Debatable	–	–	–	–

AAOS, American Academy of Orthopedic Surgeons [39]; ACS, American College of Surgeons [41]; ASHP, American Society of Health-System Pharmacists [44]; BOA, British Orthopaedic Association [38]; CDC, Centers for Disease Control and Prevention [45]; IHI, Institute for Healthcare Improvement [43]; NICE, The National Institute for Health and Care Excellence [46]; SAOA, South African Orthopedic Association [40]; SCIP, Surgical Care Improvement Project [42]; SIGN, Scottish Intercollegiate Guidelines Network [47]; WHO, World Health Organization [48].

perioperative antibiotic prophylaxis, the current literature does not support this strong conclusion.

Question 4: Should patients undergoing outpatient total joint arthroplasty receive additional postoperative prophylactic antibiotics?

Recommendation:

Despite the current guidelines from the Centers for Disease Control and Prevention (CDC) advocating for a single dose of perioperative antibiotics, the studies utilized to form these guidelines are underpowered and primarily in specialties outside orthopedics. The limited evidence suggests that a single perioperative dose of antibiotics, compared to multiple doses, does not increase the rates of subsequent SSIs/PJIs. A randomized prospective study in patients undergoing elective arthroplasty is underway, which should help answer this question definitively.

Level of Evidence: Limited

Delegate Vote: Agree: 94%, Disagree: 4%, Abstain: 2% (Super Majority, Strong Consensus)

Rationale:

Administration of prophylactic antibiotics during total joint arthroplasty (TJA) has been demonstrated to be an important step in the prevention of surgical site infections and periprosthetic joint infections (PJIs). During the early years of arthroplasty, prophylactic antibiotics for a few days postoperatively were routine. Over the last decade or so, there has been a movement toward reducing the amount of prophylactic antibiotics administered to TJA patients. Currently, antibiotics are administered to patients undergoing primary TJA for a period of 24 hours. The number of doses of antibiotics that need to be administered to TJA patients is not known.

In recent years, and with the increase in popularity of outpatient TJA, many patients undergoing primary TJA may only receive a single dose of antibiotics. It is not known if a single dose of antibiotics may predispose these patients to higher incidences of surgical site infections/PJIs. Recent guidelines for prevention of surgical site infection issued by the World Health Organization and the Centers for Disease Control and Prevention recommend against the administration of additional postoperative antibiotics [41,63,64]. The recommendation by these organizations is in an antibiotic stewardship practice intended to limit liberal use of antibiotics that can result in emergence of antimicrobial resistance, and also expose the patients to adverse effects associated with administration of prolonged antibiotics [41,65,66]. Although the Centers for Disease Control and Prevention guidelines issued this statement as a strong recommendation with high-quality evidence, there is limited literature in arthroplasty to support this recommendation.

A systematic review and meta-analysis by Thornley et al have examined the issue of the number of doses of antibiotic prophylaxis after TJA. The analyses revealed that the incidence of infections was 3.1% (63/2055) in patients receiving multiple doses of antibiotics compared with the infection rate of 2.3% (45/1981) in patients receiving a single dose of antibiotics [47]. They concluded that postoperative antibiotics did not have additional benefits in reducing the rate of infections. The authors of the systematic review did acknowledge that the quality of evidence related to this subject in TJA is low. Of the 4 available randomized controlled trials, 3 include teicoplanin, which is currently unavailable in the United States [45,50,51]. Furthermore, studies are usually underpowered with 1 randomized trial enrolling only 196 patients when comparing a single dose of cefuroxime to 24 hours of prophylaxis [46]. In addition, Wymenga et al compared a cohort of patients who received a single preoperative dose of cefuroxime to a cohort who received 3 total doses in 3013 patients and found no significant differences in infections between the 2 groups [49]. However, the authors recognized that their sample size was too small to detect a difference given the infrequency of PJI and recommended continuing the use of postoperative prophylaxis until larger studies could be performed [49]. In addition, in a national registry study, Engsaeseter et al demonstrated higher revision rates in patients receiving a single dose of antibiotics compared with 4 doses given on the day of surgery [54]. Finally, a retrospective study by Tan et al demonstrated no difference in the 90-day or 1-year PJI in 4523 outpatient TJA patients that received a single dose of antibiotics compared with 16,159 patients that received 24 hours of antibiotics, regardless of the patient's preoperative risk of PJIs [67].

When comparing infection rates between outpatient and inpatient TJA, the majority of the literature demonstrates no difference in the rate of postoperative infection. In a large retrospective review of the PearlDiver Database, Arshi et al found that patients who underwent outpatient total knee arthroplasty demonstrated an increased risk of prosthesis explantation (adjusted odds ratio [OR] 1.35, 95% CI: 1.07-1.72) and irrigation and debridement (adjusted OR 1.50, 95% CI: 1.29-1.77) compared with inpatients [68]. Despite these findings, multiple large national database studies have demonstrated no difference in postoperative infection between outpatient and inpatient TJAs [69–72].

Question 5: Does extended prophylactic antibiotics therapy for patients undergoing aseptic revision help reduce the risk of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

Recommendation:

In the absence of concrete evidence, we recommend the use of routine antibiotic prophylaxis (maximum 24 hours) for patients undergoing revision arthroplasty as long as the infection has been properly ruled out before surgery.

Level of Evidence: Limited

Delegate Vote: Agree: 81%, Disagree: 15%, Abstain: 4% (Super Majority, Strong Consensus)

Rationale:

Infections are common causes of failures after aseptic revisions, occurring after 5-9% for total knee arthroplasties and 1.35% to 17.3% for total hip arthroplasties [73–78]. One of the modalities to prevent surgical site infections (SSIs) and/or periprosthetic joint infections (PJIs) after arthroplasty is administration of prophylactic antibiotic therapy [2,44,79]. Considering the high rate of SSI and PJI after revision arthroplasties, one can argue that extended prophylaxis for longer than 24 hours may be indicated in these types of surgeries. Several studies have been conducted in primary total knee arthroplasty and total hip arthroplasty, indicating no difference in the rate of SSI in patients who received prophylaxis for 24 hours and in those who received it for longer than 24 hours [38,80–83].

A comprehensive literature search was performed to identify studies evaluating the potential role of extended antibiotic prophylactic therapy after aseptic revision arthroplasty. A single retrospective study conducted by Claret et al on 341 patients undergoing revision arthroplasty was identified [84]. In the latter study, the authors compared the rate of PJI after changing their local protocol from administering teicoplanin and ceftazidim before surgical incision and again after 2 hours as antibiotic prophylaxis (2007-2010) to prolonging this regimen until the fifth day after revision surgery (2010-2013). Several criteria concerning inflammatory markers, imaging, and synovial fluid analysis were performed to rule out infection before revision surgery. They observed that the PJI rate, occurring within 3 months after revision surgery, was lower in the long-prophylaxis group compared with the short-prophylaxis group (2.2% vs 6.9%, $P = .049$). In addition, prolonged antibiotic prophylaxis was the only variable independently associated with a lower rate of PJI in their analysis (OR: 0.27,

95% CI: 0.07–0.99). These data suggest that there might be a protective effect of prolonging antibiotic prophylaxis. However, although no other protocol modifications were made during the study period according to the authors, bias cannot be completely ruled out due to the retrospective nature of the study, especially as diagnostic methods to rule out an infection before revision surgery have been improved during the recent years. Thus, there is a need for a randomized controlled trial that can examine this question. The PARITY trial, an international prospective randomized controlled trial currently conducted in the field of orthopedic oncology, may provide us additional evidence about the potential benefits of extended antibiotic prophylaxis in high-risk patients undergoing joint arthroplasty [85].

Question 6: Should duration and the type of antibiotic prophylaxis be altered in patients with a prior PJI?

Recommendation:

In patients with a prior PJI, antibiotic prophylaxis should be tailored when undergoing another subsequent elective primary or revision joint arthroplasty. Antibiotic prophylaxis should cover the initial causative organism(s) as well as the most common pathogens that can cause periprosthetic joint infection (PJI), with either single or dual antibiotics.

Level of Evidence: Limited

Delegate Vote: Agree: 93%, Disagree: 6%, Abstain: 1% (Super Majority, Strong Consensus)

Rationale:

Patients with prior periprosthetic joint infections (PJIs) have a significantly higher risk for PJI in another prosthetic joint. Murray et al [86] described for the first time the risk of metachronous infections in multiple joints due to hematogenous spread. Studies by Parvizi et al [87] and Leung et al [88] both demonstrated that the majority of recurrent infections following PJI due to methicillin-resistant *Staphylococcus aureus* (MRSA) were reinfected with the same organism (66.7 and 89.9%, respectively).

Preexisting PJI was identified as a significant risk factor for a subsequent infection in a study by Luessenhop et al in 1996 [89]. The presence of rheumatoid arthritis and a prior sepsis were shown to be significantly associated with a higher risk for development of subsequent PJI ($P < .001$ and $P < .0001$, respectively).

Another study by Jafari et al [90] retrospectively identified 55 patients with PJI who had another prosthetic joint in place at the time of presentation. Eleven of them (20%) developed a PJI in a second joint, with the same bacteria in 36% of cases. Zmistowski et al [91] found that recurrent PJI was due to the same organism as the index infection (PJI persistence) in 31.5% of 92 relapsed cases, after 2-stage arthroplasty failure. A new organism (PJI reinfection) was observed in 68.5% of these cases. The only independent predictor of PJI persistence vs new infection was the original infecting organism, specifically Staphylococci (MRSA in particular). Moreover, polymicrobial PJI were more frequently involved in immunocompromised hosts.

Bedair et al [92] confirmed these observations in a multicenter, retrospective cohort study with 90 patients previously treated for PJI undergoing a second primary total joint arthroplasty (total hip arthroplasty and total knee arthroplasty). The study showed that patients with a history of PJI had a higher risk of developing PJI in a subsequent total hip arthroplasty or total knee arthroplasty (10 of 90, vs 0 of 90 in the control group; relative risk: 21.00; 95% CI, 1.25-353.08; $P = .04$). The authors found that a second PJI occurred more frequently in those whose initial infection was by a staphylococcal species (OR, 4.26 $P = .04$). The infecting organisms were the same species in the first and second PJI in 40% of cases, and all 4 of these were caused by Staphylococci.

Based on the available data, it appears that patients with a prior PJI who are undergoing elective arthroplasty are at higher risk of subsequent infection. The infecting organism for the second joint is most of the time same as the first infecting organism. Taken together, we feel that antibiotic prophylaxis for patients with a prior PJI who are undergoing an elective primary or revision arthroplasty needs to be altered. These patients may require administration of an alternative or additional antibiotic(s). For example, patients with a prior PJI by a gram-negative organism should receive prophylactic antibiotics against gram-negative bacteria. The same applies to patients with a prior MRSA infection and so on.

Question 7: Should prophylactic antibiotic therapy be administered for an extended duration in patients admitted to the intensive care unit (ICU)?

Recommendation:

Surgical prophylactic antibiotic therapy should not be administered for an extended duration in patients admitted to the intensive care unit (ICU).

Level of Evidence: Limited

Delegate Vote: Agree: 82%, Disagree: 13%, Abstain: 5% (Super Majority, Strong Consensus)

Rationale:

The literature on surgical site infections (SSIs) classifies SSI risk factors into intrinsic (patient) related (eg, age and underlying morbidity) and extrinsic (procedure) related (procedure, facility, preoperative and intraoperative factors), both being either modifiable or not [93]. Admittance to the intensive care unit (ICU) is not treated as an independent risk factor, although risk factors for SSIs and risk factors for ICU admittance are correlated (age, comorbidity, complexity of procedure). Using the published search algorithm from the World Health Organization (WHO) guideline's literature review and narrowing it with the term "ICU" and expanding it with the term "observational study," 180 articles were retrieved from October 1, 2015 until present (PubMed 39, Embase 84, Central 57). All abstracts were screened, but none found relevant for the question of extending antibiotic duration in patients admitted to the ICU. Using the unaltered WHO search algorithm (without narrowing with "ICU" and expanding with "observational study"), another 23 PubMed articles not covered within the first search were identified, but none of the screened abstracts were relevant. An unsystematic search in the PubMed Clinical Queries search was then performed with the terms "Therapy/Broad [filter]) AND (antibiotic prophylaxis extended)" returning 245 articles. All titles were screened and abstracts of putative relevance were reviewed, and none were found to be relevant. The 34 articles retrieved with a modified search term (Therapy/Broad [filter]) AND (antibiotic prophylaxis prolonged ICU) were not found to be relevant either. Thus, no studies were found examining extended antibiotic prophylaxis in ICU patients when these patients are considered as a separate patient category, and there are no data to support or refute an extended duration for preventing SSIs solely based on the admittance to the ICU.

However, ICU patients are included in the core randomized controlled trials (RCTs) showing no benefit of extending antibiotic prophylaxis past wound closure [94,95] albeit not specifically for arthroplasty patients. Since the publication of the Proceedings of the International Consensus Meeting on Periprosthetic Joint Infections in 2013, 3 major literature reviews and guidelines on prevention of SSI have been published from the WHO [94], Centers for Disease Control and Prevention (CDC) [95], and American College of Surgeons and Surgical Infection Society [93], respectively. The CDC and WHO guidelines agree on not extending prophylaxis past wound closure based on a comprehensive systematic literature review, but the strength of the data supporting the recommendation for arthroplasty have been questioned [46,56,58,59,61,96–98]. The American College of Surgeons and Surgical Infection Society

makes an exception for prophylactic antibiotics past wound closure for joint arthroplasty, on the grounds that optimal antibiotic therapy for these patients remains unknown, but refers to the American Society of Health-System Pharmacists/Infectious Diseases Society of America/Surgical Infection Society/Society for Healthcare Epidemiology of America guidelines for a total antibiotic prophylaxis duration ≤24 hours [24]. A recently published meta-analysis and review on postoperative antibiotic prophylaxis in knee and hip arthroplasty did not find evidence to show efficacy of extended antibiotic prophylaxis for the prevention of SSI in patients undergoing total hip or knee arthroplasty. It did however question the quality of the existing evidence and call for new and sufficiently powered RCTs to settle the issue [24]. None of the guidelines or the extensive literature reviews underpinning them thus makes a distinction or specific recommendation for patients admitted to the ICU in general or for use of extended antibiotic prophylaxis for ICU patients in particular. However, ICU patients are included in the core RCTs forming the basis for the strong recommendations of not extending antibiotic prophylaxis after completion of the operation.

ICUs are heterogeneous, and ICU capacity varies greatly across hospitals and countries. Consequently, both patient morbidity and hospital policies for ICU admittance will vary, making studies examining extended antibiotic prophylaxis based on ICU admittance unlikely. Should they be undertaken, their external validity would for the aforementioned reasons be questionable.

The purpose of prophylactic antibiotic therapy in orthopedic surgery is to prevent SSIs, for which a narrow-acting antibiotic with gram-positive coverage is a proven and sufficient option [47]. Prevention of remote infections in patients admitted to the ICU would have required a different prophylactic approach, including administration of broad-spectrum antibiotics and selective digestive decontamination, as opposed to the narrow spectrum antibiotics for SSI prevention. Although there are some data to support such a strategy, mainly from ICUs with low levels of antibiotic resistance [99], it remains highly controversial due to concerns of long-term resistance promotion and disturbance to the gut microbiome [100]. There is currently insufficient evidence to recommend its use in settings with high levels of antibiotic resistance [101]. Although an in-depth discussion of the issue is beyond the scope of the assigned question, the increased sense of urgency regarding resistance prevention following the 2014 WHO report on global resistance [102] speaks strongly against adoption of this strategy.

In addition to high awareness, prompt diagnostic workup and early initiations of broad empiric antibiotic therapy are the core interventions for reducing infection-related complications in the ICU [103]. The continuation of a narrow-acting antibiotic therapy from the operating theater into the ICU may give a false sense of security and both obscure and delay these interventions, or even harm patients by promoting antimicrobial-resistant bacteria [104,105].

Arguably, the immunosuppressed state following surgery and trauma could be enhanced in patients ill enough to require treatment in the ICU, thus justifying implementation of antibiotic prophylaxis recommendation for immunosuppressed patients. However, despite not identifying studies addressing extended surgical antimicrobial pprophylaxis in arthroplasty for immunocompromised patients, the CDC guidelines give a strong recommendation (category 1a) against extended surgical antimicrobial pprophylaxis in the immunocompromised patients based on their inclusion in the core RCTs with high-quality evidence for surgical antimicrobial pprophylaxis ≤24 hours postoperatively [2].

In an editorial commenting on a survey of 67 ICUs finding 50% of antibiotic prescriptions being continued beyond 72 hours despite the absence of a definitive infectious source [106], the editor states that “there is a pervasive belief that an error of commission” (continuation of empiric antibiotics in the absence of evidence of infection) “is somehow better or safer than an error of omission” (ceasing antibiotic therapy when there is some chance, however slim, that the patient will benefit) [107]. This statement also applies fittingly to the question of extended prophylaxis in patients admitted to ICU; with a real threat of running out of effective antibiotics due to indiscriminate use, extending prophylaxis on the sole ground of ICU admittance should be avoided as there is neither theoretical rationale nor clinical evidence to support the practice.

Question 8: Does the use of allografts alter the recommended duration of prophylactic antibiotics?

Recommendation:

No. Allografts are avascular materials that are prone to contamination and may serve as a scaffold for bacterial colonization and biofilm production, similar to a prosthesis or osteosynthetic material. However, it is difficult to establish a causal relationship between the use of an allograft and subsequent infection. Thus, there is no evidence to support the use of extended antibiotic prophylaxis.

Level of Evidence: Limited

Delegate Vote: Agree: 91%, Disagree: 6%, Abstain: 3% (Super Majority, Strong Consensus)

Rationale:

Allografts are typically utilized to address bone defects or damaged tendons at the time of revision procedures for patients who have already undergone multiple operations. By virtue of their operative history, these patients are already associated with a higher risks of infections (2-3 times) [108] compared to primary total joint arthroplasty patients. One recent study of 50 consecutive extensor mechanism allograft reconstructions in total knee arthroplasty reported an infection rate of 10% [109]. The pooled infection rate from a systematic review and meta-analysis of proximal femoral allograft in revision total hip arthroplasty (THA) was reported to be 8% [110]. Allografts are avascular materials that, similar to a prosthesis or osteosynthetic material, are prone to contamination and may serve as a scaffold for bacterial colonization and biofilm production. However, it is difficult to establish a causal relationship between the use of an allograft and subsequent infection. The question of whether the antibiotic prophylaxis in such complex cases should be altered is a separate discussion from treating infections arising from undetected contamination of the allograft.

There are no high-quality studies available comparing differences between the duration of systemic antibiotic prophylaxis with and without allograft use in primary or revision total joint arthroplasty. Allograft bone may be utilized in different forms including untreated or processed, gamma-irradiated, chemically sterilized, and as fresh-frozen product. A contamination rate of up to 23% immediately after aseptic procurement of unprocessed and unsterilized allograft has been reported [110]. Alternatively, sterilization reduces bacterial contamination rates approaching 0% after multiple decontamination processes [111]. An efficient “prophylaxis” may only be expected after using processed or sterilized allografts [112], perhaps by conferring additional local antimicrobial protection [113].

Two-stage procedures for infected total knee arthroplasty [114] and THA [115] with allograft bone demonstrated no differences with respect to short and long durations of antibiotic therapy and reinfection rates; however, antibiotic impregnated bone cement was utilized in these cases. Withholding systemic antibiotic therapy has also been reported and recommended following revision THA for periprosthetic joint infection with adjunctive local antibiotic bone cement elution except in cases of multiple-operated patients infected with highly resistant organisms [116]. High-quality studies evaluating the optimal duration of prophylactic antibiotics during allograft reconstructive procedures are warranted.

References

[1] Charalambous CP, Charalambous C, Tryfonidis M, Swindell R, Lipsett AP. When should old therapies be abandoned? A modern look at old studies on topical ampicillin. J Infect 2003;47:203–9.

[2] Berríos-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, et al. Centers for disease control and prevention guideline for the prevention of surgical site infection, 2017. JAMA Surg 2017;152:784. https://doi.org/10.1001/jamasurg.2017.0904.

[3] American Academy of Orthopaedic Surgeons. Recommendations for the use of intravenous antibiotic prophylaxis in primary total joint arthroplasty. 2004. http://www.aaos.org/about/papers/advistmt/1027.asp.

[4] Illingworth KD, Mihalko WM, Parvizi J, Sculco T, McArthur B, El Bitar Y, et al. How to minimize infection and thereby maximize patient outcomes in total joint arthroplasty: a multicenter approach. J Bone Joint Surg Am 2013;95:e50. https://doi.org/10.2106/JBJS.L.00596.

[5] Rezapoor M, Parvizi J. Prevention of periprosthetic joint infection. J Arthroplasty 2018;30:902–7. https://doi.org/10.1016/j.arth.2015.02.044.

[6] Tornero E, Garcí-Ramiro S, Martínez-Pastor JC, Bori G, Bosch J, Morata L, et al. Prophylaxis with teicoplanin and cefuroxime reduces the rate of prosthetic joint infection after primary arthroplasty. Antimicrob Agents Chemother 2015;59:831–7. https://doi.org/10.1128/AAC.03949-14.

[7] Kheir MM, Tan TL, Azboy I, Tan DD, Parvizi J. Vancomycin prophylaxis for total joint arthroplasty: incorrectly dosed and has a higher rate of periprosthetic infection than cefazolin. Clin Orthop Relat Res 2017;475:1767–74. https://doi.org/10.1007/s11999-017-5302-0.

[8] Meehan J, Jamali AA, Nguyen H. Prophylactic antibiotics in hip and knee arthroplasty. J Bone Joint Surg Am 2009;91:2480–90. https://doi.org/10.2106/JBJS.H.01219.

9 Parvizi J, Gehrke T, Chen AF. Proceedings of the International Consensus on Periprosthetic Joint Infection. Bone Joint J. 2013;95(B):1450–2. https://doi.org/10.1302/0301-620X.95B11.33135.

[10] Hawn MT, Richman JS, Vick CC, Deierhoi RJ, Graham LA, Henderson WG, et al. Timing of surgical antibiotic prophylaxis and the risk of surgical site infection. JAMA Surg 2013;148:649–57. https://doi.org/10.1001/jamasurg.2013.134.

[11] Ponce B, Raines BT, Reed RD, Vick C, Richman J, Hawn M. Surgical site infection after arthroplasty: comparative effectiveness of prophylactic antibiotics. J Bone Joint Surg Am 2014;96:970–7. https://doi.org/10.2106/JBJS.M.00663.

[12] Courtney PM, Melnic CM, Zimmer Z, Anari J, Lee GC. Addition of vancomycin to cefazolin prophylaxis is associated with acute kidney injury after primary joint arthroplasty. Clin Orthop Relat Res 2015;473:2197–203. https://doi.org/10.1007/s11999-014-4062-3.

[13] Bosco JA, Tejada PRR, Catanzano AJ, Stachel AG, Phillips MS. Expanded gram-negative antimicrobial prophylaxis reduces surgical site infections in hip arthroplasty. J Arthroplasty 2016;31:616–21. https://doi.org/10.1016/j.arth.2015.09.051.

[14] Tan TL, Gomez MM, Kheir MM, Maltenfort MG, Chen AF. Should preoperative antibiotics be tailored according to patient's comorbidities and susceptibility to organisms? J Arthroplasty 2018;32:1089–1094.e3. https://doi.org/10.1016/j.arth.2016.11.021.

[15] Malhas AM, Lawton R, Reidy M, Nathwani D, Clift BA. Causative organisms in revision total hip & knee arthroplasty for infection: increasing multi-antibiotic resistance in coagulase-negative Staphylococcus and the implications for antibiotic prophylaxis. Surgeon 2015;13:250–5. https://doi.org/10.1016/j.surge.2014.04.002.

[16] Torkington MS, Davison MJ, Wheelwright EF, Jenkins PJ, Anthony I, Lovering AM, et al. Bone penetration of intravenous flucloxacillin and gentamicin as antibiotic prophylaxis during total hip and knee arthroplasty. Bone Joint J 2017;99B:358–64. https://doi.org/10.1302/0301-620X.99B3.BJJ-2016-0328.R1.

[17] Mollan RA, Haddock M, Webb CH. Teicoplanin vs cephamandole for antimicrobial prophylaxis in prosthetic joint implant surgery: (preliminary results). Eur J Surg Suppl 1992;567:19–21.

[18] Wall R, Klenerman L, McCullough C, Fyfe I. A comparison of teicoplanin and cefuroxime as prophylaxis for orthopaedic implant surgery: a preliminary report. J Antimicrob Chemother 1988;21:141–6.

[19] Hickson CJ, Metcalfe D, Elgohari S, Oswald T, Masters JP, Rymaszewska M, et al. Prophylactic antibiotics in electivehip and knee arthroplasty: an analysis of organisms reported to cause infections andnational survey of clinical practice. Bone Joint Res 2015;4:181–9. https://doi.org/10.1302/2046-3758.411.2000432.

[20] Yuasa T, Yamakawa J, Maezawa K, Kaneko K. Prospective study on antimicrobial prophylaxis in total hip arthroplasty. Eur J Orthop Surg Traumatol 2015;25:737–40. https://doi.org/10.1007/s00590-014-1540-y.

[21] Robertsson O, Thompson O, W-Dahl A, Sundberg M, Lidgren L, Stefánsdóttir A. Higher risk of revision for infection using systemic clindamycin prophylaxis than with cloxacillin. Acta Orthop 2017;88:562–7. https://doi.org/10.1080/17453674.2017.1324677.

[22] Angthong C, Krajubngern P, Tiyapongpattana W, Pongcharoen B, Pinsornsak P, Tammachote N, et al. Intraosseous concentration and inhibitory effect of different intravenous cefazolin doses used in preoperative prophylaxis of total knee arthroplasty. J Orthop Traumatol 2015;16:331–4. https://doi.org/10.1007/s10195-015-0370-y.

[23] Whiteside LA. Prophylactic peri-operative local antibiotic irrigation. Bone Joint J 2016;98-B:23–6. https://doi.org/10.1302/0301-620X.98B1.36357.

[24] Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Surg Infect (Larchmt) 2013;14:73–156. https://doi.org/10.1089/sur.2013.9999.

[25] Pai MP, Bearden DT. Antimicrobial dosing considerations in obese adult patients. Pharmacotherapy 2007;27:1081–91. https://doi.org/10.1592/phco.27.8.1081.

[26] Koopman E, Nix DE, Erstad BL, Demeure MJ, Hayes MM, Ruth JT, et al. End-of-procedure cefazolin concentrations after administration for prevention of surgical-site infection. Am J Health Syst Pharm 2007;64:1927–34. https://doi.org/10.2146/ajhp070047.

[27] Forse RA, Karam B, MacLean LD, Christou NV. Antibiotic prophylaxis for surgery in morbidly obese patients. Surgery 1989;106:750–6. discussion 756–757.

[28] Yamada K, Matsumoto K, Tokimura F, Okazaki H, Tanaka S. Are bone and serum cefazolin concentrations adequate for antimicrobial prophylaxis? Clin Orthop Relat Res 2011;469:3486–94. https://doi.org/10.1007/s11999-011-2111-8.

[29] Edmiston CE, Krepel C, Kelly H, Larson J, Andris D, Hennen C, et al. Perioperative antibiotic prophylaxis in the gastric bypass patient: do we achieve therapeutic levels? Surgery 2004;136:738–47. https://doi.org/10.1016/j.surg.2004.06.022.

[30] Swank ML, Wing DA, Nicolau DP, McNulty JA. Increased 3-gram cefazolin dosing for cesarean delivery prophylaxis in obese women. Am J Obstet Gynecol 2015;213:415.e1–8. https://doi.org/10.1016/j.ajog.2015.05.030.

[31] Grupper M, Kuti JL, Swank ML, Maggio L, Hughes BL, Nicolau DP. Population pharmacokinetics of cefazolin in serum and adipose tissue from overweight and obese women undergoing cesarean delivery. J Clin Pharmacol 2017;57:712–9. https://doi.org/10.1002/jcph.851.

[32] Young OM, Shaik IH, Twedt R, Binstock A, Althouse AD, Venkataramanan R, et al. Pharmacokinetics of cefazolin prophylaxis in obese gravidae at time of cesarean delivery. Am J Obstet Gynecol 2015;213:541.e1–7. https://doi.org/10.1016/j.ajog.2015.06.034.

[33] Catanzano A, Phillips M, Dubrovskaya Y, Hutzler L, Bosco J. The standard one gram dose of vancomycin is not adequate prophylaxis for MRSA. Iowa Orthop J 2014;34:111–7.

[34] Crawford T, Rodvold KA, Solomkin JS. Vancomycin for surgical prophylaxis? Clin Infect Dis 2012;54:1474–9. https://doi.org/10.1093/cid/cis027.

[35] Panzer JD, Brown DC, Epstein WL, Lipson RL, Mahaffey HW, Atkinson WH. Clindamycin levels in various body tissues and fluids. J Clin Pharmacol New Drugs 1972;12:259–62.

[36] Nicholas P, Meyers BR, Levy RN, Hirschman SZ. Concentration of clindamycin in human bone. Antimicrob Agents Chemother 1975;8:220–1.

[37] Schurman DJ, Johnson BL, Finerman G, Amstutz HC. Antibiotic bone penetration. Concentrations of methicillin and clindamycin phosphate in human bone taken during total hip replacement. Clin Orthop Relat Res 1975:142–6.

[38] Hansen E, Belden K, Silibovsky R, Vogt M, Arnold WV, Bicanic G, et al. Perioperative antibiotics. J Arthroplasty 2014;29:29–48. https://doi.org/10.1016/j.arth.2013.09.030.

[39] Parvizi J, Shohat N, Gehrke T. Prevention of periprosthetic joint infection: new guidelines. Bone Joint J 2017;99–B:3–10. https://doi.org/10.1302/0301-620X.99B4.BJJ-2016-1212.R1.

[40] Anderson DJ, Podgorny K, Berríos-Torres SI, Bratzler DW, Dellinger EP, Greene L, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 2014;35:605–27. https://doi.org/10.1086/676022.

[41] WHO | Global guidelines on the prevention of surgical site infection. WHO. http://www.who.int/gpsc/ssi-prevention-guidelines/en/. [Accessed 19 November 2017].

[42] Guidelines library | infection control | CDC. https://www.cdc.gov/infectioncontrol/guidelines/index.html. [Accessed 19 November 2017].

[43] Leaper D, Burman-Roy S, Palanca A, Cullen K, Worster D, Gautam-Aitken E, et al. Prevention and treatment of surgical site infection: summary of NICE guidance. BMJ 2008;337:a1924.

[44] Parvizi J, Gehrke T, Chen AF. Proceedings of the international consensus on periprosthetic joint infection. Bone Joint J 2013;95–B:1450–2. https://doi.org/10.1302/0301-620X.95B11.33135.

[45] Kanellakopoulou K, Papadopoulos A, Varvaroussis D, Varvaroussis A, Giamarellos-Bourboulis EJ, Pagonas A, et al. Efficacy of teicoplanin for the prevention of surgical site infections after total hip or knee arthroplasty: a prospective, open-label study. Int J Antimicrob Agents 2009;33:437–40. https://doi.org/10.1016/j.ijantimicag.2008.10.019.

[46] Ritter MA, Campbell E, Keating EM, Faris PM. Comparison of intraoperative versus 24 hour antibiotic prophylaxis in total joint replacement. A controlled prospective study. Orthop Rev 1989;18:694–6.

[47] Thornley P, Evaniew N, Riediger M, Winemaker M, Bhandari M, Ghert M. Postoperative antibiotic prophylaxis in total hip and knee arthroplasty: a systematic review and meta-analysis of randomized controlled trials. CMAJ Open 2015;3:E338–43. https://doi.org/10.9778/cmajo.20150012.

[48] Heydemann JS, Nelson CL. Short-term preventive antibiotics. Clin Orthop 1986:184–7.

[49] Wymenga A, van Horn J, Theeuwes A, Muytjens H, Slooff T. Cefuroxime for prevention of postoperative coxitis. Acta Orthop Scand 1992;63:19–24. https://doi.org/10.3109/17453679209154842.

[50] Periti P, Stringa G, Mini E. Surgery the ISG for AP in O. Comparative multicenter trial of teicoplanin versus cefazolin for antimicrobial prophylaxis in prosthetic joint implant surgery. Eur J Clin Microbiol Infect Dis 1999;18:113–9. https://doi.org/10.1007/s100960050238.

[51] Suter F, Avai A, Fusco U, Gerundini M, Caprioli S, Maggiolo F. Teicoplanin versus cefamandole in the prevention of infection in total hip replacement. Eur J Clin Microbiol Infect Dis 1994;13:793–6. https://doi.org/10.1007/BF02111338.

[52] Tang WM, Chiu KY, Ng TP, Yau WP, Ching PTY, Seto WH. Efficacy of a single dose of cefazolin as a prophylactic antibiotic in primary arthroplasty. J Arthroplasty 2003;18:714–8.

[53] van Kasteren MEE, Manniën J, Ott A, Kullberg B-J, de Boer AS, Gyssens IC. Antibiotic prophylaxis and the risk of surgical site infections following total hip arthroplasty: timely administration is the most important factor. Clin Infect Dis 2007;44:921–7. https://doi.org/10.1086/512192.

[54] Engesaeter LB, Lie SA, Espehaug B, Furnes O, Vollset SE, Havelin LI. Antibiotic prophylaxis in total hip arthroplasty: effects of antibiotic prophylaxis systemically and in bone cement on the revision rate of 22,170 primary hip replacements followed 0-14 years in the Norwegian arthroplasty register. Acta Orthop Scand 2003;74:644–51. https://doi.org/10.1080/00016470310018135.

[55] Backes M, Dingemans SA, Dijkgraaf MGW, van den Berg HR, van Dijkman B, Hoogendoorn JM, et al. Effect of antibiotic prophylaxis on surgical site infections following removal of orthopedic implants used for treatment of foot, ankle, and lower leg fractures: a randomized clinical trial. JAMA 2017;318:2438–45. https://doi.org/10.1001/jama.2017.19343.

[56] Buckley R, Hughes GN, Snodgrass T, Huchcroft SA. Perioperative cefazolin prophylaxis in hip fracture surgery. Can J Surg 1990;33:122–7.

[57] Garcia S, Lozano ML, Gatell JM, Soriano E, Ramon R, Sanmiguel JG. Prophylaxis against infection. Single-dose cefonicid compared with multiple-dose cefamandole. J Bone Joint Surg Am 1991;73:1044–8.

[58] Garotta F, Pamparana F. Antimicrobial prophylaxis with ceftizoxime versus cefuroxime in orthopedic surgery. Ceftizoxime orthopedic surgery Italian study group. J Chemother 1991;3(Suppl 2):34–5.

[59] Hellbusch LC, Helzer-Julin M, Doran SE, Leibrock LG, Long DJ, Puccioni MJ, et al. Single-dose vs multiple-dose antibiotic prophylaxis in instrumented lumbar fusion–a prospective study. Surg Neurol 2008;70:622–7. https://doi.org/10.1016/j.surneu.2007.08.017. discussion 627.

[60] Liebergall M, Mosheiff R, Rand N, Peyser A, Shaul J, Kahane Y, et al. A double-blinded, randomized, controlled clinical trial to compare cefazolin and cefonicid for antimicrobial prophylaxis in clean orthopedic surgery. Isr J Med Sci 1995;31:62–4.

[61] Gatell JM, Garcia S, Lozano L, Soriano E, Ramon R, SanMiguel JG. Perioperative cefamandole prophylaxis against infections. J Bone Joint Surg Am 1987;69:1189–93.

[62] Karachalios T, Lyritis GP, Hatzopoulos E. Antibiotic prophylaxis in the surgical treatment of peritrochanteric fractures: a comparative trial between two cephalosporins. Chemotherapy 1990;36:448–53. https://doi.org/10.1159/000238803.

[63] CDC guideline for the prevention of surgical site infection, 2017 | critical care medicine | JAMA surgery | the JAMA network. https://jamanetwork.com/journals/jamasurgery/fullarticle/2623725. [Accessed 12 February 2018].

[64] Shohat N, Parvizi J. Prevention of periprosthetic joint infection: examining the recent guidelines. J Arthroplasty 2017;32:2040–6. https://doi.org/10.1016/j.arth.2017.02.072.

[65] WHO | Antibiotic resistance. WHO. http://www.who.int/mediacentre/factsheets/antibiotic-resistance/en/. [Accessed 19 November 2017].

[66] Allegranzi B, Zayed B, Bischoff P, Kubilay NZ, de Jonge S, de Vries F, et al. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis 2016;16:e288–303. https://doi.org/10.1016/S1473-3099(16)30402-9.

[67] Tan TL, Shohat N, Rondon A, Foltz C, Goswami K, Ryan S, et al. Perioperative antibiotic prophylaxis in total joint arthroplasty: a single-dose is as effective as multiple-doses. Rothman Orthop J 2018.

[68] Arshi A, Leong NL, D'Oro A, Wang C, Buser Z, Wang JC, et al. Outpatient total knee arthroplasty is associated with higher risk of perioperative complications. J Bone Joint Surg Am 2017;99:1978–86. https://doi.org/10.2106/JBJS.16.01332.

[69] Courtney PM, Boniello AJ, Berger RA. Complications following outpatient total joint arthroplasty: an analysis of a national database. J Arthroplasty 2017;32:1426–30. https://doi.org/10.1016/j.arth.2016.11.055.

[70] Courtney PM, Froimson MI, Meneghini RM, Lee G-C, Della Valle CJ. Can total knee arthroplasty be performed safely as an outpatient in the medicare population? J Arthroplasty 2018;33(7S):S28–31. https://doi.org/10.1016/j.arth.2018.01.003.

[71] Lovecchio F, Alvi H, Sahota S, Beal M, Manning D. Is outpatient arthroplasty as safe as fast-track inpatient arthroplasty? a propensity score matched analysis. J Arthroplasty 2016;31(Supplement):197–201. https://doi.org/10.1016/j.arth.2016.05.037.

[72] Nelson SJ, Webb ML, Lukasiewicz AM, Varthi AG, Samuel AM, Grauer JN. Is outpatient total hip arthroplasty safe? J Arthroplasty 2017;32:1439–42. https://doi.org/10.1016/j.arth.2016.11.053.

[73] Leta TH, Lygre SHL, Skredderstuen A, Hallan G, Furnes O. Failure of aseptic revision total knee arthroplasties. Acta Orthop 2015;86:48–57. https://doi.org/10.3109/17453674.2014.964097.

[74] Jafari SM, Coyle C, Mortazavi SMJ, Sharkey PF, Parvizi J. Revision hip arthroplasty: infection is the most common cause of failure. Clin Orthop Relat Res 2010;468:2046–51. https://doi.org/10.1007/s11999-010-1251-6.

[75] Suarez J, Griffin W, Springer B, Fehring T, Mason JB, Odum S. Why do revision knee arthroplasties fail? J Arthroplasty 2008;23:99–103. https://doi.org/10.1016/j.arth.2008.04.020.

[76] Mortazavi SMJ, Schwartzenberger J, Austin MS, Purtill JJ, Parvizi J. Revision total knee arthroplasty infection: incidence and predictors. Clin Orthop Relat Res 2010;468:2052–9. https://doi.org/10.1007/s11999-010-1308-6.

[77] Badarudeen S, Shu AC, Ong KL, Baykal D, Lau E, Malkani AL. Complications after revision total hip arthroplasty in the medicare population. J Arthroplasty 2017;32:1954–8. https://doi.org/10.1016/j.arth.2017.01.037.

[78] Kosashvili Y, Backstein D, Safir O, Lakstein D, Gross AE. Dislocation and infection after revision total hip arthroplasty: comparison between the first and multiply revised total hip arthroplasty. J Arthroplasty 2011;26:1170–5. https://doi.org/10.1016/j.arth.2011.04.022.

[79] Bryson DJ, Morris DLJ, Shivji FS, Rollins KR, Snape S, Ollivere BJ. Antibiotic prophylaxis in orthopaedic surgery: difficult decisions in an era of evolving antibiotic resistance. Bone Joint J 2016;98-B:1014–9. https://doi.org/10.1302/0301-620X.98B8.37359.

[80] Williams DN, Gustilo RB. The use of preventive antibiotics in orthopaedic surgery. Clin Orthop Relat Res 1984;190:83–8.

[81] Nelson CL, Green TG, Porter RA, Warren RD. One day versus seven days of preventive antibiotic therapy in orthopedic surgery. Clin Orthop Relat Res 1983:258–63.

[82] Bratzler DW, Houck PM. Surgical infection prevention guidelines writers workgroup, american academy of orthopaedic surgeons, american association of critical care nurses, american association of nurse anesthetists, et al. Antimicrobial prophylaxis for surgery: an advisory statement from the national surgical infection prevention project. Clin Infect Dis 2004;38:1706–15. https://doi.org/10.1086/421095.

[83] de Beer J, Petruccelli D, Rotstein C, Weening B, Royston K, Winemaker M. Antibiotic prophylaxis for total joint replacement surgery: results of a survey of Canadian orthopedic surgeons. Can J Surg 2009;52:E229–34.

[84] Claret G, Tornero E, Martínez-Pastor J-C, Piazuelo M, Martínez J, Bosch J, et al. A prolonged post-operative antibiotic regimen reduced the rate of prosthetic joint infection after aseptic revision knee arthroplasty. Surg Infect (Larchmt) 2015;16:775–80. https://doi.org/10.1089/sur.2015.044.

[85] Prophylactic antibiotic regimens in tumor surgery (PARITY) - full text view - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01479283. [Accessed 3 August 2018].

[86] Murray RP, Bourne MH, Fitzgerald RH. Metachronous infections in patients who have had more than one total joint arthroplasty. J Bone Joint Surg Am 1991;73:1469–74.

[87] Parvizi J, Azzam K, Ghanem E, Austin MS, Rothman RH. Periprosthetic infection due to resistant staphylococci: serious problems on the horizon. Clin Orthop Relat Res 2009;467:1732–9.

[88] Leung F, Richards CJ, Garbuz Ds, Masri BA, Duncan CP. Two-stage total hip arthroplasty: how often does it control methicillin-resistant infection? Clin Orthop Relat Res 2011;469:1009–15.

[89] Luessenhop CP, Higgins LD, Brause BD, Ranawat CS. Multiple prosthetic infecions after total joint arthroplasty. Risk factor analysis. J Arthroplasty 1996;11:862–8.

[90] Jafari SM, Casper DS, Restrepo C, Zmistowski B, Parvizi J, Sharkey PF. Periprosthetic joint infection: are patients with multiple prosthetic joints at risk? J Arthroplasty 2012;27:877–80.

[91] Zmistowski B, Tetreault MW, Alijanipour P, Chen AF, Della Valle CJ, Parvizi J. Recurrent periprosthetic joint infection: persistent or new infection? J Arthroplasty 2013;28:1486–9.

[92] Bedair H, Goyal N, Dietz MJ, Urish K, Hansen V, Manrique J, et al. A history of treated periprosthetic joint infection increases the risk of subsequent different site infection. Clin Orthop 2015;473:2300–4.

[93] Ban KA, Minei JP, Laronga C, Harbrecht BG, Jensen EH, Fry DE, et al. American college of surgeons and surgical infection society: surgical site infection guidelines, 2016 update. J Am Coll Surg 2017;224:59–74. https://doi.org/10.1016/j.jamcollsurg.2016.10.029.

[94] Global guidelines for the prevention of surgical site infection. Geneva: World Health Organization; 2016.

[95] Leaper DJ, Edmiston CE. World Health Organization: global guidelines for the prevention of surgical site infection. J Hosp Infect 2017;95:135–6. https://doi.org/10.1016/j.jhin.2016.12.016.

[96] Ali M, Raza A. Role of single dose antibiotic prophylaxis in clean orthopedic surgery. J Coll Physicians Surg Pak 2006;16:45–8. doi:1.2006/JCPSP.4548.

[97] Wymenga AB, Hekster YA, Theeuwes A, Muytjens HL, van Horn JR, Slooff TJ. Antibiotic use after cefuroxime prophylaxis in hip and knee joint replacement. Clin Pharmacol Ther 1991;50:215–20.

[98] Takemoto RC, Lonner B, Andres T, Park J, Ricart-Hoffiz P, Bendo J, et al. Appropriateness of twenty-four-hour antibiotic prophylaxis after spinal surgery in which a drain is utilized: a prospective randomized study. J Bone Joint Surg Am 2015;97:979–86. https://doi.org/10.2106/JBJS.L.00782.

[99] de Smet AMGA, Kluytmans JaJW, Cooper BS, Mascini EM, Benus RFJ, van der Werf TS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. N Engl J Med 2009;360:20–31. https://doi.org/10.1056/NEJMoa0800394.

[100] Kollef MH, Micek ST. Rational use of antibiotics in the ICU: balancing stewardship and clinical outcomes. JAMA 2014;312:1403–4. https://doi.org/10.1001/jama.2014.8427.
[101] Plantinga NL, Bonten MJM. Selective decontamination and antibiotic resistance in ICUs. Crit Care 2015;19:259. https://doi.org/10.1186/s13054-015-0967-9.
[102] Organization WH. Antimicrobial resistance: global report on surveillance. Geneva: World Health Organization; 2014.
[103] Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 1999;115:462–74.
[104] Terpstra S, Noordhoek GT, Voesten HG, Hendriks B, Degener JE. Rapid emergence of resistant coagulase-negative staphylococci on the skin after antibiotic prophylaxis. J Hosp Infect 1999;43:195–202. https://doi.org/10.1053/jhin.1999.0636.
[105] Hoth JJ, Franklin GA, Stassen NA, Girard SM, Rodriguez RJ, Rodriguez JL. Prophylactic antibiotics adversely affect nosocomial pneumonia in trauma patients. J Trauma 2003;55:249–54. https://doi.org/10.1097/01.TA.0000083334.93868.65.
[106] Thomas Z, Bandali F, Sankaranarayanan J, Reardon T, Olsen KM. Critical care pharmacotherapy trials network. A multicenter evaluation of prolonged empiric antibiotic therapy in adult ICUs in the United States. Crit Care Med 2015;43:2527–34. https://doi.org/10.1097/CCM.0000000000001294.
[107] Rimawi RH. Just say “stop”: avoiding prolonged empiric antibiotics. Crit Care Med 2015;43:2675–6. https://doi.org/10.1097/CCM.0000000000001417.
[108] Voigt J, Mosier M, Darouiche R. Antibiotics and antiseptics for preventing infection in people receiving revision total hip and knee prostheses: a systematic review of randomized controlled trials. BMC Infect Dis 2016;16:749. https://doi.org/10.1186/s12879-016-2063-4.
[109] Brown NM, Murray T, Sporer SM, Wetters N, Berger RA, Della Valle CJ. Extensor mechanism allograft reconstruction for extensor mechanism failure following total knee arthroplasty. J Bone Joint Surg Am 2015;97:279–83. https://doi.org/10.2106/JBJS.N.00759.
[110] Rogers BA, Sternheim A, De Iorio M, Backstein D, Safir O, Gross AE. Proximal femoral allograft in revision hip surgery with severe femoral bone loss: a systematic review and meta-analysis. J Arthroplasty 2012;27:829–836.e1. https://doi.org/10.1016/j.arth.2011.10.014.
[111] Paolin A, Trojan D, Petit P, Coato P, Rigoli R. Evaluation of allograft contamination and decontamination at the treviso tissue bank foundation: a retrospective study of 11,129 tissues. PLoS One 2017;12:e0173154. https://doi.org/10.1371/journal.pone.0173154.
[112] Hinsenkamp M, Muylle L, Eastlund T, Fehily D, Noël L, Strong DM. Adverse reactions and events related to musculoskeletal allografts: reviewed by the World Health Organisation project NOTIFY. Int Orthop 2012;36:633–41. https://doi.org/10.1007/s00264-011-1391-7.
[113] Winkler H, Haiden P. Allograft bone as antibiotic carrier. J Bone Jt Infect 2017;2:52–62. https://doi.org/10.7150/jbji.17466.
[114] Hoad-Reddick DA, Evans CR, Norman P, Stockley I. Is there a role for extended antibiotic therapy in a two-stage revision of the infected knee arthroplasty? J Bone Joint Surg Br 2005;87:171–4.
[115] Stockley I, Mockford BJ, Hoad-Reddick A, Norman P. The use of two-stage exchange arthroplasty with depot antibiotics in the absence of long-term antibiotic therapy in infected total hip replacement. J Bone Joint Surg Br 2008;90:145–8. https://doi.org/10.1302/0301-620X.90B2.19855.
[116] Ammon P, Stockley I. Allograft bone in two-stage revision of the hip for infection. Is it safe? J Bone Joint Surg Br 2004;86:962–5.