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Editor's Spotlight/Take 5: Vancomycin Prophylaxis for Total Joint Arthroplasty: Incorrectly Dosed and Has a Higher Rate of Periprosthetic Infection Than Cefazolin

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Weight-based dosing of medications is not a foreign concept to most of us. We learned it in medical school, especially while rotating on the pediatrics service. We did it while in residency, ordering weight-based gentamicin for certain open fractures [10]. And when we order antibiotics for

treatment, we sometimes adjust the dose to ensure therapeutic dosing. But for prophylactic antibiotics before surgery, somehow the fixed 1-g dose has become common practice. Most patients receive a 1-g dose of cefazolin, and for those patients with a beta-lactam allergy, 1-g dose of vancomycin is sometimes substituted. But patients come in different sizes.

There is good evidence suggesting that failing to recognize this may increase the risk of prosthetic joint infection (PJI). A recent study [21] looking at trabecular bone harvested from patients who underwent TKA demonstrated that vancomycin levels

in bone varied with BMI, where higher concentrations were seen in patients with lower BMI. Additionally, the study points to the pharmacokinetic properties of vancomycin, where it has greater deposition in soft tissues when compared to cefazolin; therefore, a smaller proportion of vancomycin is available in trabecular bone. Surgeons may use vancomycin for prophylaxis in patients colonized with methicillin-resistant *Staphylococcus aureus* (MRSA), and this practice may become more widespread as the prevalence of MRSA infection is increasing [9, 19]. However, we sometimes use vancomycin for patients with a history of penicillin allergy, a practice that perhaps should be abandoned. There is, in fact, little risk that a patient with a reported allergy to penicillin will experience anaphylaxis when given cefazolin [3, 14].

The question we are most concerned about, though, is whether patients are adequately dosed with whatever antibiotic they do receive, and whether those who are underdosed

A note from the Editor-In-Chief:
In "Editor's Spotlight," one of our editors provides brief commentary on a paper we believe is especially important and worthy of general interest. Following the explanation of our choice, we present "Take Five," in which the editor goes behind the discovery with a one-on-one interview with an author of the article featured in "Editor's Spotlight."

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are more likely to develop PJI, which is a dreaded complication. In this context, the work of Dr. Kheir and his team from Thomas Jefferson University in Philadelphia, PA, USA should matter to all orthopaedic surgeons. They found that among primary TJAs, patients receiving vancomycin had a higher rate of PJI compared with patients receiving cefazolin prophylaxis, and that the majority of patients given vancomycin prophylaxis were underdosed based on the weight-based dosage recommendations. In a glimmer of bright news, MRSA did not occur in patients who were adequately dosed with vancomycin. In addition to adequate dosing, this paper gives us an important reminder that surgeons should use vancomycin judiciously and rarely as a sole agent. Please join me for the Take-5 interview with Dr. Michael M. Kheir, as we dig deeper into this critically important clinical problem.

Take-5 Interview with Michael M. Kheir MD, primary author of “Vancomycin Prophylaxis for Total Joint Arthroplasty: Incorrectly Dosed and Has a Higher Rate of Periprosthetic Infection Than Cefazolin”

M. Daniel Wongworawat MD: *What prompted your interest in looking at*

Michael M. Kheir MD

compliance with vancomycin dosing recommendations? Why did you think there might be low acceptance/implementation of the weight-based dosing guidelines for vancomycin administration?

Michael M. Kheir MD: As a large institution, we have surgeons with diverse practices—some who administer vancomycin prophylaxis routinely, and others only in light of patient-specific factors such as being MRSA-positive or having a history of anaphylaxis to penicillin. We were interested in studying this because recent guidelines have demonstrated that vancomycin should be weight-based [2, 7], yet many surgeons at our practice and around the country are accustomed to a fixed 1-g dose of vancomycin.

The low acceptance of weight-based dosing guidelines may simply be due to unawareness. The guidelines

were introduced in the last few years [2, 7], and although they are well-known among infectious disease specialists, orthopaedic surgeons and anesthesiologists may be less familiar since they are not traditionally trained to give weight-based doses of antibiotics. This puts the onus on orthopaedic surgeons to seek consultation and guidance with infectious disease colleagues. Furthermore, with increasing prevalence of obesity in the United States, the “standard” doses that once were given appear no longer to apply to contemporary practice. Finally, there seemed to be lack of evidence showing whether switching to a weight-based dose made any noticeable clinical differences.

Dr. Wongworawat: *Previous studies suggest an increased risk of acute kidney injury [11]. Based on your findings and recommendations for weight-based dosing, many patients will need higher doses. Are you concerned about the risk of acute kidney injury?*

Dr. Kheir: It is reasonable to be cautious and to monitor kidney function when you are increasing the administered dosage of a nephrotoxic drug like vancomycin, for all patients and particularly in patients with chronic kidney disease. Using higher doses highlights the importance of having medical comanagement with hospitalists to monitor serum creatinine and glomerular filtration rates. In our

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study, however, we did not find any difference in the rate of acute kidney injury among the various dosage groups, which is encouraging data to support weight-based dosing, even if that results in giving more than 1 g of vancomycin.

Dr. Wongworawat: *The risk of MRSA PJI was higher in patients underdosed with vancomycin. Might the difference in PJI risk between vancomycin alone versus cefazolin alone diminish if patients were adequately dosed?*

Dr. Kheir: That is a great point and may certainly be the case, which would require further study with a larger sample size of an adequately dosed vancomycin group. It is difficult to determine in our study since most patients were given a fixed 1-g dose of vancomycin. Furthermore, patients may have been selected to receive vancomycin based on other variables such as colonization or history of MRSA, and these confounding variables were not taken into account. However, the PJI rate in our adequately-dosed group was no different than the PJI rate across all vancomycin dosage groups (2%), which is higher than the PJI rate in the cefazolin group (1%). This direct comparison without accounting for confounding variables does suggest that we may still find a difference in PJI risk between vancomycin alone and cefazolin alone.

Dr. Wongworawat: *With geographical differences of organisms and susceptibility in mind, how might antibiograms help in the decision-making, such as when cefazolin has a high likelihood of being ineffective?*

Dr. Kheir: Antibiograms are essential to adequately cover organisms. Vancomycin may be considered for patients in institutions with high rates of MRSA, however there is currently not a universal threshold that signifies a “high” rate of MRSA. It may be worthwhile to review an institution’s microbiological profile to observe if there is any local trend in resistance toward antibiotics, as well as consulting with surgeons, infection disease specialists, and infection prevention personnel regarding appropriate antibiotic prophylaxis in the region.

Dr. Wongworawat: *Given the low risk of cross-reactivity in beta-lactam allergy with cephalosporins and the inferior effectiveness of vancomycin as a sole prophylactic agent, can you outline your decision algorithm for antibiotic dosing in patients who undergo arthroplasty?*

Dr. Kheir: Patient-reported penicillin allergy has important consequences for antibiotic selection, as cephalosporin agents normally used for perioperative prophylaxis are avoided due to the potential for cross-reactivity, even though the associated risks

are unclear [3, 8, 15]. Of consequence, administering suboptimal antibiotics can increase the risk of infection in these patients [5, 13, 18, 22]. The current guidelines established by the International Consensus Meeting on PJI recommends that vancomycin substitution only be in cases of severe anaphylactic penicillin allergy [6, 20]. However, compliance is limited by the lack of proper allergy classification [12, 17]. Reported allergies are rarely validated with proper testing, and the lack of symptom classification prevents the distinction of non-IgE-mediated reactions and true, life-threatening Type 1 hypersensitivity reactions [1, 12, 17].

To better establish an antibiotic regimen for patients who report an allergy to a beta-lactam, a clear characterization of the penicillin allergy is essential. Of paramount importance is taking an appropriate clinical history for diagnosis and characterization of the patient’s prior allergic reaction to the antibiotic. Risk stratification is important because patients with recent, severe anaphylactic reactions to cephalosporins should not receive cephalosporins, while patients with milder reactions may benefit from cephalosporin administration [16]. Therefore, we propose that for patients with severe reactions to penicillin or cephalosporins, such as recent anaphylactic events (< 10 years prior), [4]

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a severe rash (involving mucous membranes), or if the patient required emergent medical treatment (epinephrine injection or admission to a hospital), an alternative antibiotic is warranted. However, since the cross-reactivity of penicillin and cephalosporin is much lower than recently suggested [8, 16], patients with penicillin allergies may want to be tested for a cephalosporin allergy. If negative, these patients may be given a cephalosporin as prophylaxis. The ideal environment to receive an antibiotic may be the operating room under the watchful eye of an anesthesiologist where reversal agents can be quickly administered.

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