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CORR Insights®: Vancomycin Prophylaxis for Total Joint Arthroplasty: Incorrectly Dosed and Has a Higher Rate of Periprosthetic Infection Than Cefazolin

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Where Are We Now?

In 2010, US patients underwent more than 1 million total joint arthroplasties (TJAs), and the number is projected to reach 4 million by 2030 [4, 10]. With a recent

surveillance study reporting a post-TJA infection risk of 2% in the United States [19], it seems likely that there were tens of thousands of post-TJA infections in 2010 alone. If we cannot decrease the infection rate, there will be approximately 80,000 in 2030. These patients generally experience multiple operations, long periods of disability, and extended treatment with antibiotics [7], all of which contribute to a major economic burden [9].

In the past 15 years, we have seen a rise in the prevalence of methicillin-resistant staphylococci [1, 15], leading to an intense debate about switching the routine approach to antimicrobial prophylaxis from a cephalosporin to a glycopeptide. In addition, 10% to 20%

of patients undergoing TJA self-report allergy to penicillin [13, 17], and many of them receive vancomycin as prophylaxis under current guidelines [3].

Recent studies [2, 5, 6] comparing beta-lactams to glycopeptides found no differences in effectiveness for preventing surgical site infection. For the glycopeptide cohort, infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) were less frequent and were offset by an increase in both methicillin-sensitive *S aureus* (MSSA) and Gram-negative bacilli (GNB). These findings are not entirely surprising considering that vancomycin has a lower bactericidal activity than beta-lactams against susceptible staphylococci and has no activity against GNB [17]. More worrisome are the results from the current study and another recent study [16], which showed a higher risk of infection using prophylaxis with vancomycin alone.

Prophylaxis with vancomycin alone reduces MRSA infections, but it is associated with a higher risk of MSSA and GNB compared to cephalosporins.

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Indeed, vancomycin is associated with a lower cure rate than beta-lactams in patients with MSSA bacteremia [11]. A potential explanation, among others, could be insufficient vancomycin dosing [6]. There are no data directly evaluating the best prophylactic dose of vancomycin, but current guidelines [3] recommend the administration of 15 mg/kg (according to actual body weight) in order to obtain a serum concentration ≥ 15 mg/L until the end of surgery. Unfortunately, the standard protocol in many centers is 1 g of vancomycin, without regard for body weight.

Where Do We Need To Go?

The current study's findings raises the question whether higher doses should be evaluated. A recent study in cardiac surgery demonstrated that 20 mg/kg resulted in all patients achieving therapeutic vancomycin levels [8].

There are other questions to consider: (1) Using weight-based dosing regimens means that some patients will receive more than 1 g of vancomycin, resulting in infusion times exceeding 60 minutes. How disturbing is this for the normal function of operating theaters? (2) In vascular surgery, Payne and colleagues [14] administered 1 g of vancomycin over 2

hours if the patient weighed < 70 kg or 1.5 g over 2.5 hours if (s)he weighed ≥ 70 kg, followed by a constant infusion of 0.5 g to 2.5 g according to renal function, which was maintained for 24 hours. Is continuous infusion of vancomycin a potential solution to guarantee a stable and sufficient concentration during surgery? (3) For patients who are colonized with heteroresistant vancomycin-intermediate *S aureus*, is it necessary to increase the vancomycin dose, or should we consider alternatives such as daptomycin, linezolid, or dalbavancin? (4) Merrer and colleagues [12] did not find an increased risk of vancomycin-resistant enterococci or staphylococci colonization in a cohort of patients receiving vancomycin as prophylaxis. But is more data still needed, considering there are populations where these resistant strains are widespread? (5) Considering the lack of vancomycin activity against GNB, should a second antibiotic be added to the regimen for patients who receive vancomycin as primary prophylaxis?

How Do We Get There?

For patients who are not at risk for MRSA, first- or second-generation cephalosporins remain the standard antibiotic prophylaxis, however, only a small number have severe cephalosporin

allergies. Orthopaedic surgeons should be aware that vancomycin monotherapy is less effective than cephalosporins against methicillin-sensitive staphylococci, which are among the most common pathogens in periprosthetic joint infections (PJIs). Therefore, it is necessary to take a precise medical history to differentiate between adverse events (abdominal pain, nausea, vomiting) and allergic reactions (rash, oedema). If there is any doubt, orthopaedic surgeons should perform a skin test to (1) determine whether the so-called allergy is indeed an allergic reaction at all, and (2) whether the penicillin-allergic patient is also allergic to cephalosporins, since in fact most are not [13]. This is important, since the large majority of patients with true penicillin allergies still can take cephalosporins, which remain the preferred prophylaxis for routine TJA. Establishing a clinical pathway in a preoperative clinic, including allergy consultation consisting of penicillin and cephalosporin skin testing, will reduce vancomycin overuse. In the few patients with documented cephalosporin allergy, the current recommendation is vancomycin. However, this antibiotic is not active against GNBs. Therefore, for this specific patient population, vancomycin should be combined with an aminoglycoside or fluoroquinolone.

Beyond patients with cephalosporin allergy or colonized by MRSA, the

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incidence of PJI due to methicillin-resistant coagulase-negative staphylococci is increasing [1, 15] and it is higher in particular subgroups of patients such as those with obesity or rheumatoid arthritis. Therefore, it is time to evaluate the potential benefit of dual prophylaxis by adding a glycopeptide in an effort to globally reduce the incidence of PJI. Tornero and colleagues [18] found that adding 800 mg of teicoplanin to cefuroxim during primary arthroplasty considerably reduced the risk of PJI and a major benefit was observed in patients with obesity (BMI ≥ 30 kg/m²). A randomized and double-blind clinical trial comparing a cephalosporin to dual prophylaxis (cephalosporin plus teicoplanin) could confirm this finding.

In addition, the study should evaluate the prevalence of multidrug resistant micro-organisms in nares and feces of patients at baseline and after antibiotic prophylaxis to determine the impact on normal bacterial flora when dual prophylaxis is chosen. In the future, it will be beneficial to individualize antibiotic prophylaxis based on the current and potential risk factors for infection.

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