

QUESTION 9: What are the indications for dual perioperative antibiotic prophylaxis in patients undergoing orthopaedic procedures? What are the optimal combinations of antibiotics?

RECOMMENDATION: In the absence of high-level data, we recommend that dual antibiotic prophylaxis should be reserved only for patients at high risk of infection, such as those undergoing revision surgery or at high risk for methicillin-resistant *S. aureus* (MRSA) infection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 80%, Disagree: 15%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

A comprehensive literature review was performed to identify all studies related to the indications for dual antibiotic prophylaxis in patients undergoing orthopaedic surgery as well as the optimal combination of antibiotics. Searches for the terms “total joint arthroplasty,” “orthop(a)edic,” “antibiotic prophylaxis,” “dual” and “combination” in various combinations and with different Boolean operators were performed through February 2018 using the search engines Medline, Embase and Cochrane. Inclusion criteria for our systematic review were all English studies (level I to IV evidence) that reported on dual perioperative antibiotics for total joint arthroplasty. Exclusion criteria were non-English language articles, studies over ten years old, non-human studies, retracted papers, case reports, review papers, studies with less than ten patients in the sample size, studies without clinical follow-up/infection rates and technique papers without patient data. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria were followed. The initial search resulted in 2,283 papers. After removal of duplicates, 201 titles were evaluated, 35 full-text papers were read and 13 studies met the full inclusion and exclusion criteria to allow for the analysis.

While the use of first or second-generation cephalosporins is recommended as first-line perioperative antibiotics due to their broad range of pathogen coverage [1–3], patients who are proven or potential carriers of MRSA or those with a cephalosporin allergy (not penicillin allergy) may receive alternative antibiotics. For penicillin-allergic patients, the use of a third or fourth-generation cephalosporin (such as cefuroxime and ceftriaxone) with dissimilar side chains than the offending penicillin carries a negligible risk of cross-reaction [4]. The most common alternative used is vancomycin that has poor gram-negative coverage and should not be used as monoprohylaxis; and, hence its use should be combined with another antibiotic such as an aminoglycoside for gram-negative coverage. In addition, vancomycin dosing should be weight-based at 15 mg/kg [5]. Recent studies have demonstrated that vancomycin monotherapy is associated with an increased risk of infection compared with ceftazolin [5,6], particularly by gram-negative organisms [7]. Furthermore, despite the reduction in the rate of MRSA infections, vancomycin should be used with caution due to the potential for the emergence of organism resistance, most notably vancomycin-resistant *enterococcus* (VRE) and vancomycin-resistant *Staphylococcus aureus* [8], and its potential for nephrotoxicity [9]. There are no randomized controlled trials, but there are several retrospective studies examining the use of dual perioperative antibiotic prophylaxis (Table 1).

TABLE 1. Summary of studies that evaluated the efficacy of dual antibiotic prophylaxis including a beta-lactam and a glycopeptide

Author/Year	Type of Study (Period)	Type of Surgery	Antibiotic Prophylaxis (n)*	Outcome	Infection Rate (P-value)	MRSA Rate
Capdevila 2016 [22]	Retrospective cohort study (2012-2013)	Femoral neck fracture	Cefuroxime 1.5 gm induction of anaesthesia + 1.5 gm after 2h + teicoplanin 800 mg (657)	SSI according to CDC criteria	2%	0.15%

Sewick 2012 [10]	Retrospective cohort study (2008-2010)	Primary THA and TKA	Cefazolin (500) vs. cefazolin + vancomycin (1328)	SSI according to CDC criteria	1.4% vs. 1.1% (> 0.05)	0.8% vs. 0.07%
Ponce 2014 [6]	Retrospective cohort study (2005-2009)	Primary THA and TKA	Cefazolin (15422) vs. vancomycin (1500) vs. cefazolin + vancomycin (1062) vs. clindamycin (846)	SSI	1.3% vs. 2.3% vs. 1.5% vs. 1.1% (< 0.05 for cefazolin vs. vancomycin)	Information not collected
Tornero 2015 [20]	Retrospective cohort, before and after changing the prophylaxis regime (2010-2013)	Primary THA and TKA	Cefuroxime 1.5 gm induction of anaesthesia + 1.5 gm after 2h (995) vs. cefuroxime + teicoplanin 800 mg (791)	PJI according to MSIS criteria	3.5% vs. 1.3% (< 0.05)	0.5% vs. 0%
Branch-Elliman 2017 [12]	Retrospective cohort study (2008-2013)	Primary THA and TKA	Single (beta-lactam or vancomycin) vs. beta-lactam + vancomycin	SSI within 30 days	1.26% vs. 1.43% ($p > 0.05$)	Information not collected
Burger 2018 [18]	Retrospective cohort study (2012-2016)	Primary THA and TKA	Cefazolin (1044) vs. cefazolin + vancomycin 1 gm B45 (476) vs. cefazolin + vancomycin W45 1 gm (477)	PJI according to MSIS criteria	2.1% vs. 0.2% vs. 2.9% ($p = 0.01$)	0.4% vs. 0% vs. 0.3%
Liu 2014 [13]	Retrospective cohort, before and after changing the prophylaxis regime (2009-2012)	Revision TKA	Cefazolin (190) vs. cefazolin + vancomycin 1 gm (1.5 gm > 80 kg) (224)	SSI according to CDC criteria	7.89% vs. 3.13% (< 0.05)	2.63% vs. 0%

CDC, Centers for Disease Control and Prevention; MSIS; Musculoskeletal Infection Society; PJI, prosthetic joint infection; SSI, surgical site infection; THA, total hip arthroplasty; TKA, total knee arthroplasty; B45, vancomycin infusion was initiated 45 minutes before the surgical incision; W45, vancomycin infusion was initiated less than 45 minutes before the surgical incision.

* Antibiotic dose is given when the information was provided in the report.

Sewick et al. [10] retrospectively reviewed 1,828 primary total joint arthroplasties (TJAs) that received either a dual antibiotic regimen of cefazolin and vancomycin or received cefazolin alone in order to determine the rate of surgical site infections (SSIs) as well as the microbiology of subsequent SSIs. There were 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, $p = 0.636$). However, while the addition of vancomycin to cefazolin did not decrease the rate of SSIs, it did decrease the incidence of MRSA infections (0.08 vs. 0.8% $p = 0.022$), but with a high number needed to treat. Ponce et al. [6], in a recent study, reported that there was no difference in SSI rate between patients receiving cefazolin monotherapy or cefazolin plus vancomycin. Elliot et al. [11] developed an economic model to explore the cost-effectiveness of vancomycin and/or cephalosporin as antibiotic prophylaxis in patients undergoing total hip arthroplasty (THA). Combination therapy (such as vancomycin plus a cephalosporin) was recommended when the rate of MRSA SSI was 0.25% or greater, and the rate of non-MRSA SSI was 0.2% or greater. Branch-Elliman et al. [12] demonstrated that dual antibiotics (beta-lactam plus vancomycin) versus single antibiotic (vancomycin or a beta-lactam) had no differences in SSI rates after total joint arthroplasty (1.43 vs. 1.26%, adjusted rate ratio (RR): 1.09).

While the literature does not support the use of dual antibiotics for primary TJA, a recent study by Liu et al. [13] has demonstrated that the targeted use of vancomycin and cefazolin among patients undergoing revision total knee arthroplasty (TKA) significantly reduced the rate of overall infections (7.89 to 3.13%, $p = 0.046$), particularly MRSA (4.21 to 0.89%, $p = 0.049$). It is important to note that the author's institution had a high baseline rate of PJIs due to MRSA and methicillin-susceptible *S. epidermidis* (MRSE). Thus, there may be a potential indication to use a combination of cefazolin and vancomycin for high-risk surgical patients, including revision cases where infection risk is higher than a primary TJA or in regions or institutions with high MRSA rates.

Ahmed et al. [14] retrospectively reviewed 1,500 patients undergoing hip fracture surgery comparing the use of gentamicin plus flucloxacillin (dual antibiotics) vs. cefuroxime alone in order to evaluate the rate of deep SSIs. Paradoxically, there was an increase in deep SSIs in the dual antibiotic group compared to the cefuroxime group (2.5 vs. 1.1%), reaching statistical significance ($p = 0.036$).

Another precaution for using dual antibiotics is the propensity for developing acute kidney injury, which is not an infrequent situation with the use of antibiotic combinations, particularly those including gentamicin [15–17] and vancomycin [9]. It should be noted that in the study by Courtney et al. [9], dual antibiotic (vancomycin plus cefazolin) prophylaxis was found to be an independent risk factor for acute kidney injury (AKI) after primary THA/TKA (adjusted odds ratio (OR): 1.82, 95% confidence interval (CI) 1.25 to 2.64, $p = 0.002$). In contrast, Burger et al. [18] did not find a higher difference in renal toxicity when combination antibiotic prophylaxis was used. A potential explanation is that in the first study is that vancomycin was administered for 24 hours, while in the second study only one intraoperative dose of vancomycin was given. Since teicoplanin is less nephrotoxic than vancomycin and could be infused in < 20 minutes with a very low risk of Redman Syndrome, we consider that teicoplanin should be the glycopeptide of choice in countries that have it available. The recommended dose is 800 mg administered during the induction of anaesthesia. Since teicoplanin is not available in the USA, vancomycin would still be the first-line option. Current guidelines [2] recommend that the administration of 15 mg/kg of vancomycin (according to actual body weight) in order to obtain a serum concentration ≥ 15 mg/L until the completion of surgery. In order to avoid Redman Syndrome, it should be infused at a maximum rate of 1 gm per hour. A recent study showed that only 28% of cases received a correct dose of vancomycin [5]. The authors calculated the expected levels using pharmacokinetic equations and demonstrated that a weight-based protocol would have resulted in fewer patients having unacceptably low vancomycin levels (< 15 mg/L). Indeed, a previous study in cardiac surgery demonstrated that a dose of 20 mg/kg resulted in achieving therapeutic vancomycin levels in all patients [19]. Therefore, it is necessary to adjust the vancomycin dose based on body weight.

As mentioned above, when using dual antibiotics, teicoplanin can be used as an alternative to vancomycin. It can be infused over 20 minutes without the risk of Redman Syndrome and has a better safety profile than vancomycin. Tornero et al. [20] showed a reduction in the rate of PJIs when using teicoplanin and cefuroxime in combination was compared to cefuroxime as monotherapy (1.26 vs. 3.51%, $p = 0.002$). Soriano et al. [21] demonstrated similar results when evaluating antibiotic prophylaxis for patients with femoral neck fractures undergoing surgery and found that the combination of teicoplanin and cefuroxime reduced infection rates compared to cefuroxime as monotherapy (2.36% vs. 5.07%, $p < 0.05$). In a follow-up study from the same institution, Capdevila et al. [22] retrospectively reviewed the rate of infection in the same cohort ten years after the implementation of dual antibiotic prophylaxis in patients with femoral neck fractures and found that the rate of infection remained low at 2%.

Bosco et al. [23] demonstrated that the addition of an EGNAP (expanded gram-negative antimicrobial prophylaxis), such as gentamicin or aztreonam, to cefazolin decreased the rate of PJIs in patients undergoing primary THA but not in TKAs. This is partly because at their institution, gram-negative organisms caused 30% of the SSIs following hip procedures and only 10% of SSIs after knee procedures.

One should note the importance of timing of administration of vancomycin. Burger et al. included in their analysis the moment of starting vancomycin infusion. In one group, vancomycin administration was initiated 45 minutes before the surgical incision, and, in the other group, the infusion was initiated less than 45 minutes before the surgical incision. The infection rate was significantly

lower when the infusion of vancomycin was started earlier than the group who had the infusion closer to the start of the procedure [18].

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