Workgroup 3:

Perioperative Antibiotics

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QUESTION 1: What is the optimal timing of the preoperative dose of antibiotics?

Consensus: The preoperative dose of antibiotics should be administered within one hour of surgical incision; this can be extended to two hours for vancomycin and fluoroquinolones. Furthermore, surveillance measures are critical in ensuring clinician compliance with this objective.

Delegate Vote: Agree: 97%, Disagree: 2%, Abstain: 1% (Strong Consensus)

Justification:

The scientific rationale for antibiotic prophylaxis is to inhibit or eliminate contaminating microorganisms that gain access to the surgical site during the procedure, which reduces the probability of an established infection. Thus, the goal of administering preoperative antibiotics is to allow for adequate tissue (blood, soft tissue, and bone) concentrations by the time of incision. These antibiotics should exceed the minimum inhibitory concentration (MIC) for the organisms likely to be encountered for the duration of the operation. This depends on the antibiotic used. There are a number of studies which validate the importance of the preoperative dose of antibiotics in decreasing perioperative joint infection (PJI) and surgical site infection (SSI) in total joint arthroplasty (TJA). However, there are conflicting opinions as to the optimal timing of this dose. Some studies suggest that within 2 hours of incision is best, while others recommend scheduling the dose as close to surgical incision as possible. There are several institutional guidelines which support a one hour preoperative dose of antibiotics as a Surgical Care Improvement Project (SCIP) measure. In addition to these guidelines, it is critically important to have surveillance measures in place to document compliance with these protocols.

The American Academy of Orthopaedic Surgeons (AAOS), the Centers for Disease Control (CDC), and SCIP guidelines recommend that prophylactic antibiotics be completely infused within one hour before the surgical incision [1]. The AAOS recommendation for the use of intravenous antibiotic prophylaxis in primary TJA, recommendation 2, states that “timing and dosage of antibiotic administration should optimize the efficacy of the therapy. Prophylactic antibiotics should be administered within one hour before skin incision.” Due to extended infusion time, vancomycin and fluoroquinolones should be started within 2 hours before incision. When a proximal tourniquet is used, the antibiotic must be completely infused before inflation of tourniquet [2]. The US advisory statement recommends that antimicrobial prophylaxis be administered within one hour before incision and discontinued within 24 hours after the end of the operation [3], while European guidelines recommend a single dose within 30 minutes before incision [4].

Timing <2 hours: The seminal article on this subject studied the timing of administration of prophylactic antibiotics and the risk of surgical wound infections in clean and clean-contaminated cases at a large community hospital [5]. In a study of 2,847 patients, 313 (11%) received TJA. The authors found that the rate of infection was lowest for patients who received an antibiotic from 0 to 2 hours before the incision [5]. Specifically, of the 1,708 patients who received prophylactic antibiotics during this time frame, only 10 (0.6%) subsequently developed SSI compared to 14 (3.8%) of 369 patients who received antibiotics 2 to 24 hours preoperatively, 4 (1.4%) of 282 patients who received antibiotics within 3 hours after incision, and 16 (3.3%) of 488 patients who received antibiotics 3–24 hours following incision. However, this study was conducted in 1985–1986, when there was considerable variation in timing of administration of the prophylactic antibiotic, and only 35% of patients received their dose within the contemporary standard of one hour prior to incision. Furthermore, the study did not find a significant difference in SSI rates when antibiotics were administered within 1–2 hours prior to incision compared with antibiotics administered 0–3 hours postoperatively.

Timing <1 hour: The leadership of the Medicare National Surgical Infection Prevention Projected hosted the Surgical Infection Prevention Guideline Writers Workgroup (SIPGWW) meeting and utilized the available literature to draft a consensus paper. The position of the SIPGWW is that the infusion of the first antimicrobial dose should begin within 60 minutes before incision [3,6].

Galandiuk et al combined the results of two prospective randomized controlled trials (RCTs) that compared antibiotic prophylaxis (either single-dose piperacillin with multi-dose cefoxitin) in elective surgical procedures of the gastrointestinal tract. The authors found that among other negative predictors, administration of an antibiotic for longer than 60 minutes preoperatively was associated with a higher rate of infectious complications [7].
In a large, retrospective cohort study using National Veterans Affairs data on prophylactic antibiotics of 32,459 surgical procedures from 2005 to 2009, Hawn et al found that higher SSI rates were observed for antibiotic administration more than 60 minutes prior to incision (unadjusted odds ratio (OR) 1.34, 95% confidence interval (CI) 1.08–1.66) compared with procedures in which antibiotics were administered within one hour of incision. However, in generalized additive models adjusted for patient, procedure, and antibiotic variables, no significant association was seen between prophylactic antibiotic timing and SSI [8].

Timing 30–60 minutes: In a prospective cohort study at a single academic hospital analyzing the incidence of SSI by the timing of antimicrobial prophylaxis in a consecutive series of 3,836 surgical procedures, Weber et al determined that administration of single-shot prophylactic cefuroxime is more effective when given 30–59 minutes before incision than administration during the last 30 minutes. The overall SSI rate for this mixed cohort of general, vascular, and orthopaedic surgeries was 4.7% (180), and antimicrobial prophylaxis was administered within the final 30 minutes in 59% of all procedures. Multivariable logistic regression analysis showed a significant increase in the odds of SSI when antimicrobial prophylaxis was administered fewer than 30 minutes (crude OR 2.01; adjusted OR 1.95; 95% CI 1.4–2.8; P = 0.001) and 60–120 minutes (crude OR 1.75; adjusted OR 1.74; 95% CI 1.0–2.9; P = 0.035) when compared with the reference interval of 30–59 minutes before incision [9].

Timing <30 minutes: In a large, prospective, multicenter observational study examining the relationship between antibiotic timing and SSI risk, Steinberg et al determined that SSI risk increased incrementally as the interval of time between antibiotic infusion and creation of the incision increased. The authors analyzed the antimicrobial prophylaxis of 4,472 randomly selected cardiac, hip or knee arthroplasty, and hysterectomy cases from 29 contributing hospitals, and ascertained SSI through the National Nosocomial Infections Surveillance system methodology. When antibiotics requiring long infusion times (eg vancomycin) were excluded, the infection risk following administration of antibiotics within 30 minutes was 1.6% compared with 2.4% associated with administration of antibiotic between 31 and 60 minutes prior to surgery (OR 1.74; 95% CI 0.98–3.04) [10].

In another recent multicenter, observational study from the Netherlands assessing risk factors for postoperative infections in 1,922 total hip arthroplasty (THA) cases, the authors found a similar pattern with a decreased rate of infection in those who received prophylaxis within 30 minutes prior to incision, although it did not reach statistical significance [4]. These authors collected data about SSI and potential risks factors related to prophylaxis, the patient, and procedure from 11 hospitals that participated in the Surgical Prophylaxis and Surveillance Intervention project and used multivariate logistic regression analysis to identify those variables that were predictive of SSI. Although there was a non-significant trend for the lowest SSI rate in those patients who received prophylaxis 30 minutes before surgery, the highest odds ratios for SSI were found in patients who received prophylaxis after incision (2.8, 95% CI 0.9–8.6, P = 0.07) and prolonged duration of surgery was the only statistically significant risk factor for SSI following THA.

Timing with tourniquet use: In an RCT of 22 patients in which cefuroxime prophylaxis was administered at various intervals (5, 10, 15, or 20 minutes) before inflation of the tourniquet for total knee arthroplasty (TKA), Johnson et al measured antibiotic levels of bone and subcutaneous fat throughout the operation. They found that an interval of 10 minutes prior to tourniquet inflation was necessary to obtain adequate prophylaxis. While the patients obtained adequate levels in bone at 5 minutes, an interval of 10 minutes or more was required for patients to have therapeutic levels in the subcutaneous fat [11].

In another similar RCT, 24 patients undergoing TKA were randomized to receive cefazolin 1, 2, or 5 minutes before tourniquet inflation. Serum, soft tissue, and bone samples were measured for adequate cefazolin concentration (defined as >-MIC 90 (MIC 90 = 1 microgram/ml). The median percentage of cefazolin penetration into soft tissue and bone for the 5, 2, and 1 minute groups was 14.5% and 4.6%, 6.7% and 3.0%, and 5.9% and 4.6% respectively. The authors also noted that the percentage of patients achieving the ratio of 4×MIC 90 for soft tissue and bone was highest in the 5 minute group compared with either the 2 or 1 minute group [12].

In another prospective study by Soriano et al, 908 patients undergoing TKA were randomized to receive either 1.5 g of cefuroxime 30 minutes before inflation of tourniquet and placebo 10 minutes before release of tourniquet (standard group) or placebo 30 minutes before inflation of tourniquet and 1.5 g cefuroxime 10 minutes before release of tourniquet. There was no difference among the patients with regard to various risk factors for SSI/PJI. The authors did not find a significant difference in the incidence of infection at 3.6% for the standard group and 2.6% for the control group at 12 months. The authors concluded that administration of antibiotics just prior to release of tourniquet was not inferior to a standard prophylactic regimen [13].

Surveillance measures: In a study evaluating the impact of a new national project meant to reduce infections in arthroplasty surgery in Sweden, Dahl et al found that only 57% of patients received preoperative antibiotics during the recommended time frame. In 2009, following the introduction of the World Health Organization surgical checklist and a new Swedish Knee Arthroplasty Register (SKAR) reporting form, which included the time for administration of prophylactic antibiotics, the number of patients receiving appropriately-timed doses of preoperative antibiotics increased to 69% in 2009 and 79% in 2010 [14].

**QUESTION 2: Is there an optimal antibiotic that should be administered for routine perioperative surgical prophylaxis?**

**Consensus:** A first or second-generation cephalosporin (cefazolin or cefuroxime) should be administered for routine perioperative surgical prophylaxis. Isoxazolyl penicillin is used as an appropriate alternative.

**Delegate Vote:** Agree: 89%, Disagree: 8%, Abstain: 3% (Strong Consensus)

**Justification:**

A first or second generation cephalosporin should be administered for routine perioperative surgical prophylaxis because of its broad spectrum of action, cost-effectiveness, and the need to preserve newer and more expensive therapies for drug-resistant microorganisms and emerging pathogens. These antibiotics cover gram-positive organisms and clinically important aerobic gram-negative bacilli and anaerobic gram positive organisms [6]. Additionally, they have excellent distribution profiles in bone, synovium, muscle, and hematomas [15]. Many studies have documented that minimum bactericidal concentrations for most non methicillin-resistant *Staphylococcus aureus* (MRSA) organisms are achieved rapidly in these tissues—ie within minutes after their administration [16,17]. The optimal prophylactic antibiotic should be bactericidal (penicillin, cephalosporin, vancomycin, or aminoglycosides), not simply bacteriostatic (clindamycin, which is a lincosamide). The agent should also have a half-life that covers the decisive interval (the first 2 hours after incision or contamination) with therapeutic concentrations from time of incision to wound closure. Failure to maintain tissue concentrations above the MIC increases the risk of wound infection [18]. In Scandinavia and elsewhere, isoxazolyl penicillin, such as cloxacinil, flucloxacillin, nafcillin, or oxacillin was used as an appropriate alternative. Some institutions administer carbapenems (namely imipenem/ cilastin and meropenem) to patients with penicillin allergy, as they felt that the
In a multicenter, placebo RCT, Hill et al convincingly demonstrated the efficacy of cefazolin for antimicrobial prophylaxis in reducing the risk of PJI. In 2,137 THA patients randomized to either 5 days of cefazolin or placebo antibiotic prophylaxis reduced the incidence of deep infection from 3.3% to 0.9% (P < 0.01) [20].

Tyllianakis et al performed an RCT comparing cefuroxime to two specific antistaphylococcal agents (fusidic acid and vancomycin) for prophylaxis in THA and TKA in an institution where MRSA and methicillin-resistant <i>S. epidermidis</i> (MRSE) prevalence exceeded 25% of orthopaedic infections. In 435 patients (260 hips and 175 knees) followed for a minimum of 2 years, the authors found no statistically significant difference between the treatment groups for either THA or TKA, although the authors concede that the power to detect meaningful statistical differences between the groups was low and it was therefore difficult to provide any definitive conclusions [21].

The efficacy of one day of cefuroxime vs. 3 days of cefazolin on postoperative wound infections was studied by Mauherhan et al in a double-blind, multicenter trial of 1,354 patients undergoing hip and knee arthroplasty. The authors found no statistically significant difference between the two regimens. For the TKA patients, the rate of PJI was 0.6% (1/178) for those receiving cefuroxime vs 1.4% (3/207) for those receiving cefazolin. For the THA patients, the rate of PJI was 0.5% (1/187) for those receiving cefuroxime as compared to 1.2% (2/168) for those receiving cefazolin [22].

In a study investigating the bacterial colonization and resistance patterns of a cohort of patients undergoing primary joint arthroplasty in Sweden, Stefansdottir et al noted that in Scandinavia, isoxazolyl penicillin derivative cloxacillin is the most commonly used prophylactic antibiotic. Moreover, these β-lactams were effective against 99% of the <i>S. aureus</i> strains and 80% of the coagulase-negative <i>Staphylococcus</i> (CNS) strains colonizing patients undergoing primary TJA. Furthermore, the gentamicin-laden bone cement used in many of these cases covers against most of the additional CNS strains [23].

### QUESTION 3: What is the choice of antibiotic in patients who have pre-existing prostheses such as heart valves?

**Consensus:** The choice of antibiotics for patients with pre-existing prostheses such as heart valves, is the same as routine elective arthroplasty.

**Delegate Vote:** Agree: 94%, Disagree: 3%, Abstain: 3% (Strong Consensus)

**Justification:**

Patients with preexisting prostheses such as heart valves are at risk for infective endocarditis due to bacteremia, which is relatively rare but can lead to catastrophic complications and death. Guidelines for the prevention of infective endocarditis have been published by the American Heart Association (AHA) for more than 50 years. The first 9 guidelines (published between 1955 and 1997) were based on low-level evidence; only more recently have the guidelines been stratified based on lifetime risk of infective endocarditis. Similar to the change in recommendations regarding dental prophylaxis for patients undergoing TJA, the 2007 antibiotic prophylaxis guidelines for infective endocarditis from the AHA and the Infectious Disease Society of America (IDSA) recommend antibiotic prophylaxis only for patients at the highest risk of infective endocarditis and only for selected dental procedures (eg those that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa) [24].

Infections that complicate heart valve replacement and prosthetic joint replacement have several features in common. <i>S. aureus</i> and <i>S. epidermidis</i> are common pathogens and infection rates are similar [23–25]. It is generally accepted that antimicrobial prophylaxis reduces the frequency of early postoperative infections; however, when such infections do occur, they are difficult to control without removing the prosthesis. The antibiotics that are recommended for endocarditis prophylaxis are similar to that of prophylaxis against PJI. Similarly, if an infection is known or suspected to be caused by <i>S. aureus</i>, the antibiotic regimen should contain an antistaphylococcal penicillin or a cephalosporin; whereas vancomycin should be used in those whom an infection is known or suspected to be caused by MRSA [25].

While there is literature to support the use of prophylactic antibiotics up to 48 hours postoperatively in cardiac surgery, this is to prevent deep and superficial sternal wound infection and is not relevant to our discussion of TJA surgery in a patient with a preexisting heart valve [26,27]. Interestingly, there have been some studies showing an increase in the routine use of vancomycin for routine valve surgery prophylaxis over the past years. Haydon et al reviewed the national practice patterns for antibiotic prophylaxis in cardiac surgery in Australia and found that between 2004 and 2008, there was a doubling in the proportion of cardiac units using vancomycin for routine prophylaxis from 31% to 62% (P < 0.001) [28].

### QUESTION 4: What alternatives are available for routine prophylaxis when cephalosporins are not an option?

**Consensus:** Currently teicoplanin and vancomycin are reasonable alternatives when routine antibiotic prophylaxis cannot be administered.

**Delegate Vote:** Agree: 73%, Disagree: 22%, Abstain: 5% (Strong Consensus)

**Justification:**

Teicoplanin has proven to be an effective and safe prophylactic agent in prosthetic implant surgery in Europe, but is not yet available in the US, Canada, or China [29–32]. Due to the increased frequency of MRSA and MRSE infections in recent years, the prophylactic use of alternative antibiotics such as glycopeptides (vancomycin and teicoplanin) in hospitals where MRSA/MRSE are prevalent may be justified [33]. As vancomycin is more difficult to administer and has a shorter half-life and poorer tolerability profile than teicoplanin, the latter may be a better choice in these settings [34]. Teicoplanin is notable for having a long half-life (32–176 hours), low toxicity, and good tissue penetration, which allows it to achieve therapeutic concentrations in bone and surrounding soft tissues [33,35].

Ceftaroline (fifth generation cephalosporin) has the same spectrum of activity as ceftriaxone with additional MRSA activity. The US Food and Drug Administration and the European Medicines Agency have provided indications for the use of ceftaroline for treatment of complicated skin and soft tissue infections only and not for prophylaxis.

In one multicenter RCT, Periti et al compared administration of a single dose of teicoplanin (400 mg intravenous (IV) bolus at time of anesthesia) versus that of 5 doses of cefazolin over a 24 hour period (2 g at induction and 1 g every 6 hours postoperatively) as prophylaxis in patients undergoing TJA. They randomized 846 patients and noted that 6 patients (1.5%) in the teicoplanin group and 7 patients (1.7%) in the cefazolin group developed a surgical wound infection during their hospital stay, which was a non-significant difference. Additionally, a non-significant difference in adverse events was recorded in the two groups, with 3 (0.7%) of the teicoplanin patients and 9 (2.1%) of the cefazolin patients [32].
QUESTION 5A: What antibiotic should be administered in a patient with a known anaphylactic penicillin allergy?

Consensus: In a patient with a known anaphylactic reaction to penicillin, vancomycin or clindamycin should be administered as prophylaxis. Teicoplanin is an option in countries where it is available.

Delegate Vote: Agree: 88%, Disagree: 10%, Abstain: 2% (Strong Consensus)

QUESTION 5B: What antibiotic should be administered in a patient with a known non-anaphylactic penicillin allergy?

Consensus: In a patient with a reported non-anaphylactic reaction to penicillin, a second-generation cephalosporin can be used safely as there is limited cross-reactivity. Penicillin skin testing may be helpful in certain situations to clarify whether the patient has a true penicillin allergy.

Delegate Vote: Agree: 87%, Disagree: 9%, Abstain: 4% (Strong Consensus)

Justification:

When patients present with a penicillin allergy, further information should be obtained to determine whether an immunoglobulin E (IgE)-mediated response (anaphylaxis) occurred. In patients with a documented IgE-mediated response to penicillin, third and fourth generation cephalosporins can be used. First and second generation cephalosporins with R1 side chains similar to that of penicillin (cefaclor, cefadroxil, cefazolin, cefprozil, cephalixin, or cephadrine) should be avoided; first and second generation cephalosporins with different R1 side chains can be given.

Vancomycin and clindamycin are recommended as alternative agents for patients who have a true type I β-lactam allergy, manifested by immediate urticaria, laryngeal edema, or bronchospasm [3]. Clindamycin is a preferred alternative for persons with an established β-lactam allergy or with contraindications to its use and at institutions with low rates of MRSA infection. Clindamycin has good bioavailability and at 30 minutes after infusion has been shown to exceed the MICs for S. aureus in both animal and human cortical bone samples [36]. However, clindamycin is a bacteriostatic agent. In addition vancomycin alone has a relatively poor activity against S. aureus and clinical studies implicate that vancomycin as prophylaxis alone increases the risk for SSI.

Therefore a second agent should be considered (levofoxacin, moxi-floxacin) in addition to vancomycin [8].

Cross-reactivity between penicillin and cephalosporin is over-estimated and much lower than reported in earlier studies. The 10% estimate of risk of allergic reactions to cephalosporins in penicillin-allergic patients is based on data collected and reviewed in the 1960s and 1970s. It is due in large part to the widely referenced reviews of Dash and Petz, which reported allergic reactions in 7.7% and 8.1% respectively of penicillin-allergic patients (allergy was based on patient history) and only included first generation cephalosporins and second-generation cefamandole [37,38]. The high cross-reactivity found in earlier studies may be due in part to contamination of the study drugs with penicillin during the manufacturing process [39,40]. Moreover, the authors of the early studies had a broader definition of allergy and did not account for the fact that penicillin-allergic patients have an increased risk of adverse reactions to any medication [41,42]. Skin testing in penicillin-allergic patients cannot reliably predict an allergic response to a cephalosporin, particularly to compounds with dissimilar side chains [43]. However, skin testing may be useful in determining whether a true allergy to penicillin exists [44].

Twenty-seven articles on the topic of the cross-reactivity of penicillin and cephalosporin were reviewed, of which 2 were meta-analyses, 12 were prospective cohorts, 3 were retrospective cohorts, 2 were surveys, and 9 were laboratory studies. The authors demonstrated that penicillin has a cross allergy with first generation cephalosporins (OR 4.8; CI 3.7–6.2) and a negligible cross-allergy with second generation cephalosporins (OR 1.1; CI 0.6–2.1). Moreover, laboratory and cohort studies indicate that the R1 side chain, not the β-lactam ring, is responsible for this cross-reactivity. The authors conclude that the overall cross-reactivity between penicillin and cephalosporin is lower than previously reported, at 10%, although there is a strong association between amoxicillin and ampicillin with first and second generation cephalosporins that share a similar R1 side chain. The overall cross-reactivity between penicillin and cephalosporin in individuals who report a penicillin allergy is approximately 1% and in those with a confirmed penicillin allergy 2.55%. For penicillin-allergic patients, the use of third or fourth generation cephalosporin or cephalosporins (such as cefuroxime and ceftriaxone) with dissimilar side chains than the offending penicillin carries a negligible risk of cross allergy [45].

A similar review of 44 articles on the evidence of cross-reactivity between cephalosporin and penicillin in human and animal studies supports the finding that cephalosporin can be safely prescribed to a patient with a non-life threatening reaction to penicillin (including type I, IIA, type III, Stevens-Johnson syndrome, toxic epidermal necrolysis, and angioedema) [46]. The relative risk of an anaphylactic reaction to cephalosporin ranges from 1:1,000 to 1:1,000,000 and this risk is increased by a factor of 4 in patients with a history of penicillin allergy [47].

Based on an analysis of 9 articles that compare allergic reactions to a cephalosporin in penicillin-allergic and non-penicillin-allergic subjects, Pichichero et al found that first generation cephalosporins have a cross-allergy with penicillin, but cross-allergy is negligible with second and third generation cephalosporins. Specifically, a significant increase in allergic reactions to cephalexin (OR 2.5, CI 1.1–5.5), cephalexin (OR 8.7, 95% CI 5.9–12.8), and cefepime (OR 5.8, CI 3.6–9.2) and all first generation cephalosporins plus cefamandole (OR 48, CI 3.7–6.2) was observed in penicillin-allergic patients; no increase was observed with second generation cephalosporins (OR 1.1, CI 0.6–2.1) or third generation cephalosporin (OR 0.5, CI 0.2–1.1) [41,42].

In a retrospective cohort of 2,933 patients who received a cephalosporin (usually cefazolin) during their procedure, including 413 who were allergic to penicillin, only one of the penicillin-allergic patients may have had an allergic reaction to the cephalosporin; and one of the non-penicillin-allergic patients developed a rash while the antibiotic was infused, requiring discontinuation of the antibiotic [48].

In a large, retrospective review of 534,810 patients who received penicillin followed by a cephalosporin at least 60 days later, Apter et al noted that a total of 3,877 patients had an allergic-like event (ALE) after penicillin administration, but only 43 (1.1%) experienced a second ALE after receiving cephalosporin (unadjusted risk ratio (RR) 10.0; 95% CI 7.4–13.6). Interestingly, in a separate analysis reviewing sulfonamide antibiotics, 1.6% of penicillin-sensitive patients experienced a second ALE after receiving a sulfonamide (7.2%; 95% CI 3.8–12.5), suggesting that patients who are allergic to penicillin are at a higher likelihood of being allergic to other medications in general, not necessarily indicating that cross-reactivity had occurred [49].

Park et al performed a retrospective cohort study to determine whether patients with a penicillin allergy were at an increased risk of adverse drug reactions when administered cephalosporin. Eighty-five patients with a history of penicillin allergy and positive penicillin skin test and 726 patients with a history of penicillin allergy and a negative penicillin skin test were administered a first generation cephalosporin.
Five (6%) of 85 cases had an adverse drug reaction to cephalosporin compared to 5 (0.7%) of 726 of the control population ($P = 0.0019$). The rate of presumed IgE-mediated adverse drug reactions to the cephalosporin among the cases was 2 (2%) of 85 compared to 1 (0.1%) of 726 among the reference population ($P = 0.03$) [50].

**QUESTION 6: What are the indications for administration of vancomycin?**

**Consensus:** Vancomycin should be considered for patients who are current MRSA carriers or have anaphylactic allergy to penicillins.

Consideration should be given to screening high risk patients such as:
- Patients in regions with a high prevalence of MRSA
- Institutionalized patients (nursing home residents, dialysis-dependent patients, and those who have been in the intensive care unit)
- Healthcare workers.

**Delegate Vote:** Agree: 93%, Disagree: 7%, Abstain: 0% (Strong Consensus)

**Justification:**

The AAOS recommendation for the use of IV antibiotic prophylaxis in primary TJA, recommendation 2, states that “vancomycin may be used in patients with known colonization with MRSA or in facilities with recent MRSA outbreaks” [51]. Similarly, the consensus position of the Medicare National Surgical Infection Prevention Project’s SPICWW meeting was that “for patients with known MRSA colonization, vancomycin should be considered the appropriate antimicrobial agent for prophylaxis” [6]. Additionally, the Society for Healthcare Epidemiology of America recently recommended routine surveillance cultures at the time of hospital admission for patients at high risk for carriage of MRSA [52].

**QUESTION 7: Is there evidence to support the routine use of vancomycin for preoperative prophylaxis?**

**Consensus:** No. Routine use of vancomycin for preoperative prophylaxis is not recommended.

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

**Justification:**

Current data suggest that the role of vancomycin in orthopaedic surgery prophylaxis should be limited. There is ample evidence that vancomycin is inferior against methillin-sensitive strains of staphylococcal species when compared to cephalosporin and penicillinase-resistant penicillin [8,53].

Several systematic analyses concluded that no clear benefit in clinical or cost effectiveness has been demonstrated for the routine use of vancomycin compared with cephalosporin for prophylaxis. However, most of these studies were conducted before the increasing prevalence of MRSA and may not accurately reflect the current environment. In some hospitals, community-associated MRSA (CA-MRSA) strains are now responsible for a significant portion of SSI. However, there is no consensus about what constitutes a high prevalence of methillin resistance and no evidence that routine use of vancomycin for prophylaxis in institutions with perceived high risk of MRSA infection results in fewer SSIs than the use of a cephalosporin. Although two RCTs have been conducted in institutions with a high MRSA prevalence, the differences in SSI rates and outcomes were conflicting. Similarly, several studies have utilized decision analysis models to calculate MRSA prevalence thresholds for which vancomycin would have clinical benefit and be more cost-effective than cephalosporin for surgical prophylaxis. However, these studies all suffer from the same limitation, the lack of randomization to provide baseline probabilities for the clinical effectiveness of each treatment at different rates of MRSA prevalence.

While there is a growing body of evidence to support the routine use of vancomycin for preoperative prophylaxis, this should be tempered by the fact that there is an increasing threat of colonization and infection with vancomycin-resistant enterococci (VRE) [56] and an increased prevalence of MRSA strains with reduced susceptibility to vancomycin [57,58].

The choice of drug prophylaxis should take into account the antibiotic resistance patterns in hospital systems. In a recent study by Fulkerson et al, the susceptibilities of $S.\text{epidermidis}$ and $S.\text{aureus}$ to cefazolin at two high-volume academic centers in New York and Chicago were only 44% and 74%, respectively [59]. Of the most common organisms infecting patients undergoing TJA at these hospitals, 26%–56% were resistant to the standard recommended prophylactic agent. Thirty-three of the 194 infections were diagnosed within a month after the surgery. Of these, 8 were due to $S.\text{epidermidis}$ and 16 were due to $S.\text{aureus}$. Of these, only 2 of the 8 (25%) of the $S.\text{epidermidis}$ infections and 11 of the 16 (69%) of the $S.\text{aureus}$ infections were sensitive to cefazolin. However, these infections were 100% susceptible to vancomycin.

In a study of deep infections following hip and knee arthroplasty over a 15-year period at The Royal Orthopaedic Hospital and Queen Elizabeth Hospital in England, 22 of 75 hip and knee infections (29%) were caused by microorganisms that were resistant to the antibiotic used for prophylaxis (cefuroxime). These included all 3 MRSA infections, all 3 $Pseudomonas\text{aerugino}sa$ infections, and 11 coagulase-negative $Staphylococcus$ infections [60,61]. Wiesel and Esterhai recommend administration of vancomycin in institutions where the prevalence of MRSA is greater than 10%–20% [62].

In a hospital with a high prevalence of MRSA, Merrer et al conducted a prospective, observational study comparing the incidence of SSI after vancomycin or cefazolin prophylaxis before femoral neck fracture surgery, as well as the impact of antibiotic prophylaxis on the emergence of VRE and $S.\text{aureus}$. The authors found no significant difference in the rate of SSI, as a total of 8 (3%) occurred, 4% in the cefazolin group and 2% in the vancomycin group ($P = 0.47$). At one week after surgery, there were a total of 6 patients (2%) who had hospital-acquired MRSA, corresponding to 0.7% in the cefazolin group and 5% in the vancomycin group ($P = 0.04$), none of which were resistant to glycopeptides. Additionally, 3 patients (1%) acquired VRE, all of which were in the cefazolin group ($P = 0.27$) [63].

Cranney et al used a combination of systematic reviews and economic modeling in order to answer questions about whether there is a level of MRSA prevalence at which a switch from non-glycopeptide to glycopeptide antibiotics for routine prophylaxis is indicated in surgical environments with a high risk of MRSA infection. The effectiveness reviews identified 16 RCTs with a further 3 studies included for adverse events only. They found no evidence to support that glycopeptides are more effective than non-glycopeptides in preventing SSI. Most of the trials did not report either the baseline prevalence of MRSA at the participating surgical units or MRSA infections as an outcome. The cost-effectiveness review included 5 economic evaluations of glycopeptide prophylaxis. Only one study incorporated health-related quality of life and undertook a cost-utility analysis. In conclusion, the authors indicate that there is currently insufficient evidence to determine whether there is a threshold prevalence of MRSA at which switching from non-glycopeptide to glycopeptide antibiotic prophylaxis might be cost effective [64].
Bolon et al performed a meta-analysis of 7 RCTs published in the cardiothoracic surgery literature that compared SSIs in subjects receiving glycopeptide prophylaxis with those who received β-lactam prophylaxis. While neither agent proved to be superior for prevention of the primary outcome, occurrence of SSI at 30 days (RR 1.14, 95% CI 0.91–1.42), vancomycin prophylaxis was superior for the prevention of SSI caused by methicillin-resistant gram-positive bacteria (RR, 0.54; 95% CI 0.33–0.90) at 30 days after surgery [65].

The AAOS recommendations for the use of IV antibiotic prophylaxis in primary TJA, recommendation 2, state that “vancomycin may be used in patients with known colonization with MRSA or in facilities with recent MRSA outbreaks” [1]. The Hospital Infection Control Practices Advisory Committee guideline also suggests that a high frequency of MRSA infection at an institution should influence the use of vancomycin for prophylaxis but acknowledges that there is no consensus about what constitutes a high prevalence of methicillin resistance [66].

Two prospective RCTs have evaluated antibiotic prophylaxis in hospitals with a high prevalence of MRSA. Taccioni et al randomized patients undergoing surgery for cerebrospinal shunt placement to receive either vancomycin or cefazolin. The prevalence of MRSA in 2001 for this 1,700-bed university hospital was reported as one new case of MRSA infection per 100 hospital admissions. Shunt infections developed in 4% of patients receiving vancomycin (4/88) and 14% receiving cefazolin (12/88, RR, 0.22; 95% CI 0.11–0.99, P = 0.03). The infecting pathogen was MRSA in 2 of 4 patients (50%) receiving vancomycin and 9 of 12 (75%) patients receiving cefazolin [67]. Finkelstein et al randomized 855 patients undergoing cardiothoracic surgery to either a vancomycin or cefazolin group. The prevalence of new cases of MRSA infection in the cardiac surgery ward was reported to be 3.0 and 2.6 per 100 admissions in 1995 and 1996 respectively. The overall rates of SSI were similar in both groups (9.5% for vancomycin and 9.0% for cefazolin). A trend toward more methicillin-resistant gram-positive infections was observed in the cefazolin group (4.2% vs 2.0%; P = 0.09), while more methicillin-sensitive Staphylococcus infections were seen in patients receiving vancomycin (3.7% vs 1.3%; P = 0.04) [68].

Three other clinical studies have used preintervention and postintervention periods to assess the effect of switching to vancomycin for surgical prophylaxis in patients undergoing cardiothoracic or orthopaedic surgery. Garey et al demonstrated that a change from cefuroxime to vancomycin prophylaxis decreased the average monthly SSI rate by 2.1 cases/100 coronary artery bypass graft (CABG) procedures when compared with patients undergoing cardiac valve replacement surgery. This was attributed to a lower rate of infections caused by MRSA and coagulase negative Staphylococcus (CNS) during this 4-year study of nearly 6,500 patients [69]. Similarly, Spelman et al reported a decrease in SSI rates from 10.5% to 4.9% (P < 0.001) after switching the antibiotic prophylaxis regimen from cefazolin to vancomycin plus rifampin in 1,114 CABG procedures. This was attributed to a decrease in the incidence of MRSA infections from 67% during the one year pre-intervention period to 0% in the one year post-intervention period [70]. Smith et al retrospectively reviewed total and MRSA PJIs in 5,036 primary TJs as well as the cure rate of PJIs in a 2 year pre-intervention period when cefazolin was the antibiotic prophylaxis of choice to the 2 year postintervention period when vancomycin was the antibiotic prophylaxis of choice. They found that with the use of vancomycin the total rate of PJI was significantly reduced (1.0% vs 0.5%, P = 0.03) and the rate of MRSA PJI was also reduced (0.23% vs 0.07%, P = 0.14). Furthermore, PJs were more successfully treated with irrigation and debridement only, not requiring antibiotic spacers (76.9% vs 22.2%, P = 0.002) [71].

A study published on Australian Surveillance Data (Victorian Healthcare Associated Surveillance System [VHCSS]) of over 20,000 cardiac and arthroplasty procedures identified 1,610 case in which vancomycin was administered as compared to 20,939 cases in which a β-lactam was used. The adjusted OR for an SSI with methicillin-sensitive S. aureus (MSSA) was 2.79 (95% CI 1.6–4.9) when vancomycin prophylaxis was administered (P < 0.001), whereas the unadjusted OR for an SSI with MRSA was 0.44 (OR 0.19–1.004; P = 0.05) [72].

Several recent studies have developed decision analysis models to determine the threshold of MRSA prevalence at which vancomycin would minimize the incidence and cost of SSI. For CABG surgery, the authors of two studies have recommended an MRSA prevalence threshold of 3% among infections caused by S. aureus [73–75]. Miller et al suggested that lower rates of MRSA prevalence (eg 3%–10%) were within the error of their model and that surgical prophylaxis with vancomycin may have a modest effect in reducing the incidence of SSI. For vascular surgery, an MRSA prevalence of 50% was suggested before a β-lactam agent is replaced with vancomycin for surgical prophylaxis [76]. The authors also suggested that an aminoglycoside should be added to the prophylactic regimen once the prevalence of MRSA reaches 10%, which is in agreement with the recent guidelines from the British Society of Antimicrobial Chemotherapy [77]. Elliot et al developed an economic model to explore the cost-effectiveness of vancomycin and/or cephalosporin for surgical prophylaxis in patients undergoing THA. Vancomycin was recommended when the rate of MRSA SSIs is ≤0.15% and the rate of non-MRSA SSIs is ≥0.1%, or when the rate of MRSA infections is ≤0.2% and the rate of other infections is >0.2% [78]. Each of these decision analysis studies noted that their biggest limitation was the lack of available evidence from RCTs, with a high prevalence of MRSA infections as one of the most important factors that influenced modeling assumptions.

**QUESTION 8: Is there a role for routine prophylactic use of dual antibiotics (cephalosporins and aminoglycosides or cephalosporins and vancomycin)?**

Consenus: Routine prophylactic use of dual antibiotics is not recommended.

Delegate Vote: Agree: 85%, Disagree: 14%, Abstain: 1% (Strong Consensus)

Justification:

Clinical studies have used preintervention and postintervention periods to assess the effect of switching to vancomycin for surgical prophylaxis in patients undergoing cardiothoracic surgery. Walsh et al implemented a comprehensive MRSA bundle program in which vancomycin was added to the routine cefazolin prophylaxis regimen for patients who tested positive for nasal MRSA carriage. Other components of the program included decolonization of all cardiothoracic staff who screened positive for nasal MRSA, application of nasal mupirocin ointment for 5 days in all patients starting one day before surgery, application of topical mupirocin to exit sites after removal of chest and mediastinal tubes, and rescreening of patients for MRSA colonization at the time of hospital discharge. This program resulted in a significant reduction in the SSI rate (2.1%–0.8%, P < 0.001) as well as a 93% reduction in postoperative MRSA wound infections (from 32 infections/2,767 procedures during the 3-year pre-intervention period to 2 infections/2,496 procedures during the 3-year post-intervention period) [79].

Dhadwal et al conducted a double-blind RCT to compare the efficacy of a 48 hour, weight-based dosing of vancomycin plus gentamicin and rifampin versus a 24 hour cefuroxime regimen for antibiotic prophylaxis of sternal wound infections in a high-risk group of patients undergoing CABG surgery. The infection rates significantly decreased from 23.6% (25/106) in the cefuroxime group to 8.4% (8/95) in the combination vancomycin group (P = 0.004) [80]. Patrick et al...
conducted an RCT to compare cefazolin and combinations of cefazolin and either vancomycin or daptomycin in 181 low-risk patients undergoing vascular surgery. Only 6 postoperative MRSA infections were reported (2 in the cefazolin group, 4 in the vancomycin plus cefazolin group, and 0 in the daptomycin plus cefazolin group), making the interpretation of the differences between antibiotic regimens difficult [81].

Sewick et al retrospectively reviewed 1,828 primary TJs that received either a dual antibiotic regimen of cefazolin and vancomycin or received cefazolin alone in order to determine the rate of SSI as well as the microbiology of subsequent SSI. There was a total of 22 SSIs (1.2%) with no significant difference in the infection rate between the dual antibiotic prophylaxis group compared to the single antibiotic regimen (1.1% and 1.4% respectively, P = 0.636), while the prevalence of subsequent MRSA infection was significantly lower (0.002% vs 0.08%, P = 0.02) [82]. Ritter et al administered a single prophylactic dose of vancomycin and gentamicin in a cohort of 201 consecutive TJA patients and documented bactericidal blood concentrations during and for 24 hours after surgery with no postoperative infections [83].

Elliott et al developed an economic model to explore the cost effectiveness of vancomycin and/or cephalosporin for surgical prophylaxis in patients undergoing THA. Combination therapy (such as vancomycin plus a cephalosporin) was recommended when the rate of MRSA SSIs is ≥0.25% and the rate of non-MRSA SSIs is ≥0.2% [78]. Thus, based on the available literature, this workgroup feels that dual antibiotics may be utilized to allow broad coverage in institutions or regions where there is a high rate of MRSA infection for which prophylactic vancomycin use is deemed appropriate under question 6 above.

**QUESTION 9: What should be the antibiotic of choice for patients with abnormal urinary screening and/or an indwelling urinary catheter?**

**Consensus:** The presence of urinary tract symptoms should trigger urinary screening prior to TJA. Asymptomatic patients with bacteriuria may safely undergo TJA provided that routine prophylactic antibiotics are administered. Patients with acute UTI need to be treated prior to elective arthroplasty.

**Delegate Vote:** Agree: 82%, Disagree: 12%, Abstain: 6% (Strong Consensus)

**Justification:**

There is sparse literature on the risk of deep joint infection in patients with abnormal perioperative urinalysis. While several case reports in the 1970s linked postoperative UTIs to PJI [84,85], the literature supporting the correlation between preoperative UTIs and PJI following TJA is inadequate [86]. Only 3 studies have directly addressed the relationship between preoperative bacteriuria and PJI following TJA, none of which observed a positive correlation [87–89]. To our knowledge there are no studies of patients with symptomatic UTI undergoing TJA with routine perioperative prophylactic antibiotics. There is no evidence either in support of or against proceeding with surgery in this cohort of patients.

The presence of UTI symptoms should serve as a preliminary screening tool for surgical clearance of the TJA candidate. Symptoms can then be classified as either irritative or obstructive. Irritative symptoms (such as dysuria, urgency, or frequency) may or may not be related to bacteriuria and a noncentrifuged clean catch midstream urine sample should be evaluated for white blood cells (WBCs) in these patients. In patients with >10^5 WBC/mL, a bacterial count and culture should be obtained and in patients with >4 WBC/high power field (HPF) and bacterial count >10^7/mL, surgery should be postponed until an appropriate course of microbe-specific antibiotics is administered and repeat urinalysis is obtained. On the other hand, asymptomatic patients with bacteriuria may safely undergo TJA provided routine prophylactic antibiotics are administered. Patients with obstructive symptoms should undergo urologic evaluation before arthroplasty, as postoperative urinary retention has been shown to be a risk factor for PJI [86,90,91].

In a prospective, multicenter study of 362 knee and 2,651 hip arthroplasty cases, the authors reported a deep joint infection rate of 2.5% for knee and 0.64% for hip cases at one year follow-up. While univariate analysis showed no association between deep joint infection and preoperative UTI (>10^5 CFU/mL), multivariate regression analysis indicated that postoperative UTI increased the risk of hip PJI [88].

Of 1,934 surgical cases (1,291 orthopaedic surgeries) performed at a Veterans Administration hospital, a preoperative urine culture was obtained in 25% (489) of cases. Of these, bacteriuria was detected in 54 (11%) patients, of which only 16 received antimicrobial drugs. The incidence of SSI was similar between those with bacteriuria and those without (20% vs 16%, P = 0.56), while the rate of postoperative UTI was more frequent among patients with bacteriuria than those without (9% vs 2%, P = 0.01). Among the 54 patients with a positive urinary culture, treated and untreated patients were compared. Unexpectedly, a greater proportion of treated patients developed an SSI (45% vs 14%, P = 0.03). This effect was greatest among patients with high count bacteriuria (>10^6 CFU/mL), with SSI occurring in 4 of 8 (50%) of treated vs 1 of 15 (7%) of untreated (P = 0.03). These results led the authors to conclude that in this system preoperative urinary cultures were inconsistently ordered and that when they were, they were rarely positive for bacteriuria. Even when bacteriuria was detected, it was usually not treated. The authors noted that treating bacteriuria associated with SSI is likely confounded by factors that contributed to the initial decision to administer antimicrobials in the first place [92].

A retrospective study of 274 THAs found that 5 patients with PJI had perioperative UTIs. However, the same organism was isolated from the urinary tract and hip in only 3 patients. Of these, only one had a documented preoperative urinalysis [93]. A retrospective analysis of 277 patients (364 TJs) showed that 35 patients had evidence of preoperative or perioperative UTI with colony counts greater than 10^5 CFU/mL on preoperative clean-catch urine specimens. Only 3 patients (1.1%) developed joint infections at 9, 19, and 45 months respectively, and none was thought to be due to perioperative UTI [87]. Another retrospective analysis found 57 (55 asymptomatic, 2 symptomatic) of 299 arthroplasty patients had bacteriuria on admission. Twenty of the 57 patients went to surgery before the routine culture results were available, but postoperatively received appropriate antibiotics for treatment of the UTI. Another 18 patients underwent surgery during their treatment course for preoperatively-diagnosed UTI, while the other 19 patients completed an appropriate antibiotic course prior to surgery. None of the patients developed a PJI, which led the authors to conclude that a treatment course of antibiotics can be implemented at any time perioperatively once culture data are obtained [89].

The incidence of bacteriuria rises from 0.5% to 1% for a single in-and-out catheterization, 10% to 30% for catheters in place for up to 4 days, and up to 95% for catheters in place for 30 days or more [94,95].

**QUESTION 10: Should the preoperative antibiotic choice be different in patients who have previously been treated for another joint infection?**

**Consensus:** The type of preoperative antibiotic administered to a patient with prior septic arthritis or PJI should cover the previous
infecting organism of the same joint. In these patients, we recommend the use of antibiotic-impregnated cement, if a cemented component is utilized.

Delegate Vote: Agree: 84%, Disagree: 10%, Abstain: 6% (Strong Consensus)

Justification:

There is no evidence that septic arthritis or a PJI can be completely cured. Jerry et al conducted a study of 65 patients who underwent TKA and had a history of prior sepsis or osteomyelitis around the knee. They reported rates of deep PJI of 4% and 15% respectively [96].

Lee et al studied a consecutive series of 20 primary TKAs in 19 patients with a history of prior septic arthritis or osteomyelitis around the knee. They performed a preoperative workup to evaluate for infection that included serologies and plain radiographs in all patients, while 8 patients additionally had tagged WBC scans and 7 patients had a knee aspiration. Intraoperatively, frozen section for evidence of acute inflammation was used to guide decisions on whether the procedure was done as a single or staged procedure. All TKA components were implanted with antibiotic cement containing 1 g of vancomycin and 1.2 g of tobramycin/batch of Simplex bone cement. Of the 17 patients with a minimum of 2 years follow-up, only one developed a PJI approximately 3.5 years from the index arthroplasty. Of note, this was one of the two patients that had been treated in a staged manner and additionally had immunosuppressive comorbidities, including rheumatoid arthritis, insulin-dependent diabetes mellitus, and taking daily doses of prednisone [97].

Larson et al performed a retrospective matched case control study to review the clinical results of 19 patients who underwent TKA after infected tibial plateau fractures, comparing them to 19 control subjects matched for age, gender, and arthroplasty year, who underwent TKAs for tibial plateau fractures without a history of infection. Of the 19 case patients, 13 underwent one-stage TKA, while the remainder underwent a staged TKA with either an antibiotic spacer or debridement and intravenous antibiotic therapy. Antibiotic cement was used in the majority of patients. Previously infected knees were 4.1 times more likely to require additional procedures for complications compared with knees with no previous infection (95% CI 1.2–18.3, P = 0.02). The 5 year infection-free survival was 73% ± 10% in the case group compared with 100% in the control group (P = 0.023). The authors recommended that in patients at high risk less than one year since active evidence of infection, a two-stage TKA be performed, with antibiotic therapy and a 4 to 6 week delay between procedures [98].

QUESTION 11: Should postoperative antibiotics be continued while a urinary catheter or surgical drain remains in place?

Consensus: No. There is no evidence to support the continued use of postoperative antibiotics when urinary catheter or surgical drains are in place. Urinary catheters and surgical drains should be removed as soon as safely possible.

Delegate Vote: Agree: 90%, Disagree: 7%, Abstain: 3% (Strong Consensus)

Justification:

Short-term use of an indwelling catheter after surgery reduces the incidence of urinary retention and bladder over-distension without increasing the rate of UTI and is therefore common practice in many hospitals [99]. However, it has been shown that there is an increased risk of UTIs when a catheter is employed for more than 48 hours [100,101]. Urinary retention as well as catheterization can both lead to bacteriuria [101–103], which increases the risk of deep PJI from 3 to 6 times [87,88,104,105].

Literature in the field of surgical oncology demonstrates that bacterial colonization of surgical drains used in breast and axillary procedures is a significant risk factor for the development of SSI and the microorganisms that caused SSIs were the same as those that colonized the drainage tube in 83% of cases [106]. Other studies have demonstrated that there is an association between longer duration of drain use and increased incidence of SSI [107].

The AAOS recommendations for the use of IV antibiotic prophylaxis in primary TJA, recommendation 3, state that the “duration of prophylactic antibiotic administration should not exceed the 24 hour postoperative period. Prophylactic antibiotics should be discontinued within 24 hours of the end of surgery. The medical literature does not support the continuation of antibiotics until all drains or catheters are removed and provides no evidence of benefit when they are continued past 24 hours” [2].

Colonization of drains by skin organisms can certainly occur, but in only 10% of cases with positive drain tip culture does overt infection develop [108]. Michelson et al conducted an RCT of 100 TJA patients using two methods of bladder management: short term (<24 hours) indwelling catheters and intermittent catheterization. All patients received the same perioperative cefazolin prophylaxis. The authors reported a lower incidence of urinary retention in the indwelling catheter group (27% vs 52%, P < 0.01) and a lower rate of bladder distension (7% vs 45%, P < 0.01). Moreover, patients who had an indwelling catheter for more than 48 hours had a significantly higher rate of bladder infection (35%) than patients who were straight catheterized and/or who had an indwelling catheter for fewer than 48 hours (6%, P < 0.01) [99].

Van den Brand et al performed a prospective RCT to determine whether an indwelling catheter for 48 hours or intermittent catheterization leads to less postoperative bacteriuria or a UTI with a single dose of cefazolin prophylaxis in primary hip and knee arthroplasties. In their protocol, patients received 48 hours of IV prophylactic cefazolin during the postoperative period. Patients who had an indwelling catheter in place after the IV antibiotics were completed were treated with oral antibiotic prophylaxis (norfurantoin) until catheter removal. Of the 99 patients who completed the study, 14 patients (5 men, 9 women) developed postoperative bacteriuria. The indwelling catheter group had a bacteriuria rate of 24% (11/46) compared with 6% (3/53) in the intermittent catheterization group (P = 0.018) [109].

Similar findings were reported by Oishi et al, who reviewed 95 consecutive patients who had been managed with either an indwelling catheter (72 hours) or intermittent catheterization. Patients who were treated with an indwelling catheter had significantly lower incidences of urinary retention (7% vs 84% respectively; P < 0.005) and bladder distension (7% vs 41%; P < 0.005) than those who were treated with straight catheterization. While not statistically significant, though no patient in the indwelling catheter group developed infection, in the intermittent catheterization group one patient (2%) had bacteriuria and one patient (2%) had a UTI (P > 0.1) [110].

Koulouvaris et al performed a retrospective case control study to determine whether a treated preoperative or postoperative UTI or asymptomatic bacteriuria increases the risk of deep PJI and whether the organisms are the same for the UTI and PJI. The authors matched 58 patients who had wound infections with 58 patients who did not develop wound infection based on age, gender, surgeon, joint, year of surgery, and length of follow-up. The authors found no association between preoperative UTI and wound infection (OR 0.34; 95% CI 0.086–1.357, P = 0.13), and no association between postoperative UTI and wound infection (OR 4.22; 95% CI 0.46–38.9, P = 0.20). Only one patient had the same bacteria (Enterococcus faecalis) cultured in the urine and the wound [111].
In a survey of the members of the American Society of Breast Surgeons regarding the use of perioperative antibiotics for breast operations requiring drains, respondents continued antibiotic prophylaxis for 2–7 days or until all drains were removed (38% and 39% respectively) in cases without reconstruction, while in reconstruction cases 33% of respondents continued antibiotic prophylaxis for 2–7 days or until all drains were removed [112]. A similar study surveying the American and Canadian societies of Plastic Surgeons regarding drain use and perioperative antibiotic prophylaxis in cases of breast reconstruction found that 72% of plastic surgeons prescribed postoperative outpatient antibiotics in reconstruction patients with drains, with 46% continuing antibiotics until drains were removed [113].

QUESTION 12: What is the evidence for the optimal duration of postoperative antibiotics in decreasing SSI or PJI?

Consensus: Postoperative antibiotics should not be administered for greater than 24 hours after surgery.

Delegate Vote: Agree: 87%, Disagree: 10%, Abstain: 3% (Strong Consensus)

Justification:

Many studies across surgical specialties have been performed to compare durations of antibiotic prophylaxis and the overwhelming majority have not shown any benefit in antibiotic use for more than 24 hours in clean elective cases [114–116]. Prolonged postoperative prophylaxis should be discouraged because of the possibility of added antimicrobial toxicity, selection of resistant organisms, and unnecessary expense [24].

The AAOS recommendations for the use of IV antibiotic prophylaxis in primary TJA, recommendation 3, state that “duration of prophylactic antibiotic administration should not exceed the 24 hour postoperative period. Prophylactic antibiotics should be discontinued within 24 hours of surgery” [1].

McDonald et al performed a systematic review across surgical disciplines to determine the overall efficacy of single versus multiple dose antimicrobial prophylaxis for major surgery. They included only prospective RCTs which used the same antimicrobial in each treatment arm whose results were published in English. Regardless of fixed models (OR 1.06, 95% CI 0.89–1.25) or random effects (OR 1.04; 95% CI 0.86–1.25), there was no significant advantage of either single or multiple dose regimens in preventing SSI. Furthermore, subgroup analysis showed no significant differences in the type of antibiotic used, length of the multiple dose arm (>24 hours vs ≤24 hours), or type of surgery (obstetric-gynecological vs other) [117].

Mauerhan compared the efficacy of a one-day regimen of cefuroxime with a 3-day regimen of cefazolin in a prospective, double-blinded, multicenter study of 1,354 patients treated with arthroplasty and concluded that there was no significant difference in the prevalence of wound infections between the two groups. In the group treated with primary THA, the prevalence of deep wound infection was 0.5% (1/187) for those treated with cefuroxime compared with 1.2% (2/168) for those who had received cefazolin. In the group treated with a primary TKA, the rate of deep wound infection was 0.6% (1/178) for those treated with cefuroxime compared with 1.4% (3/207) for those who had received cefazolin [22].

Heydemann and Nelson, in a study of hip and knee arthroplasty procedures, initially compared a 24-hour regimen of either nafcillin or cefazolin with a 7-day regimen of the same and found no difference in the prevalence of infection. They then compared a single preoperative dose with a 48-hour regimen and again found no difference in infection prevalence. A total of 466 procedures were performed during the 4-year study. No deep infections developed in either the one-dose or 48-hour antibiotic protocol group. A deep infection developed in one (0.8%) of the 127 patients in the 24-hour protocol group and in two (1.6%) of the 128 patients in the 7-day protocol group for an overall infection rate of 0.6% (3/466). The authors recognized that as a result of the small sample sizes, the study lacked the power to compare the one dose and the more than one dose categories [118].

Stone et al performed two separate prospective, placebo RCTs of variable-duration antibiotic prophylaxis in patients undergoing elective gastric, biliary, or colonic surgery and then in patients undergoing emergency laparotomy and found that in both cases no significant difference was seen in the rate of SSI. Specifically, in a prospective RCT of 220 patients undergoing elective general surgery who were randomized to either perioperative cefamandole plus 5 days of placebo or perioperative plus 5 postoperative days of cefamandole, there was no significant difference in the rate of wound infection (6 and 5% respectively). In the second prospective RCT of patients undergoing emergent laparotomy in which cephalothin was utilized perioperatively, there was no significant difference in the rate of peritoneal infection between those who received perioperative therapy only (8 and 4% respectively) compared to those who had 5 to 7 days of additional postoperative therapy (10 and 5% respectively) [119].

In a retrospective review of 1,341 TJAs, Williams and Gustilo found no difference in deep infection rates between a 3-day and 1-day course of prophylactic antibiotics, but emphasized the importance of the preoperative dose, which was 2 g of cefazolin [120].

Clinical studies have used preintervention and postintervention periods to assess the effect of antibiotic duration for surgical prophylaxis. One institution launched a surgical wound infection surveillance program to monitor all orthopaedic surgeries and changed the prophylactic antibiotic regimen from intravenous cefuroxime (one preoperative and 2 postoperative doses every 8 hours) to one single preoperative dose of intravenous cefazolin for all clean elective orthopaedic cases. The authors of this study found no significant difference in the superficial and deep wound infection rates in 1,367 primary arthroplasties performed with a single preoperative dose of cefazolin versus 3 doses of cefuroxime. The deep wound infection rate for THA was 1.1% (95% CI, 0%–3.3%) in the cefuroxime group and 1.1% (95% CI, 0%–2.2%) in the cefazolin group (P = 1.0). The deep wound infection rate of TKA was 1.6% (95% CI, 0%–3.8%) in the cefuroxime group and 1.0% (95% CI, 0.3%–1.7%) in the cefazolin group (P = 0.63) [121].

QUESTION 13: Until culture results are finalized, what antibiotic should be administered to a patient with a presumed infection?

Consensus: In a patient with a presumed infection when culture results are pending, empiric antibiotic coverage should depend on the local microbiological epidemiology. Culture data should assist in the tailoring of antibiotic regimens.

Delegate Vote: Agree: 96%, Disagree: 1%, Abstain: 3% (Strong Consensus)

Justification:

Guidelines based on individual institutional microbiological epidemiology should be developed [122]. In the US, vancomycin is recommended for gram-positive coverage due to a high rate of resistance to methicillin in many cases and gentamicin or a third or fourth generation cephalosporin is recommended for gram-negative coverage. However, in areas with low MRSA prevalence, vancomycin...
should not be recommended as the first choice of drug until culture results are obtained and other antibiotics should be chosen instead.

Sharma et al. classified the spectrum and antibiotic susceptibility of bacteria isolated from revision hip and knee arthroplasty specimens in order to recommend appropriate empiric perioperative antibiotics before definitive cultures are obtained. They identified 147 patients with positive specimens, yielding 248 microorganisms from 195 tissue specimens, 43 fluid specimens, and 10 swabs. Of the 248 isolated microorganisms, Staphylococcus species was the most common genus encountered (53%), followed by gram-negative isolates (24%). Eighty-eight percent of gram-negative organisms were detected within 48 hours of inoculation and 94% of gram-positive organisms within 96 hours. Overall, 46% of isolates were susceptible to cephalothin, while only 35% of CNS were sensitive to cephalothin. No gram-positive vancomycin resistance was encountered. Therefore the authors concluded that empiric prophylactic antibiotics for revision hip and knee arthroplasty should include vancomycin for gram-positive organisms and gentamicin for gram-negative bacteria; and if infection is suspected, vancomycin and gentamicin should be continued postoperatively for 96 and 48 hours respectively, unless culture or histology results suggest otherwise [123].

Knee: In a retrospective review of 121 patients who underwent revision TKA for infection between 1994 and 2008 in the United Kingdom, the most common organism was CNS (49%) and S. aureus (13%). The prevalence of CNS appears to be increasing, while that of S. aureus and other organisms are decreasing. Vancomycin and teicoplanin were the most effective antibiotics, with overall sensitivity rates of 100% and 96% respectively. Also, the authors reported that based on their theoretical model of comparing microorganism sensitivities against specific antibiotics, gentamicin combined with vancomycin or teicoplanin is the most effective empirical regimen. While the authors recognized the potential serious nephrotoxic side effects, these antibiotics may be added to bone cement relatively safely. The authors also suggested that this empirical regimen can potentially allow for a one-stage revision procedure to be conducted when deep infection arises [124].

In early, delayed, and late infections observed from data from the SKAR from 1986 to 2000 in 426 surgically revised cases, CNS was most prevalent (105/299, 35.1%) and twice as common as S. aureus (55/299, 18.4%). In hematogenous infections, S. aureus was the dominating pathogen (67/99, 67.7%), followed by streptococci and gram-negative bacteria. Methicillin resistance was found in 1/84 tested isolates of S. aureus and 62/100 tested isolates of CNS. During the study period of 1986–2000, methicillin resistance among CNS increased (P = 0.002). Gentamicin resistance was found in 1/28 tested isolates of S. aureus and 19/29 tested CNS isolates. Therefore, the authors conclude that empiric antibiotics should cover CNS, as most early infections were caused by this organism. They also raised the concern that due to high rate of gentamicin resistance among CNS in infected TKA, other antibiotics should be used in bone cement at revision [23].

Data from the SKAR have previously been used to report on the microbiology of 357 TKA infections in patients operated on before the year 1986. S. aureus was the most common pathogen (45.4%) followed by CNS (18%) [122]. In later studies, staphylococci continued to be the most common pathogens, with S. aureus reported to account for 13%–51% of the infections and CNS accounting for 15%–49% [124–126].

In a study examining the microbiology of contaminating bacteria during primary THA, Al-maiyah et al cultured the gloved hands (n = 627 impressions) of the surgical team in 50 THA cases after draping, at 20 minute intervals, and then before cementation. They found contamination present in 57% (9%) of impressions and a total of 106 bacterial isolates, with CNS being the most frequent (68.9%), micrococcci (12.3%) and diphtheroids (9.4%) following, and S. aureus only representing 6.6% of cases. Interestingly, only half (52%) of the CNS isolates were sensitive to cefuroxime, the institutional prophylactic agent of choice, suggesting alternate agents may be indicated [128].

Phillips et al reviewed the microbiology of deep infection following hip and knee arthroplasty at a specialist orthopaedic hospital in the United Kingdom over a 15 year period. At their institution, CNS was the most common infecting organism (36%), followed by S. aureus (25%), Enterococcus (9%), and MRSA (4%). Of the infecting organisms, 72% were sensitive to routine prophylactic agents. There was no significant change in microbiology over that time period at this institution [129].

Timing of infection: A retrospective analysis of 146 patients who had a total of 194 positive cultures obtained at time of revision total hip or knee arthroplasty was performed. Seventy percent of the infections were classified as chronic, 17% as acute postoperative, and 13% as acute hematogenous. Gram-positive organisms caused the majority of the infections (87% or 168/194). The microorganisms were sensitive to cefazolin in 61% of cases, gentamicin in 88% of cases, and vancomycin in 62% of cases. The most antibiotic-resistant bacterial strains were from patients for whom prior antibiotic treatment had failed. Acute postoperative infections had a greater resistance profile than did chronic or hematogenous infections. Bacteria isolated from a hematogenous infection had a high sensitivity to both cefazolin and gentamicin. This led to the following recommendations:

- Until final cultures are available, acute hematogenous infections should be treated with cefazolin and gentamicin.
- All chronic and acute postoperative infections with gram-positive bacteria and all cases in which a gram stain fails to identify bacteria should be managed with vancomycin.
- Infections with gram-negative bacteria should be managed with third or fourth generation cephalosporin.
- Infections with mixed gram-positive and gram-negative bacteria should be managed with a combination of vancomycin and third or fourth generation cephalosporin.
- As 93% (180) of the 194 cultures tested positive by the fourth postoperative day, the authors recommend that if culture results are not positive by the fourth postoperative day, termination of empiric antibiotic therapy should be considered [59].

In a retrospective review of 97 patients (106 infections in 98 hips), Tsukayama et al noted that aerobic gram-positive cocci accounted for 109 (74%) of the 147 isolates; gram-negative bacilli, 21 (14%); and anaerobes, 12 (8%). Of the CNS species 27 (48%) were oxacillin-resistant, while all 33 (100%) of the coagulase-positive Staphylococcus species were sensitive to oxacillin. The authors noted that most of the gram-negative isolates came from the early postoperative and late chronic infections, while isolates from the acute hematogenous infections were exclusively gram-positive cocci [130].

Irrigation and debridement (I&D): A retrospective review was conducted to describe the microbiological spectrum of PJI in 112 patients managed with I&D or arthroscopic washout of infected prosthetic joints between 1998 and 2003 in order to guide the choice of empirical antibiotics. Overall, the most frequently isolated organisms were CNS (47%) and MSSA (44%); while 8% were MRSA and 7% were anaerobes. In their series, 60% of CNS isolates were resistant to methicillin. Most gram-negative isolates were resistant to cefuroxime and all were sensitive to meropenem. Based on the high rate of early polymicrobial infection, cephalosporin resistance among
gram-negative organisms, β-lactamase resistance among gram-negative organisms, and β-lactam resistance among CNS, the authors recommend glycopeptides with a carbapenem in the initial regimen, with modification when culture and sensitivity results are available [131].

**QUESTION 14: What is the appropriate preoperative antibiotic for a second-stage procedure?**

**Consensus:** The appropriate preoperative antibiotic for the second stage should include coverage of the prior organism(s). Cemented arthroplasty components should be inserted with antibiotic-laden bone cement.

**Delegate Vote:** Agree: 66%, Disagree: 31%, Abstain: 3% (Strong Consensus)

**Justification:**

Patients undergoing reimplantation surgery following a two-stage exchange procedure are at risk of developing recurrent infection [132,133]. The recurrent infection may be either due to incomplete eradication of the prior bacteria during the antibiotic spacer exchange or to a new infection. In order to properly address both potential scenarios, the appropriate preoperative antibiotic should include coverage of the prior organism as well as the most common infecting microorganisms.

Antibiotic-laden bone cement has been shown to decrease septic failure following TJA in high-risk individuals and it is US Food and Drug Administration-approved for use during reimplantation of components in a two-stage exchange. While there is no evidence to support the practice, it makes theoretical sense to add antibiotics that are effective in treating the index infection.

In a systematic review of 31 studies that compared the clinical outcomes achieved with one- and two-stage revision TKA with different types of spacers, the authors noted that after the index revision for infection, deep joint infection was detected in 0%–31% of cases. Of these, the infection was considered recurrent in 0%–18% of cases, while new infection rates varied from 0 to 31%. While the length of follow-up did not appear to influence the rate of recurrent infections, the studies with <4 years of clinical follow-up had fewer new infections [134].

Azzam et al retrospectively reviewed 33 patients who had failed an initial two-stage exchange arthroplasty, of whom 18 eventually went on to undergo a second two-stage procedure. Of this cohort, the isolated organism was different from the previous infecting organism in only one of 18 patients [132].

In a similar study, Kalra et al retrospectively reviewed 11 patients who developed reinfection after two-stage revision for infected THA and were subsequently treated with a two-stage re-revision. In their series, the infecting microorganisms were polymicrobial in 3 patients and only 2 had reinfection by the initial offending microbe [133].

In a review of the outcomes of 69 patients with PJ shoulder infection, Mont et al determined that in 8 of 9 cases reinfections were from the organism that had caused the initial infection, although in 6 of the 8 patients the sensitivity of the organism to antibiotics had changed [126].

Kubista et al published results on 368 patients treated with a two-stage revision for infected TKA. Of this cohort, 58 (15.8%) developed reinfection and a causative organism was identified in 47/58 (81%) of patients [135].

In a retrospective review of 117 patients who underwent two-stage exchange arthroplasty for PJ of the knee, 33 of 117 patients (28%) required reoperation for infection. At the time of reimplantation, antibiotic-laden bone cement (1.2 g tobramycin and 1 g vancomycin per 40 g of cement) was used for fixation of the prosthesis, but there was no note of the parenteral or perioperative antibiotics utilized at the second stage [136].

**QUESTION 15: For surgeries of longer duration, when should an additional dose of antibiotic be administered intraoperatively?**

**Consensus:** An additional dose of antibiotic should be administered intraoperatively after two half-lives of the prophylactic agent. The general guidelines for frequency of intraoperative antibiotic administration are provided. We recommend that re-dosing of antibiotics be considered in cases of large blood volume loss (>2000 cc) and fluid resuscitation (>2000 cc). As these are independent variables, redosing should be considered as soon as the first of these parameters are met.

**Delegate Vote:** Agree: 94%, Disagree: 5%, Abstain: 1% (Strong Consensus)

**Justification:**

In cases of large blood volume loss and fluid resuscitation there is a remarkable loss of the prophylactic agent that can result in levels below the MIC. The same is true for longer surgeries that extend beyond the half-life of the agent. Thus, additional antibiotic treatment is needed to re-establish antibiotic levels that exceed the MIC. An additional dose of antibiotic has been shown to reduce SSI rates in cardiac patients and should be administered intraoperatively after two half-lives of the prophylactic agent [3,74,75].

The AAOS recommendations for the use of IV antibiotic prophylaxis in primary TJA, recommendation 2, state that “timing and dosage of antibiotic administration should be such to optimize the efficacy of the therapy” [1]. Both the IDSA and AAOS state that “Additional intraoperative doses of antibiotic are advised when the duration of the procedure exceeds one to two times the antibiotic’s half-life or when there is significant blood loss during the procedure.” The general guidelines for frequency of intraoperative antibiotic administration are as follows: cefazolin every 2–5 (4) hours, cefuroxime every 3–4 hours, clindamycin every 3–6 hours, isoxazolyl penicillin every 3 hours, and vancomycin every 6–12 hours [2,137,138].

In a prospective multicenter study exploring the relationship between timing, duration, and intraoperative redosing of surgical antimicrobial prophylaxis and the risk of SSI, Steinberg et al determined that intraoperative dosing was associated with a lower infection risk only when the preoperative antibiotic was given in the recommended time frame. In 1,062 (24%) cases, the surgical procedure lasted for at least 4 hours. Because of a longer half-life and the reduced need for redosing, cases that received vancomycin or fluoroquinolones were excluded from the analysis of the impact of redosing on infection risk (n = 372). Intraoperative redosing was given in 21% of 690 of these long operations. Of the group that had a surgical procedure with a duration of >4 hours and who received the preoperative dose within one hour, 2 of 112 (1.8%) patients who were redosed intraoperatively developed infection, compared to 22 of 400 (5.5%) of those who were not re-dosed (OR 3.08, P = 0.06) [10].

Scher et al randomized 801 patients undergoing clean contaminated operations to one of three antibiotic regimens: 1 g of cefazolin preoperatively, 1 g of cefazolin preoperatively and another dose 3 hours later, and 1 g of cefotetan preoperatively. While all regimens demonstrated similar wound infection rates for surgeries lasting less than 3 hours, for those that exceeded 3 hours, the group that only received the single preoperative cefazolin dose had a statistically significant higher wound infection rate than those who received the second cefazolin dose (6.1% vs 1.3%, P < 0.01) [139].
Shapiro et al performed a placebo-controlled RCT to test the efficacy of perioperative cefazolin in preventing infection after abdominal or vaginal hysterectomy. The authors sub-analyzed the effect of surgery duration on the efficacy of perioperative prophylaxis by calculating adjusted relative odds of infection with and without prophylaxis for different durations of surgery and found that the efficacy of prophylaxis diminishes rapidly with increasing length of surgery; by 3 hours, 20 minutes prophylaxis had no measurable effect (OR = 1) [140].

Polk et al prospectively analyzed the antibiotic levels of 3 cephalosporins (cefazolin, cephalexin, and cephalothin) given as a single preoperative dose and found that acceptable concentrations of cefazolin were maintained near the incision site until 3 hours postadministration, whereas cephalothin did not maintain wound levels consistent with effective antimicrobial activity [141].

Ohge et al prospectively examined the pancreatic tissue concentrations of cefazolin in 10 patients undergoing pancreatectomy and determined the optimal intraoperative time to repeat the dose of cefazolin. Based on their results, the authors recommended a second dose of kefzol be given 3 hours after first administration in order to maintain adequate levels of antibiotic activity. They measured MIC for 4 bacterial species, namely 360 isolates of MSSA, 204 isolates of Klebsiella pneumoniae, 314 isolates of Escherichia coli, and 30 isolates of streptococcal species, and measured tissue levels of cefazolin. Antibiotic concentrations in adipose tissue and peritoneum 3 hours after administration of kefzol were lower than the MIC 80 for Escherichia coli, and streptococcal species [142].

In a retrospective review of 131 patients with primary colorectal cancer in prolonged operations exceeding 4 hours, the surgical wound infection rates were 8.5 and 26.5% respectively for those with (n = 47) and without (n = 49) intraoperative repeated dosing, which were significantly different based on both a univariate (P = 0.031) and a multivariate analysis (P = 0.008) [143].

Zanetti et al retrospectively compared the risk of SSIs in 1,548 patients who underwent cardiac surgery lasting >240 minutes after preoperative administration of cefazolin prophylaxis. The overall risk of SSI was similar among patients with (43 (9.4%) of 459) and without (101 (9.3%) of 1089) intraoperative redosing (OR 1.01, 95% CI 0.7–1.47). However, redosing was beneficial in procedures lasting >400 minutes; infection occurred in 14 (7.7%) of 182 patients with redosing and in 32 (16.0%) of 200 patients without (adjusted OR 0.44, 95% CI 0.23–0.86). Intraoperative redosing of cefazolin was associated with a 16% reduction in the overall risk for SSI after cardiac surgery, including procedures lasting >240 minutes [74,75].

Blood loss: Swoboda et al attempted to determine the effect of intraoperative blood loss on prophylactic cefazolin and gentamicin serum and tissue concentration in a prospective study of elective spinal surgical procedures with expected large blood loss. At 60 minutes after the incision, blood loss correlated with cefazolin tissue concentrations (r = −0.66, P = 0.05) and the clearance of gentamicin from the tissues (r = 0.82, P = 0.01). Based on their measured pharmacokinetic values, additional doses of cefazolin should be administered when the operation exceeds 3 hours and blood loss is greater than 1500 mL. A dose of gentamicin greater than 1.8 mg/kg should be administered more than 30 minutes prior to the surgical incision [144].

Blood loss/volume replacement: Markantonis et al investigated the effects of surgical blood loss and fluid volume replacement on gentamicin concentrations in serum and in 3 tissue types (subcutaneous fat, epiploic fat, and colonic wall) in patients undergoing colorectal surgery. Gentamicin was administered at a standard dose of 2 mg/kg and blood and tissue samples were obtained concurrently at specific times throughout each procedure. The mean concentration at first surgical incision was 7.83 (0.82) μg/mL and decreased to 2.60 (0.28) μg/mL at skin closure, resulting in borderline effectiveness even for susceptible gram-negative microorganisms (MIC-1.0). A strong negative correlation was found between the intravenously-administered fluids and gentamicin concentrations in serum and tissues (P ≤ 0.04) [145].

Klekamp et al prospectively studied orthopaedic patients with either large or small blood loss who also received vancomycin prophylaxis to determine the effect of intraoperative volume shifts on serum vancomycin concentrations. There were 6 index patients in the large blood loss group (greater than 2 L) and 7 in the control group (less than 2 L), with mean estimated blood loss for index and controls of 4.4 L and 1.0 L, and the mean intraoperative fluid resuscitation, excluding blood products, was 12.4 L and 5.1 L respectively. There was a modest inverse correlation between blood loss and the intraoperative serum half-life of vancomycin. Although controls maintained slightly higher intraoperative vancomycin concentrations at each time point, there was no statistically significant difference between the groups with regard to absolute concentrations or rate of decline. After 8 hours, the serum concentration of vancomycin exceeded the MIC-90 for S. aureus by approximately eightfold in all but one case patient, who was morbidly obese and had massive blood loss. Thus blood loss during orthopaedic procedures has a minimal effect on the intraoperative kinetics of vancomycin and administering vancomycin every 8–12 hours seems appropriate for most patients [146].

Two well-controlled studies of surgical prophylaxis with cefazolin similarly demonstrated minimal effects of blood loss on drug concentrations during THA and spine fusion procedures. Meter et al examined the effect of intraoperative blood loss and volume resuscitation during THA on serum levels of cefazolin in 18 patients. At 4 hours after administration, the serum level of cefazolin was 45 mcg/mL, which far exceeded the MIC for S. aureus (0.5 mcg/mL), despite an average intraoperative blood loss of 1137 ± 436 mL. This led the authors to conclude that even with blood losses of 2 L, it is not necessary to redose cefazolin any earlier than 4 hours in order to maintain the MIC for most common infecting organisms [147]. The authors repeated the study in 19 patients undergoing instrumented posterior spinal fusion and found that there was no significant difference between preoperative and intraoperative cefazolin clearance and there was no correlation between blood loss and cefazolin level [148].

**QUESTION 16: Should preoperative antibiotic doses be weight-adjusted?**

**Consensus:** Preoperative antibiotics have different pharmacokinetics based on patient weight and should be weight-adjusted.

**Delegate Vote:** Agree: 95%, Disagree: 4%, Abstain: 1% (Strong Consensus)

**Justification:**

Because of the relative unpredictability of pharmacokinetics in obese individuals, doses are best estimated on the basis of specific studies for individual drugs carried out in this population. Only a few antibiotics (aminoglycosides, vancomycin, daptomycin, and linezolid) have been studied in the obese population.

AAOS recommendations for the use of IV antibiotic prophylaxis in primary TJA, recommendation 2, state that “timing and dosage of antibiotic administration should optimize the efficacy of the therapy. Dose amount should be proportional to patient weight; for patients >80 kg, the doses of cefazolin should be doubled” [2].

The recommended dose of cefazolin is based on patient’s body mass index (BMI), with 1.0 g for people who weigh <80 kg, and...
2.0 g for those who weigh >80 kg. The adult dose of cefuroxime is 1.5 g. The recommended dose of clindamycin is 600–900 mg [61]. The recommended dose of vancomycin, which is based on BMI, is 10–15 mg/kg, up to a limit of 1 g, in patients with normal renal function [149]. However, there is literature to support the use of higher doses of vancomycin, with emphasis that doses >4 g/day have been associated with increased risk of nephrotoxicity. A trough level is obtained prior to the fourth scheduled dose and in certain occasions there may be a need to shorten dosing interval to maintain therapeutic trough level (eg q12h to q8h dosing).

Because 30% of adipose is water, an empirical approach is to use the Devine formula to calculate ideal body weight (IBW), to which is added a dosing weight correction factor (DWCF) of 0.3 times the difference between actual body weight (ABW) and IBW (ABW + 0.3 × [ABW − IBW]) to arrive at a weight on which to base dosage of hydrophilic antibiotics. No studies confirm this approach for β-lactam drugs. Clinical studies suggest a DWCF of 0.4 for aminoglycosides and 0.45 for quinolones [150].

For aminoglycosides, some suggest using ABW using a dosing correction factor [151,152], while others suggest dosing based on lean body weight (LBW) with appropriate monitoring with the first dose [153]. Current guidelines for vancomycin administration are based on loading doses of vancomycin on the total body weight (TBW) of the patient and maintenance doses on the calculated creatinine clearance (CrCl) of the patient [152,154]. However, deciding whether to base CrCl calculations on ABW, IBW, or another measure is still to be determined. As a general rule, obese and morbidly obese patients require higher doses of cephalexin to achieve similar outcomes; however, there are fewer absolute dosing recommendations. At least one study demonstrated that a dose of 2 g of cefazolin should provide adequate levels for at least 4 hours even in super morbid obesity (BMI ≥50 kg/m²) [155].

Other studies confirm that vancomycin should be given on the basis of ABW, with dosage adjustments based on serum concentrations [156] whereas aminoglycoside dosing requires calculation of adjusted body weight via a correction factor [157].

Forse et al conducted a prospective RCT in morbidly obese patients undergoing gastric bypass and found that the dose and tissue levels of cefazolin were significantly lower for all morbidly obese patients who received 1 g cefazolin compared with the blood and tissue levels of the drug found in normal weight patients who received a similar dose of antibiotic. Moreover, the morbity obese patients who only received 1 g of cefazolin had antibiotic levels below the MIC of 2 mcg/ml for gram-positive cocci and 4 mcg/ml for gram-negative rods. The serum and tissue concentrations were adequate only when 2 g of cefazolin were administered. Also, relative to 1 g, the administration of cefazolin 2 g decreased the wound infection rate from 16.5 to 5.6% in these morbidly obese patients [18].

Von Kralingen et al studied the influence of body weight measures and age on pharmacokinetic parameters and evaluated unbound cefazolin concentrations over time in obese patients. Twenty morbidly obese (MO) patients (BMI 38–79 kg/m²) were studied following the administration of 2 g of cefazolin at induction of anesthesia. Blood samples were collected up to 4 hours post dosing to determine the total and unbound plasma cefazolin concentrations. Cefazolin clearance was 4.2 ± 1.0 L/h (mean ± standard deviation) and showed a negative correlation with age (P = 0.003) but not with body weight measures (P > 0.05). In all patients, unbound cefazolin concentrations remained above 1 mg/L (MIC 90) of MSSA until 4 hours post dosing [158].

Ho et al attempted to determine an optimal dosing regimen for cefazolin as a prophylactic antibiotic in surgery for patients with morbid obesity. Twenty-five patients undergoing elective surgical procedures were given a single dose of cefazolin: 10 with MO (BMI 40–50 kg/m²) received 2 g via intravenous push (IVP), 5 with MO received 2 g via 30 minute infusion, 5 with super morbid obesity (SMO, BMI >50 kg/m²) received 2 g via infusion, and 5 with SMO received 3 g via infusion. The protective duration, determined using a pharmacodynamic target for IT > MIC of 70%, was 5.1 hours for MO-IVP, 4.8 hours for MO2-IVP, 5.8 hours for SMO2-IVP, and 6.8 hours for SMO3-IVP. The authors concluded that a single 2 g dose of cefazolin appears to provide antibiotic exposure sufficient for most common general surgical procedures of <5 hour duration regardless of BMI [155].

In contrast, Edmiston et al concluded that 2 g of cefazolin may not be sufficient for patients with a BMI ≥50 kg/m², based upon measurements of total serum concentrations in morbidly obese patients undergoing gastric bypass. The authors assigned 38 patients to one of 3 BMI groups: A) BMI = 40–49 kg/m² (n = 17), B) BMI = 50–59 kg/m² (n = 11), and C) BMI ≥ 60 kg/m² (n = 10) and measured serum and tissue concentrations of cefazolin. They determined that therapeutic tissue levels were only achieved in 48.1%, 28.6%, and 10.2% in groups A, B, and C respectively. The authors measured concentrations in the serum skin, adipose tissue, and omentum, but did not evaluate unbound cefazolin concentrations, which may be expected to migrate across tissues rapidly [159].

A table listing recommended dosing by weight is provided below:

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Actual Body Weight (ABW; kg)</th>
<th>Recommended Dose (mg)</th>
<th>Perioperative Redosing Interval (hours)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>&lt;60</td>
<td>1000</td>
<td>4</td>
<td>Primary Perioperative Prophylaxis</td>
</tr>
<tr>
<td></td>
<td>60–120</td>
<td>2000</td>
<td>4</td>
<td>Primary Perioperative Prophylaxis</td>
</tr>
<tr>
<td></td>
<td>&gt;120</td>
<td>3000</td>
<td>4</td>
<td>Primary Perioperative Prophylaxis</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>No adjustments</td>
<td>1500</td>
<td>6–12</td>
<td>Perioperative Prophylaxis for current MRSA carriers and/or patients with β-lactam allergy</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>No adjustments</td>
<td>900</td>
<td>3</td>
<td>Perioperative Prophylaxis for patients with β-lactam allergy</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>No adjustments</td>
<td>400</td>
<td>NA</td>
<td>Perioperative Prophylaxis for current MRSA carriers and/or patients with β-lactam allergy</td>
</tr>
</tbody>
</table>

**QUESTION 17A: What type of perioperative antibiotic prophylaxis is recommended for current MRSA carriers?**

**Consensus:** For current MRSA carriers, vancomycin or teicoplanin is the recommended perioperative antibiotic prophylaxis.

**Delegate Vote:** Agree: 86%, Disagree: 12%, Abstain: 2% (Strong Consensus)

**QUESTION 17B: Should patients with prior history of MRSA be re-screened? What should the choice of perioperative prophylactic antibiotics be in these patients?**

**Consensus:** Patients with prior history of MRSA should be re-screened preoperatively. If patients are found to be negative for MRSA, we recommend routine perioperative antibiotic prophylaxis.
Reinfection rates after revision surgery for endoprosthetic large bone defects, ranging from 5% to 35% in some series [162]. Common complications following endoprosthetic arthroplasty of Justi (Consensus):

Delegate Vote: Agree: 76%, Disagree: 23%, Abstain: 1% (Strong Consensus)

Implementation of an MRSA prevention program may significantly reduce MRSA SSIs. However, it is unlikely that any single MRSA-specific intervention (such as adding or switching to vancomycin) can optimally prevent SSIs. Several studies provide convincing data on the clinical effectiveness of vancomycin in preventing SSIs when MRSA prevalence is high [69,70,79]. Further research is needed to determine which components of an MRSA prevention program are essential in successfully preventing MRSA SSIs [160]. It is uncertain whether decontamination should alter the type of antibiotic prophylaxis, as few studies have retested patients’ MRSA status immediately prior to surgery.

The AAOS recommendations for the use of IV antibiotic prophylaxis in primary TJA, recommendation 2, state that “vancomycin may be used in patients with known colonization with MRSA or in facilities with recent MRSA outbreaks” [1]. Additionally, the Society for Healthcare Epidemiology of America recently recommended routine surveillance cultures at the time of admission to the hospital for patients at high risk of MRSA [52].

Walsh et al implemented a comprehensive MRSA program in which vancomycin was added to the routinecefazolin prophylaxis regimen for patients who tested positive for nasal MRSA carriage. Other components of the program included decolonization of all cardiothoracic staff who screened positive for nasal MRSA carriage, application of nasal mupirocin ointment for 5 days in all patients starting one day before surgery, application of topical mupirocin to exit sites after removal of chest and mediastinal tubes, and rescreening of patients for MRSA colonization at the time of hospital discharge. This program resulted in a significant reduction in the SSI rate (2.1% vs 0.8%, P < 0.001) as well as a 93% reduction in postoperative MRSA wound infections (from 32 infections/2,767 procedures during the 3 year preintervention period to 2 infections/2,496 procedures during the 3 year postintervention period). The data suggest that a bundled approach to preventing MRSA SSIs may be more critical than a single intervention [79].

Pofahl et al published on the impact of introducing MRSA screening programs and treatment of subsequent MRSA SSIs. After an MRSA surveillance program was instituted, the rate of MRSA SSI decreased from 0.23% to 0.09%, with the most pronounced reduction seen in TJA procedures (0.30%–0%, P = 0.04). However, the authors note that changes in perioperative antibiotics in MRSA-positive patients were at the discretion of the attending surgeon [161].

QUESTION 18: What is the recommended prophylaxis, in patients undergoing major orthopaedic reconstructions for either tumor or non-neoplastic conditions using megaprosthesis?

Consensus: Until the emergence of further evidence, we recommend the use of routine antibiotic prophylaxis for patients undergoing major reconstruction.

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

Justification:

Deep infection has been reported as being one of the most common complications following endoprosthetic arthroplasty of large bone defects, ranging from 5% to 35% in some series [162–168]. Reinfection rates after revision surgery for endoprosthetic infection have been reported as high as 43% [165]. Despite this there is insufficient evidence to suggest that a different perioperative antibiotic regimen is warranted. Recently a multicenter, blinded, randomized, controlled trial, using a parallel two-arm design has been set up (PARTITY study) that will evaluate 920 patients from Canada and the USA who are undergoing surgical excision and endoprosthetic reconstruction of a primary bone tumor. The patients will receive either short (24 hours) or long (5 days) duration postoperative antibiotics. The primary outcome will be rates of deep postoperative infections in each arm. Secondary outcomes will include type and frequency of antibiotic-related adverse events, patient functional outcomes and quality-of-life scores, reoperation and mortality [167].

Another area of development involves silver coating of foreign materials, such as heart valves, cardiac catheters, and urinary catheters that has shown the ability to reduce the infection rate of medical devices; therefore, a logical extension of this work was to translate this concept to the field of endoprosthetics [168,169]. Both basic science and clinical research suggest a decreased incidence of SSI and PJI in endoprostheses coated with silver. Recently iodine-supported titanium implants have been also effective for preventing and treating infections after major orthopaedic surgery [170,171].

In a rabbit study, the infection rate of silver-coated versus noncoated prostheses after inoculation with S. aureus was determined and the silver concentrations in blood, urine, and organs with possible toxic side effects were documented. The authors convincingly demonstrated that megaprostheses coated with silver showed a significantly lower infection rate (7% vs 47%, P = 0.05) in comparison with a titanium group [172]. Furthermore, measurements of C-reactive protein, neutrophil leukocytes, rectal temperature, and body weight showed significantly lower (P < 0.05) signs of inflammation in the silver group. In a second study, authors analyzed the potential toxicological side effects of these implants and found that the silver concentration in blood (median 1.883 parts per billion (PPB)) and in organs (0.798–86.002 PPB) showed elevated silver concentrations, without pathologic changes in laboratory parameters and without histologic changes of organs [173].

In a prospective observational study, Hardes et al compared the infection rate in 51 patients with sarcoma (proximal femur, n = 22; proximal tibia, n = 29) who underwent placement of a silver-coated megaprostheses to 74 patients (proximal femur, n = 33; proximal tibia, n = 41) in whom an uncoated titanium megaprostheses were used. The authors reported a substantial reduction in the infection rate from 17.6% in the titanium group compared to 5.9% in the silver group (P = 0.06). Furthermore, while 38.5% of patients ultimately underwent amputation when PJI developed, this was not necessary in any case in the study group. However, the authors note that the operating time required for the proximal tibia replacement was significantly shorter in the silver-coated prosthesis group (P = 0.034) and that prolonged operating time was associated with a higher rate of PJI (P = 0.025).

The same group reported a lack of toxicological side effects of silver-coated megaprostheses in 20 patients with bone metastases [172]. They reported that silver levels in the blood did not exceed 56.4 PPB and can be considered non-toxic. They further excluded significant changes in liver and kidney function based on laboratory values; and histopathologic examination of the periprosthetic environment in two patients showed no signs of foreign body granulomas or chronic inflammation, despite effective silver concentrations up to 1,626 PPB directly related to the prosthetic surface [172].

Tsuchiya et al reported that iodine-supported implants were used to prevent infection in 257 patients with compromised status. Acute infection developed only in 3 tumor cases and one diabetic foot among the 257 patients. Abnormalities of thyroid gland function were not detected. None of the patients experienced loosening of the
implants. Excellent bone ingrowth was found around all hip and tumor prostheses. The results indicate that iodine-supported titanium has favorable antibacterial activity, biocompatibility, and no cytotoxicity [170].

Gosheger reviewed 197 patients with megaprostheses and discovered that those with cobalt chrome implants had more infections than those with titanium implants [174]. Reviewing 197 patients (77 patients with a cobalt chrome alloy system and 120 patients with a titanium alloy system) who underwent lower extremity reconstruction with a megaprosthesi, the authors reported a 31.2% infection rate in the cobalt chrome group compared to 14.2% in the titanium group (P < 0.01). When they performed a secondary analysis matching two identical subgroups, the cobalt chrome group was still associated with a significantly higher infection rate, with 5 infections of 26 megaprostheses vs one infection of 36 titanium megaprostheses (P < 0.05) [175].

QUESTION 19: Should antibiotic prophylaxis be different in patients who have reconstruction by bulk allograft?

Consensus: We recommend the use of routine antibiotic prophylaxis in patients who have reconstruction by bulk allograft.

Delegate Vote: Agree: 93%, Disagree: 5%, Abstain: 2% (Strong Consensus)

Justification:

The periprosthetic area is inherently a locus minoris resistance. Bulk allograft is in essence a large foreign body and therefore represents a nidus for deep infection following surgery, apart from the prosthetic components. Additionally, bulk allografts are used most often in the setting of revision arthroplasty when there is frequently additional local soft tissue and vascular compromise, which compounds the risk for infection. Therefore, it would seem reasonable to want to modify the perioperative antibiotic protocol to protect these reconstructions. Unfortunately, there is insufficient literature to support altering antibiotic regimens, as most studies on the use of bulk allograft do not indicate or detail the antibiotic regimens utilized. Even if these data were available, it would not be accurate to properly compare the infection rates of different clinical series based on their perioperative antibiotic protocols because of the heterogeneity of patient populations. However, there is a growing body of literature to support the use of antibiotic-impregnated allograft in the revision setting as a means of decreasing infection rates. In addition, there are several reports of using antibiotic-impregnated graft substitute or grafts as a way to fill bony defects and promote bony ingrowth while delivering supratherapeutic doses of antibiotics to the local environment in cases of osteomyelitis. While there is no current literature applying this technology to the use of bone defects in infected revision arthroplasty, it may be a promising technique.

Witso et al used netilmicin-impregnated allografts for reconstruction in revision hip and knee surgery and found no adverse effects [176]. Buttaro et al favorably used vancomycin-supplemented cancellous grafts for reconstruction after infected THA [174,177]. Michalak et al and Khoo et al impregnated segmental allografts with gentamicin and fluoxacillin respectively [178,179]. However, all these groups used antibiotic impregnated grafts only in the second stage of a two-stage revision, after resolution of clinical and laboratory evidence of infection.

Winkler et al performed 37 one-stage uncemented revision THAs containing cancellous allograft bone impregnated with antibiotics and noted a 92% success rate, defined as recurrent infection at a mean follow-up of 4.4 years (range 2–8 years). In addition, no adverse effects were seen and the incorporation of bone graft was comparable to unimpregnated grafts [180].

In a similar series, Buttaro analyzed the incidence of infection after one-stage aseptic revision hip reconstruction using acetabular and/or femoral vancomycin-impregnated impacted bone allograft and a THA fixed with cement containing no antibiotic. In 75 consecutive patients (80 hips), followed for a mean of 36 months (range 24–59 months), deep infection occurred in one patient for an incidence of infection of 1.25%, which occurred 2 years after the index procedure and was thought to be hematogenous in origin [181].

Cancellous bone allograft can store and release high initial local amounts of vancomycin without compromising incorporation of the graft, and some favorable results have been published following two-stage revision of infected THA with this technique [174,177,182–184].

QUESTION 20: Do patients with poorly controlled diabetes, immunosuppression, or autoimmune disease require a different perioperative antibiotic prophylaxis?

Consensus: No. Routine antibiotic prophylaxis is recommended in these patients.

Delegate Vote: Agree: 90%, Disagree: 9%, Abstain: 1% (Strong Consensus)

Justification:

Several studies have demonstrated that diabetes mellitus (DM), especially uncontrolled DM, is a risk factor for postoperative infection in THA and TKA [185–188]. A recent retrospective cohort study within the Kaiser Healthcare system found no significant increase in risk of revision or deep infection or revision whether patients had controlled (HbA1c <7%) or uncontrolled diabetes (HbA1c >7%). Specifically, compared with patients without DM, there was no association between controlled DM and risk of revision (OR 1.32; 95% CI 0.99–1.76). Similarly, compared to patients without DM, there was no association between uncontrolled DM and risk of revision (OR 1.03; 95% CI 0.68–1.54) [189].

Obesity has also been associated with a significant increase in rate of postoperative infection following TJA [190–192].

Human immunodeficiency virus (HIV) has also been associated with an alarming rate of postoperative complications, including infection. Parvizi et al reported on 6 deep infections in 21 HIV-positive patients undergoing TJA. The authors remarked that the immune status of the patients was related to their risk of deep PJL, in that 5 of the 6 patients ultimately developed Acquired Immune Deficiency Syndrome (AIDS) and the CD4 count was significantly lower at 239 ± 112 μL at last follow-up for patients who developed infection compared to 523 ± 171 μL for the study population as a whole (P < 0.001). In this study the authors reported using prophylactic antibiotics (cephalosporins) preoperatively and 3 doses postoperatively and added antibiotic powder (vancomycin and tobramycin) to the cement in 2 patients thought to be at high risk for infection [193].

Similarly, Ragno et al found a very high postoperative infection rate (26.5%) in 34 TJAs in HIV-positive hemophiliacs, all of whom had CD4 counts less than 200/μL at time of surgery [194]. Haberman et al noted an infection rate of 12.7% in their cohort of 41 patients with HIV undergoing TJA, but did not identify any difference in the outcomes relating to CD4 count [195]. Their perioperative antibiotic protocol was a 5 day course of cefuroxime and in all procedures antibiotic-containing cement (Palacos R, Zimmer, Warsaw, IN) was used. In a smaller series of 6 HIV-infected patients undergoing TJA, Wang et al noted no infectious or other complications. The authors again used antibiotic (vancomycin)-impregnated bone cement in all cases [196]. Unger et al evaluated the results of 26 TKAs in HIV-positive hemophiliacs and found no cases of deep infection, but it is

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interesting to note that the average CD4 count of these patients was 463 μl [197].

Hemophilia has historically been considered a risk factor for PJI, due in part to its relation to HIV and AIDS, but also as an independent risk factor. An article by Silva et al reviewed the long-term results of primary TKA in patients with hemophilia and noted an overall prevalence of PJI of 16% with a rate of infection in HIV-positive and HIV-negative patients of 17% and 13% respectively (P = 0.5). The authors’ perioperative protocol included 3–5 days of prophylactic antibiotics and antibiotic cement was not used [198]. In contrast, Rodriguez-Marchan reported an infection rate of only 3% of 35 TJA in hemophilic patients, but used antibiotic-laden bone cement and 2 days of perioperative antibiotic prophylaxis [199].

Asplenic patients are at increased risk of infection by encapsulated bacteria; and although there is evidence to support vaccinations and penicillin prophylaxis in patients under 16 and over 50 years of age, there is no consensus on the appropriate perioperative management of these immunocompromised patients. In a single case report by Shaarani et al of an asplenic patient who underwent a TKA, the patient ultimately developed an MRSA infection. In this case standard polymethylmethacrylate (PMMA) was used for cementing components and the patient received intravenous prophylactic dose of second generation cephalosporin preoperatively [200].

Renal disease (including renal failure, dialysis dependence, and renal transplant) has been implicated as increasing the risk of PJI. Mc Cleery et al analyzed the Scottish Arthroplasty Registry in order to determine the rates of PJI in patients with renal failure, those undergoing dialysis, and those patients with a renal transplant. They found that patients with renal failure had a significantly increased risk of early infection (1.6%, RR 1.52, P = 0.02) and late infection (4.47%, RR 2.2, P < 0.001). Patients on dialysis had a significantly increased risk of late infection (8.0%, RR 3.99, P < 0.001) and early revision (3.2%, RR 4.4, P < 0.001). Renal transplant patients had a significantly increased risk of late infection, despite whether the transplantation occurred before TKA (9.1%, RR 4.5, P = 0.03) or at any time (8.0%, RR 4.0, P = 0.05) [201]. Liebermann et al documented a deep infection rate of 19% in 16 chronic renal dialysis patients and more favorable outcomes in renal transplant patients [202]. Sakalkale et al reported a deep infection rate of 13% in 12 patients with end-stage renal failure on dialysis who underwent TJA. In this study, perioperative prophylactic antibiotics were administered for 2–5 days [203]. In contrast, other authors have reported no increased rate of infection in patients on chronic hemodialysis undergoing TJA [204,205].

Similarly, liver disease has been associated with increased morbidity following TJA. Pour et al performed a case control study of 71 non-cirrhotic patients with hepatitis C undergoing TJA and found that this cohort had higher rates of wound drainage following TJA when compared to matched controls (15 vs 3.8%, P = 0.03) [206]. Orozco et al recently published a case control study to analyze the effect of fibrosis and thrombocytopenia on the diagnosis of hepatitis C and clinical outcomes. Analyzing 72 patients (77 joint replacements), the authors found that fibrotic hepatitis C patients had higher deep infection rates (21 vs 0%, P = 0.047) and rates of cellulitis (21 vs 0%, P = 0.047), while thrombocytopenia showed a trend towards greater infection [207].

Solid organ transplant (SOT) is a risk factor for PJI due to the need for chronic use of immunosuppressant medications. Vergidis et al performed a case control study of patients with SOT who developed PJI and compared them to non-infected controls matched by transplant type, prothetic joint type, and order of organ transplantation or joint implantation. Of 367 patients with both a joint replacement and SOT, there were 12 cases of PJI, of which 8 were renal transplants, 3 were liver transplants, and 1 was a heart transplant patient. Eight infections were caused by gram-positive organisms, 2 were caused by nonnontuberculous mycobacteria, and the remaining 2 were culture negative. Of note, patients received perioperative cefazolin, or in cases of colonization or prior infection with MRSA, vancomycin [208]. Tannenbaum et al reported results on 35 TJA in 19 patients with renal or liver transplant and documented an infection in 5 patients who had the joint arthroplasty after the transplantation. There were no infections in patients who had TJA before the organ transplantation. In this series, prophylactic antibiotics were administered for at least 48 hours or until the drains were removed and bone cement when used was not impregnated with antibiotics [209].

QUESTION 21A: Should preoperative antibiotics be different for primary and revision TJA?

Consensus: No. Perioperative antibiotic prophylaxis should be the same for primary and uninfected revision arthroplasty.

Delegate Vote: Agree: 89%, Disagree: 10%, Abstain: 1% (Strong Consensus)

QUESTION 21B: Should preoperative antibiotics be different for hips and knees?

Consensus: Perioperative antibiotic prophylaxis should be the same for hips and knees.

Delegate Vote: Agree: 99%, Disagree: 1%, Abstain: 0% (Strong Consensus)

Justification:

Patients undergoing revision TJA are at higher risk of developing PJI than primary arthroplasty and those undergoing revision knee procedures are at even highest risk [210–212]. One recent study has effectively demonstrated targeting infection prevention programs at high-risk surgical patients that take into account an institution’s local epidemiology and antibiogram [213].

Liu et al determined the impact of adding vancomycin to cefazolin as antimicrobial prophylaxis in 414 patients undergoing revision TKA based on a notable increase in PJI in revision TKA patients, with many being methicillin-resistant. Following introduction of vancomycin to the routine perioperative antibiotic prophylaxis, the infection rate decreased from 7.8% to 3.1% (P = 0.046). In particular, a significant reduction in PJI resulting from methicillin-resistant organisms over this time period was seen (4.2% to 0.9%, P = 0.049) [214].

QUESTION 22: What is the best antibiotic prophylaxis to choose for patients with colonization by carbapenem resistant enterobacteriaceae or MDR-Acinetobacter spp?

Consensus: There are insufficient data to recommend expanded antibiotic prophylaxis in patients known to be colonized or recently infected with multi-drug resistant (MDR) pathogens.

Delegate Vote: Agree: 76%, Disagree: 8%, Abstain: 16% (Strong Consensus)

Justification:

There is an increasing awareness of the threat posed by K. pneumoniae strains with decreased susceptibility to carbapenems worldwide [215]. This resistance is conferred by K. pneumoniae...
carbapenemase (KPC), which is a β-lactamase that also confers resistance to broad-spectrum cephalosporins, as well as commercially available β-lactam/β-lactamase inhibitor combinations [216]. As there are few antimicrobial options, prevention of *K. pneumoniae* carbapenemase *K. pneumoniae* (KPC-KP) has become a major priority of those studying nosocomial infections [217].

While there is no evidence on the management of surgical antimicrobial prophylaxis in a patient with past infection or colonization with a resistant gram-negative pathogen, it is logical to provide prophylaxis with an agent active against MRSA for any patient known to be colonized with this gram-positive pathogen who will have a skin incision; specifically, prophylaxis for a resistant gram-negative pathogen in a patient with past infection or colonization with such a pathogen may not be necessary for a purely cutaneous procedure.

In a literature review, KPC-producing microbes are resistant to many non-β-lactam molecules. Most isolates are resistant to fluoroquinolones, aminoglycosides, and co-trimoxazole. Some isolates are susceptible to amikacin and gentamicin and most are susceptible to colistin and tigecycline [214,215,218,219].

In a prospective RCT, De Smet et al studied the elimination of colonization with MDR organisms using selective oropharyngeal and/or digestive tract decontamination (SOD/SDD) in a multicenter crossover study using cluster randomization of 5,939 intensive care unit patients in the Netherlands. SDD included 4 days of intravenous cefotaxime and topical application of tobramycin, colistin, and amphotericin B in the oropharynx and stomach. SDD consisted of oropharyngeal application only of the same antimicrobials. Using a random effects logistic regression analysis, the OR for death at day 28 in the SOD and SDD group, as compared with the standard care group, were 0.86 (95% CI 0.74-0.99) and 0.83 (95% CI 0.72-0.97) respectively [220].

Perez et al used a mouse model to examine the effect of antibiotic treatment on the establishment and elimination of intestinal colonization of KPC-KP. They administered 3 days of antibiotics (clindamycin, zosyn, tigecycline, etepenem, and ciprofloxacin) before KPC-KP was administered orogastrically. The authors reported that of the 4 antibiotics with minimal activity against the KPC-KP strain (MIC >16 mcg/mL), those that suppressed total anaerobes and Bacteroides (ie clindamycin and zosyn) promoted colonization by KPC-KP (P = 0.001), while agents that did not suppress total anaerobes and Bacteroides (ie ciprofloxacin and cepofloxacin) did not (P = 0.35). Of the antibiotics with moderate activity against KPC-KP, etepenem (MIC 4 mcg/mL) did not promote colonization by KPC-KP, while tigecycline (MIC 3 mcg/mL) did (P < 0.001), despite not reducing levels of total anaerobes and Bacteroides. Orogastroduodenal administration of gentamicin and polymyxin E-suppressed KPC-KP is of undetectable levels in the majority of mice. The authors posited that antibiotics that disturb the intestinal anaerobic microflora lack significant activity against KPC-KP promote colonization, while the administration of non-absorbed oral antibiotics may be an effective strategy to suppress colonization with this microorganism [221].

References


