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Authors

Movahed, MD, PhD, FACC, FACP, FSCAI, FCCP, Mohammad-Reza R
Kasravi, B
Bryan, C S

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Prophylactic Use of Vancomycin in Adult Cardiology and Cardiac Surgery

Brief title: Prophylactic Use of Vancomycin

Mohammad-Reza Movahed, M.D.¹

Babak Kasravi, M.D.¹

Charles S. Bryan, M.D.²

From the Department of Medicine, University of California, Irvine Medical Center, Orange, California¹ and University of South Carolina School of Medicine, Columbia, S.C.²

Address for correspondence: M. Reza Movahed, M.D., FACC
University of California Irvine Medical Center
Division of Cardiology, Building 53, Route 81, Rm 100
101 The City Drive South
Orange, CA 92868
E-mail: mmovahed@uci.edu
Telephone: (714) 456-6545
Fax: (714) 456-8895

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Abstract

The recent appearance of *S. aureus* and *S. epidermidis* strains with reduced susceptibility to vancomycin and the spread of vancomycin-resistant enterococci raise the specter of endovascular infections that will be difficult or impossible to cure with available drugs. We review issues concerning prophylactic use of vancomycin in adult cardiology and cardiac surgery with special attention to dosing and indications. There is no indication for routine use of prophylactic vancomycin in pacemaker implantations, cardiac catheterization, and transesophageal echocardiography. In institutions with high incidence of MRSA and MRSE, vancomycin may be used for antibiotic prophylaxis in place of cephalosporins for pacemaker or defibrillator implantation. Strongest evidence in support of prophylactic use of vancomycin is during cardiac surgeries particularly valvular surgeries in institutions with high prevalence of MRSA and MRSE. When vancomycin is used prior to open heart surgery, the dose should be 15 mg/kg rather than a standard 1 g dose often recommended in the literature and used by 85% of institutional pharmacists who responded to our survey. Cardiologists and cardiac surgeons should assume leadership roles in promoting its responsible use.

Condensed abstract

The emergence of vancomycin-resistant bacteria should concern cardiologists and cardiac surgeons because of the potential for untreatable endovascular infections. We review current guidelines and controversies concerning the appropriate use of this agent.

Key words for index

Antibiotics Vancomycin Endocarditis Prophylaxis

Abbreviations

HICPAC = Hospital Infection Control Practices Advisory Committee

MBC = minimum bactericidal concentration

MIC = minimum inhibitory concentration

MRSA = methicillin-resistant *Staphylococcus aureus*

MRSE = methicillin-resistant *Staphylococcus epidermidis*

VRE = vancomycin-resistant enterococci

Vancomycin is the only drug with proven therapeutic efficacy against staphylococci resistant to the β -lactam antibiotics—so-called Methicillin-Resistant *S. aureus* (MRSA) and *S. epidermidis* (MRSE). Today's high prevalence of MRSA and MRSE at most hospitals makes vancomycin an indispensable drug in adult cardiology and cardiac surgery. Recent reports of *S. aureus* and coagulase-negative staphylococcal strains with reduced susceptibility to vancomycin raise the possibility that we may soon face endovascular staphylococcal infections that are difficult or impossible to cure with available drugs (1-3). Already, heavy vancomycin use in the United States has contributed to the spread of vancomycin-resistant enterococci (VRE) (4). Guidelines for judicious use of vancomycin have been published by the Hospital Infection Control Practices Advisory Committee (HICPAC), and individual hospitals are taking steps to restrict vancomycin use (5, 6). Our purpose is to review the pharmacology, indications, and dosing of prophylactic vancomycin in cardiology and cardiac surgery and to urge cardiovascular physicians to assume leadership roles in promoting responsible use of this agent.

Overview of vancomycin pharmacology

Vancomycin was the first glycopeptide antibiotic and is the only drug in this class currently available in the United States. Newer glycopeptide antibiotics being studied include teicoplanin, daptomycin, and ramoplanin; as yet, none of these seems clearly superior to vancomycin. Vancomycin inhibits the synthesis of peptidoglycan polymers in the bacterial cell wall and is bactericidal only against multiplying organisms. Although vancomycin exerts its main effect by mimicking the D-alanyl-D-alanine precursor of peptidoglycan, multiple

mechanisms of action help account for the low frequency with which resistance emerges (7, 8).

Spectrum of activity. Vancomycin is active against nearly all gram-positive bacteria, except for the newly emerging vancomycin resistant enterococci (2). Intrinsic resistance has been encountered in only a few species, such as *Erysipelothrix*, *Pediococcus*, *Leukonostoc*, *Lactobacillus*, and three enterococci seldom implicated in human disease: *Enterococcus gallinarum*, *E. casseliflavus*, and *E. flavescens* (9). Vancomycin has no activity against most gram-negative bacteria, although a few species such as *Flavobacterium meningosepticum*, *Neisseria meningitides*, and *Neisseria gonorrhoeae* are susceptible to high concentrations.

Many physicians hold the impression that vancomycin is the most potent available antistaphylococcal antibiotic. Actually, the antistaphylococcal penicillins such as oxacillin and nafcillin surpass vancomycin for treatment of infections caused by mutually-susceptible strains of *S. aureus*. Some staphylococcal strains are relatively tolerant to the bactericidal action of vancomycin, a phenomenon manifested in vitro by minimum bactericidal concentration (MBC) values significantly higher than the minimum inhibitory concentration (MIC) values (10). This observation may explain why vancomycin sometimes fails to cure staphylococcal endocarditis in injection drug users, a setting in which oxacillin or nafcillin nearly always succeed (11, 12).

Toxicity. Unwanted effects of vancomycin include ototoxicity, enhancement of the nephrotoxicity of other drugs such as the aminoglycoside antibiotics, neutropenia, fixed drug eruptions and phlebitis. Of more concern to prophylactic use is the “red man syndrome” (RMS), variably characterized by flushing of the upper body, hypotension, itching, and—less often—chest pain and muscle spasm. Cardiac arrest has been reported (13, 14). These effects are

attributed to nonimmunologic release of histamine from mast cells, correlated with the rate of vancomycin infusion (15). Bolus infusions are especially dangerous. Recognition of the relationship between RMS and rapid infusion (< 30 min) led to the practice of slow vancomycin infusion (≥ 1 h). Pretreatment of patients with an antihistamine such as diphenhydramine or hydroxyzine prior to the first dose of vancomycin protects against RMS (16, 17). Less common anaphylactoid reactions to vancomycin include oliguria, generalized edema, and non-cardiogenic pulmonary edema (18).

Various investigators have studied the hemodynamic effects of vancomycin during cardiovascular surgery. One group observed 25% of 116 consecutive patients developed hypotension, which in one-half of the cases was severe (19). A second group determined that while initial doses of vancomycin were well-tolerated, subsequent doses caused hypotension that often required norepinephrine infusion after bypass (20). A third group concluded that the adverse reactions to vancomycin could be minimized by starting the infusion after initiating bypass (21). A fourth group found that vancomycin given over 1 hour prior to bypass did not suppress cardiac function, even though vancomycin depresses cardiac function by about 15% in animal studies (22).

Dosing. Farber et al., noted two cases of early-onset prosthetic valve endocarditis due to *S. epidermidis* in patients given preoperative vancomycin at a dosage of 7.5 mg/kg. Based on this observation, they gave 15 mg/kg of vancomycin to 10 patients undergoing cardiopulmonary bypass and observed serum levels of 7.0 ± 3.0 $\mu\text{g/ml}$ during surgery. They recommended an initial dose of 15 mg/kg just prior to surgery followed by a second dose of 10 mg/kg after

termination of bypass (23). We gave vancomycin to 12 patients according to this protocol and observed serum levels similar to those obtained by Farber et al. (Bryan CS, Morgan SL, Smith CW, unpublished observations). The use of a standard 1-gram dose will result in overmedication of small patients and undermedication of large patients (23, 24). However, some authorities recommend a 1 g dose for all patients (25). We sent a brief questionnaire to hospital pharmacists at 50 institutions throughout the United States, asking the dose of vancomycin generally used. Of 39 respondents, 33 (85%) gave the usual dose as 1 gram; one as 500 mg; and five as 15 mg/kg. Two randomized trials compared the use of different doses of vancomycin vs. cephalosporins for prophylaxis in cardiac surgery (26, 27). Only using 15mg/kg of vancomycin showed significant reduction of wound infections in comparison to cephalosporin. Therefore, it is strongly suggested that a dose of 15 mg/kg rather than a standard 1 gram dose be used. In addition, this regimen has been shown to maintain adequate therapeutic vancomycin level during prolonged cardiac surgery up to 8 hours (28, 29). In a related study, Vuorisalo et. al found therapeutic serum levels with single dose of 1.5 gm of vancomycin prophylaxis for coronary artery bypass grafting up to 8 hours from time of administration (30).

It was previously recommended that obesity be taken into account when dosing vancomycin (31). However dosing on the basis of ideal body weight can result in sub-optimal peak and trough levels in obese patients. It is now recommended that obese patients, including the morbidly obese, should be dosed on a weight basis with the admonition that trough drug levels (and perhaps peak levels) should be measured if therapy is to be prolonged (32, 33). In most situations, however, the common practice of measuring peak and trough serum levels during therapy is of questionable value (25, 34-36).

Indications and efficacy.

Cefazolin, cefamandole, and cefuroxime are the most commonly recommended drugs for prophylaxis against staphylococcal infection in surgery. Vancomycin is reserved for patients with histories of penicillin allergy or for settings in which methicillin-resistant staphylococci frequently cause wound infections (25). Experimentally, vancomycin was superior to cefazolin in preventing infection by methicillin-susceptible and -resistant strains of *S. aureus* in a guinea pig model of wound infection (37). In rat and rabbit models of experimental *S. epidermidis* endocarditis, vancomycin compared favorably with cefamandole and cefazolin (38, 39). Penetration of vancomycin into cardiac tissues and sternal bone appears to be adequate in most, but not all patients (40, 41).

Prosthetic valve surgery. Coagulase-negative staphylococci are the most common bacteria causing endocarditis within 12 months of valve replacement, and it is thought that these bacteria are usually inoculated onto the sewing ring during surgery (42). The high prevalence of MRSE at most institutions makes vancomycin an attractive antibiotic for prevention of these infections. Antunes et al. reported that a change from a cephalosporin-based protocol to a two-drug regimen of vancomycin plus an aminoglycoside (netilmicin) dramatically reduced the rate of prosthetic valve endocarditis at their institution in Portugal (43). The optimum duration of prophylactic antibiotic therapy for prosthetic valve replacement is unknown. Most authorities recommend that therapy be limited to two days, which is supported by at least one comparative study (44). Some surgeons prefer to continue therapy for a longer duration for hemodynamically-

unstable patients who require the continued presence of central venous and arterial pressure monitoring lines. This is in attempt to prevent seeding of the prostheses during the course of transient line-associated bacteremia. However, there is no data in support of prolonged antibiotic prophylaxis beyond 24-48 hours.

Other types of cardiac surgery. Substantial evidence indicates that a short course of peri-operative antibiotic therapy reduces the incidence of infections related to cardiopulmonary bypass surgery. Cephalosporins are the most commonly used antibiotics for this purpose (45-47). Maki et al. (26) gave vancomycin, cefazolin, or cefamandole to 321 adult patients undergoing cardiac or major vascular procedures. Wound infection rates were 3.7% after vancomycin, 11.5% after cefazolin, and 12.3% after cefamandole ($p < 0.05$); and there were no chest wound infections in the patients given vancomycin. Danish investigators found vancomycin to be superior to penicillin G for prevention of postoperative infections in open heart surgery (48). On the other hand, Vuorisalo et al. (49) observed no difference in the rate of surgical-site infections among 444 patients given cefuroxime (3.2%) and 440 patients given vancomycin (3.5%). Similar observation was made by Finkelstein et al and Salminen et al, comparing efficacy of cefazolin and ceftriaxone respectively with vancomycin, although the recommended dose of 15mg/kg of vancomycin was not used in those studies (27, 50). Also, Pear et al. observed that voluntary reduction of vancomycin use in favor of a cephalosporin had no effect on the rate of postoperative infections following coronary artery bypass graft surgery (51). On balance, the issue whether vancomycin or a cephalosporin should be used as a first-line agent is unresolved (52). Consultants to *The Medical Letter* recommended cefazolin, cefuroxime, or vancomycin as

drugs of choice for prophylaxis during cardiac surgery of all types with a note that vancomycin should be considered not only for patients with allergy to penicillins and cephalosporins, but also in hospital settings where MRSA and MRSE often cause wound infections (53). As already noted, MRSA and MRSE are now prevalent at most major teaching institutions in the United States.

Permanent cardiac pacemaker implantation. Infection complicates 0.13% to 19.9% of permanent cardiac pacemaker insertions (54). Endocarditis sometimes occurs and usually requires removal of the entire endocardial system followed by 6 weeks of appropriate antibiotic therapy (55). Staphylococci are the most frequent isolates, but in contrast to prosthetic valve endocarditis, the majority of cases of early-onset endocarditis after pacemaker insertion are due to *S. aureus*. This was the case with 88% of staphylococcal isolates causing pacemaker endocarditis in one large series (56). Historically, it was believed that prophylactic antibiotics do not reduce the overall infection rate. However, on the basis of two cases of severe *S. aureus* bacteremia, Hartstein et al. concluded that antibiotics might reduce the severity of infection (57, 58). More recently, four of five placebo-controlled trials and one meta-analysis indicated that prophylactic antibiotic therapy reduces the incidence of infections related to pacemaker implantation (59-64). On the basis of controlled trials and various observational studies, it seems that prophylactic antibiotics are widely used prior to permanent pacemaker implantation and also that definitive guidelines are needed since there is little or no standardization. There is no supportive literature on use of vancomycin prophylaxis for placement of permanent pacemaker as first line agent.

Cardiac defibrillator implantation. Use of prophylaxis for placement of implantable cardiac defibrillators (ICDs) is common practice (65). We are aware of no comparative trials of vancomycin for this indication. Since ICDs are implanted percutaneously similar to pacemakers, therefore prophylactic antibiotic use should follow the same guidelines.

Cardiac catheterization. Bacteremia after diagnostic cardiac catheterization and also after percutaneous transluminal coronary angioplasty (PTCA) is rare (66, 67, 68). Groin infection, septic endarteritis, and cardiac abscess have been reported after early groin repuncture, in presence of already indwelling vascular access, or delay in removal of arterial sheath after completion of procedure (69-72). Although there are no standard recommendations, prophylactic antibiotic therapy might be considered in this setting. We are aware of no data with regards to the use of vancomycin for cardiac catheterization and percutaneous intervention prophylaxis.

Transesophageal echocardiography. There are numerous studies showing no significant bacteremia associated with transesophageal echocardiography even in high risk patients. Therefore, antibiotic prophylaxis is not recommended for this procedure (73-76).

Discussion of Current issues

When and how should vancomycin be used prophylactically? Prophylactic use of vancomycin should be consistent with the HICPAC guidelines and kept brief (Table 1). Brief courses reduce the environmental pressure that promotes development of vancomycin-resistant microorganisms, and also lower the risk of superinfections caused by other bacteria and yeasts.

Should vancomycin be used more widely for prophylaxis? Conventional wisdom holds that cardiologists and cardiac surgeons should be discouraged from frequent use of vancomycin as a prophylactic agent, since wide use of vancomycin promotes emergence of drug-resistant microorganisms. Schentag and colleagues (77) recently suggested that use of cefazolin for presurgical prophylaxis promotes the emergence of MRSA, MRSE, and—indirectly—VRE. These authors point out that the activity of cefazolin after a single 1-g dose, expressed as the area-under-the-(time to serum concentration) curve-to-MIC ratio, is marginal against *S. aureus*, thereby selecting out the rare methicillin-resistant cells residing in the nares of persons colonized with predominantly-methicillin-sensitive bacteria. Such persons are then predisposed to nosocomial infections due to MRSA, treatment of which promotes the emergence of VRE. One might posit, then, that wider use of vancomycin would reduce the occurrence of MRSA and VRE infection. Should the indications expand, however, we would again suggest that therapy be kept as brief as possible.

Are there alternatives to vancomycin for patients undergoing prosthetic valve surgery and for institutions with a high prevalence of MRSA and MRSE infections? There is clearly a need for the development of alternatives to vancomycin for therapy of MRSA and MRSE infections. Quinupristin-dalfopristin, a combination of two gramacidin compounds, has activity against many MRSA, MRSE, and VRE strains and is being used for treatment. The possibility that this combination might be effective as prophylaxis deserves investigation.

What role should cardiologists and cardiac surgeons play to reduce the further spread of vancomycin-resistant bacteria? As major stakeholders in the prevention of staphylococcal infections, cardiologists and cardiac surgeons should assume leadership roles in assuring

appropriate use of vancomycin and other agents in their institutions. Cardiology training programs should pay renewed attention to issues and methods pertaining to antibiotic management and infection control.

Conclusion

Our review of the literature reveals that strongest evidence in support of prophylactic use of vancomycin, as opposed to cephalosporins, is during cardiac surgeries with particular attention to valvular surgeries in institutions with high prevalence of MRSA and MRSE. When vancomycin is used prior to open heart surgery, the dose should be 15 mg/kg rather than a standard 1 g dose commonly recommended. In institutions with high incidence of MRSA and MRSE, vancomycin may be used for antibiotic prophylaxis in place of cephalosporins for pacemaker or defibrillator implantation. The routine use of vancomycin as the first line agent in place of cephalosporins for antibiotic prophylaxis prior to cardiac surgery is still controversial.

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Indications	Administration
<ol style="list-style-type: none"> 1. Prosthetic valve surgery 2. Cardiac surgery in patients with type I allergy to β-lactam antibiotics.* 3. Cardiac surgery in institutions with a high prevalence of MRSA and MRSE. 4. Pacemaker implantations in institutions with a high prevalence of MRSA and MRSE. 5. Implantable cardiac defibrillator implantation in institutions with a high prevalence of MRSA and MRSE. 	<p><i>Premedication</i></p> <p>Hydroxyzine 50 mg**</p> <p><i>Loading dose</i></p> <p>15 mg/kg of vancomycin in a suitable diluent given IV over at least one hour to be administered one hour prior to anticipated procedure</p> <p><i>Subsequent dosing</i></p> <p>10 mg/kg in a suitable volume of diluent IV over at least one hour (one dose postoperatively) §</p>

Table 1. Protocol for prophylactic use of vancomycin in adult cardiac surgery and cardiology

* Type I allergy is defined by a history of anaphylaxis, urticaria, or angioneurotic edema, or by immediate skin test reactivity to penicillin or cephalosporin antigens.

** Premedication with an antihistamine may prevent the histamine release phenomenon (see text).

§ No subsequent dose recommended for implantation of pacemaker or implantable defibrillator.