EDITORIAL COMMENTARY

Antibiotic Prophylaxis for Cardiac Surgery: Does the Past Predict the Future?

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(See the article by Bolon et al. on pages 1357–63)

Despite the best intentions to base medical practice on evidence, many decisions must still be made under uncertainty. The choice of antibiotics for prophylaxis in cardiac surgery is one of these. Although there is a consensus that antibiotic prophylaxis is effective, few rigorous studies have compared the regimens that are most relevant to current clinical care.

Vancomycin is often used because of concern about the increasing prevalence of resistance to cephalosporins in *Staphylococcus aureus* and coagulase-negative staphylococci, the pathogens that most frequently cause surgical site infection (SSI) after cardiac surgery [1]. The debate about glycopeptide prophylaxis is lively because of the concerns that use of these agents may promote the emergence and the spread of resistance to this family of antibiotics among enterococci and staphylococci. The Centers for Disease Control and Prevention (CDC) recommends that vancomycin only be used as perioperative prophylaxis "at institutions that have a high rate of infections caused by methicillin-resistant *S. aureus* (MRSA) or methicillin-resistant *S. epidermidis*" [2, p. 3]. However, the CDC guidelines provide no guidance about what rate is sufficiently high to warrant use of vancomycin. The amount of glycopeptide use at stake is all the larger as these considerations apply to many clean surgical procedures other than cardiac surgery.

In this context, the meta-analysis by Bolon et al. [3] of studies in which prophylaxis with glycopeptides is compared with prophylaxis with β-lactam antibiotics is welcome. The authors pooled data from 5761 cardiac procedures from 7 randomized trials. They found that neither antibiotic family was superior for prevention of SSIs. Of note, however, β-lactam prophylaxis prevented 50% more chest SSIs than did glycopeptide prophylaxis.

One limitation of the study, as pointed out by the authors themselves, is that there was some degree of heterogeneity among the selected trials. These trials used different antibiotics, different definitions of SSI, and different protocols for surveillance of SSIs. Nonetheless, the authors made the best possible use of the available data and appropriately concluded that these data do not support a switch from β-lactams to glycopeptides for prophylaxis in cardiac surgery. Useful as this analysis is, some important questions remain.

- Is there a threshold value for prevalence of methicillin resistance that would justify prophylaxis with glycopeptides?

In their meta-analysis, Bolon et al. [3] found that the risk of SSI caused by β-lactam–resistant (presumably, methicillin-resistant), gram-positive organisms in patients who received prophylaxis with glycopeptides was one-half of that observed for those who received β-lactam antibiotics. Local prevalence of methicillin resistance will therefore be a key factor in the choice of a prophylactic strategy. Unfortunately, the meta-analysis does not help in choosing a threshold above which glycopeptides should be used for prophylaxis, mainly because precise data on methicillin resistance were not available in the 7 selected studies. Two of these studies were published >10 years ago and are unlikely to reflect the current prevalence of bacteriological resistance. Only the most recent study [4], which was conducted in Israel during 1997–1999, described a high prevalence of MRSA in its source popu-

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lation, although this prevalence was not precisely specified. Of note, no advantage of vancomycin prophylaxis was found overall, even in this study.

- Do glycopeptides and β-lactams have similar activity against methicillin-susceptible, gram-positive cocci?

If glycopeptides are to be used because of their advantage against methicillin-resistant pathogens, one must be sure that this advantage is not counterbalanced by a weaker effect in preventing SSI caused by methicillin-susceptible bacteria. Several lines of evidence suggest weaker activity of glycopeptides. Pharmacokinetic and pharmacodynamic studies have shown poor tissue penetration and slow bacterial killing [5, 6]. β-Lactams were repeatedly shown to be more effective than glycopeptides in animal models of endocarditis caused by methicillin-susceptible, gram-positive bacteria [7, 8]. Bolon et al. [3] conducted subgroup analyses that suggested a clinical counterpart of these experimental findings: in the pooled population, patients who received prophylaxis with a glycopeptide developed significantly more chest infections than did those who received β-lactams; they also had a nonsignificant trend towards a higher risk of deep-chest infection. However, there is not enough information to know whether the excess was due to methicillin-susceptible, gram-positive cocci or to other β-lactam–susceptible pathogens. In addition, the contradictory finding of a trend towards smaller risk of leg infection for glycopeptide recipients reminds us that the results of these subgroup analyses may be due to chance rather than to a difference in preventive efficacy between the 2 prophylactic strategies.

- What is the real impact of glycopeptide use on the epidemiology of resistance to glycopeptides?

The potential for promoting the emergence of resistance by using glycopeptides is obvious. Most of the patients who were reported to be infected with glycopeptide-resistant or glycopeptide-intermediate *S. aureus* had previously received prolonged courses of vancomycin for infections caused by MRSA [9, 10]. However, epidemiological data are still lacking to translate this paradigm into broader clinical practice. For instance, vancomycin has been less consistently reported to be a risk factor for infections caused by vancomycin-resistant enterococci, compared with cephalosporins [11]. In addition, short exposures to glycopeptides for prophylaxis in patients with non-MRSA infections are far less likely to promote resistance than are prolonged treatments, especially for MRSA infections. Additional data are warranted in this context—for instance, data obtained using time-series analyses to compare the impact of different strategies regarding use of glycopeptides on resistance [12].

We recently developed a decision-analytic model to calculate the clinical benefits and costs associated with the use of either cefazolin or vancomycin for prophylaxis in coronary artery bypass surgery [13]. In the base case, in which 40% of *S. aureus* isolates and 80% of coagulase-negative staphylococci were resistant to methicillin, cefazolin had to be 25% better than vancomycin against susceptible organisms to be more effective. A performance advantage for cefazolin against drug-susceptible organisms was required unless the prevalence of methicillin resistance was <3%. This example illustrates the uncertainty around the effects of vancomycin prophylaxis: choosing cefazolin over vancomycin for cardiac surgery may be detrimental to the individual patient in many hospitals.

The analysis of Bolon et al. [3] allows us to conclude that there is no empirical evidence supporting a switch from β-lactams to glycopeptides for routine prophylaxis for cardiac surgery. However, we continue to make decisions under uncertainty, not knowing with assurance to which environments their analysis applies. We look forward to new data and updated analyses to help clinicians make the best choice based on the most common and serious pathogens at each institution.

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