Endocarditis is a relatively common and frequently devastating complication of cardiac valve replacement. Prosthetic valve endocarditis (PVE) has an overall yearly incidence ranging from about 1 to 4 percent of prostheses recipients. 1-4 Previously, PVE has been arbitrarily divided into “early” and “late,” based on whether the infection occurred within 60 days of valve replacement or later. 4 The rationale for this time categorization was based on differing bacteriologic, pathogenetic, and prognostic associations for PVE cases acquired before vs after this 60-day breakpoint. 4, 6, 7 For example, older studies had confirmed a predominance of coagulase-negative staphylococcal, Gram-negative bacillary and fungal pathogens among early PVE cases, with streptococci being uncommon etiologic agents. 1, 4 In contrast, the oral and enterococcal streptococci, along with the staphylococci, tended to predominate in the late PVE cases. Moreover, these previous studies of PVE defined a substantially higher mortality rate associated with early vs late PVE. This prognostic difference in early vs late PVE was believed to be related to the preponderance of periannular or sewing-ring infections seen in early PVE as opposed to a higher incidence of leaflet or strut infection in late PVE. Lastly, these older investigations suggested that early PVE cases were acquired either via intraoperative (probably airborne) valve contamination 2 or hematogenously secondary to postoperative extracardiac infections, 5, 8 while late PVE cases were presumed to have been acquired by much the same mechanism as native valve endocarditis, ie, by bacteremic seeding predominantly from oral or urogenital foci. 8

However, more recent data from Calderwood and others 9, 10 have tended to blur the arbitrary time distinction between early and late PVE. These later reports have used actuarial rather than linearized methods to show that the risk of PVE is highest in the first six to 12 months after surgery and decreases to its lowest beyond one year post-valve replacement. Recent studies confirm the statistically dominant etiologic role of the coagulase-negative staphylococci (CNS) in PVE cases occurring both before and after the 60th postoperative day. 1, 11 Recent clinical and epidemiologic data also suggest that PVE caused by CNS occurring within the first year after prosthetic placement is probably acquired at the time of surgery. These data include (1) homology of plasmid and antibiogram profiling between CNS isolates colonizing patients in the operating room and PVE isolates from the same patients’ valves at time of operation, 12 and (2) an 80 to 90 percent rate of “methicillin resistance” among CNS isolated from PVE cases within the first postoperative year, suggesting nosocomial acquisition. 1, 11 These observations support extension of the breakpoint date between early vs late PVE to one-year postoperation.

It has become a “community standard of practice” to administer prophylactic antibiotics to prevent PVE in two major settings: (1) perioperatively to circumvent operative development of prosthesis colonization; and (2) during bacteremia-inducing oral, urogenital, and other medical procedures. In prescribing prophylactic antibiotics in the perioperative period, clinicians receive the secondary benefit of preventing postoperative wound infections (particularly sternal) in addition to preventing PVE. This report will deal with the controversies and current approaches in the chemoprophylaxis of PVE.
**Prevention of PVE During Placement of Prosthetic Cardiac Valves: Cephalosporin-based Prophylaxis**

Authors in most studies of surgical prophylaxis have concluded that the critical time for antibiotic administration is the periprocedural period, advocating regimens designed to assure that the appropriate agent is present in the serum and relevant tissues at the time of incision and tissue manipulation.13 This same principle applies to the prevention of PVE following prosthetic valve placement. One of the difficulties in designing studies to investigate the relative prophylactic efficacies of various antimicrobial regimens in PVE is the frequently insidious nature of this infectious syndrome.1 Thus, assessment of the preventive efficacy of any antibiotic regimen against PVE is not complete until at least one year after valve replacement. An additional difficulty in assessing prophylactic efficacy in prosthetic valve surgery is the low "attack rate" of PVE,14 necessitating a very large study sample size to see any statistically significant differences between various regimens. Lastly, administration of prophylactic antibiotics during valve replacement is so well established today that a placebo-controlled trial in this regard is probably untenable in current medical practice.

In the early era of cardiac valve replacement, it was not uncommon for surgeons to administer prolonged periods of preoperative and postoperative antibiotic "prophylaxis." With the realization that such extended prophylactic regimens could substantially alter the patient's endogenous bacterial flora, leading to infections with multi-antibiotic-resistant nosocomial organisms, a number of studies have been performed to examine both the optimal composition as well as duration of surgical prophylaxis for cardiac valve replacement. In 1972, Conte et al14 reported a prospective double-blind evaluation of perioperative single-dose vs multi-dose (five days) cephalothin prophylaxis in 37 patients undergoing cardiac valve replacement. There were no significant differences in the two prophylactic regimens as regards minor or major extracardiac infections, and there was only one case of postoperative PVE (CNS) observed, occurring in the single-dose group at six weeks after surgery. Of note, the spectrum of etiologic agents in the multidose prophylactic group tended to involve more antibiotic-resistant organisms (eg, *Serratia* sp) than in the single-dose group. Similarly, in 1976 Goldmann et al15 showed that there were no substantial differences between shorter and longer prophylactic regimens in PVE prophylaxis. They studied 157 patients undergoing prosthetic valve placement who were randomized to receive either two or six days of cephalothin therapy. No cases of PVE were observed over a two-month follow-up period. Of interest, the authors found that patients who had undetectable antibiotic serum levels at the close of surgery (predominantly patients with the longest operations) had a significantly higher postoperative wound infection rate, supporting the concept of repeated intraoperative prophylactic dosing in such settings.

Over the past 14 years, a number of studies have been performed that have evaluated various cephalosporin regimens in prophylaxis during cardiac valve replacement. These reports, mostly involving comparisons of cefazolin, cefamandole, and/or cefuroxime, are summarized in Table 1. In the largest patient population studied, Peterson et al16 compared a five-day cefamandole regimen with a two-day cefuroxime regimen in 489 patients undergoing valve replacement. No cases of PVE were reported, and the regimens were equally effective overall in preventing postoperative wound infections; however, there were significantly more sternal wound infections in the

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<th>Table 1 — Summary of Four Studies of Prophylaxis of Prosthetic Valve Endocarditis (PVE) in Cardiac Valve Surgery</th>
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<td><strong>Source</strong></td>
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*All regimens given for 2 days.
cefamandole group than in the cefuroxime group (p = 0.01). This study was a nonrandomized, open trial in which cefamandole was used exclusively for cardiovascular prophylaxis for 18 months, followed by exclusive use of cefuroxime for the ensuing 18 months. Despite this, the very large sample size evaluated lends credence to the authors' observations. Slama et al directly compared cefamandole, cefazolin, and cefuroxime in 48 patients undergoing valve replacement. No patient developed PVE over a one-year postoperative follow-up period. Also, there were no significant differences in the incidence of postoperative wound infections in this relatively small patient population, although three patients in the cefazolin-prophylaxis group required rehospitalization for either cellulitis or sternal wound infection. Kaiser et al studied 101 patients undergoing cardiac valve placements who received either cefamandole or cefazolin (with or without gentamicin) in a prospective, randomized double-blind trial. No cases of PVE were observed, and the only sternotomy wound infection recorded was fungal in cause and was seen in the cefazolin-gentamicin group.

Most of the large-scale comparative studies of antibiotic prophylaxis in cardiovascular surgery involve patients who have undergone aortocoronary bypass surgery and do not specifically address the issue of PVE. In general, the following observations appear cogent from these latter investigations: (1) Cephalosporin prophylaxis clearly reduces postoperative wound infection rates at both the leg donor site and sternotomy site as compared with placebo. (2) Compared with cefamandole and cefuroxime, cefazolin in most studies appears inferior in the prevention of postoperative wound infections, particularly related to CNS and Staphylococcus aureus. This has been linked to the greater susceptibility of cefazolin to S aureus β-lactamases than cefamandole and cefuroxime, as well as the superior anti-CNS activities of cefuroxime and cefamandole vs cefazolin. It should be pointed out, however, that in a recent report of Doebbeling et al, cefazolin was significantly better than cefuroxime in the prevention of sternal wound infections or mediastinitis following coronary artery bypass graft surgery. (3) Based on cost analyses, cefuroxime and cefazolin are the most cost-effective, while cefamandole is the most expensive of the three prophylactic regimens. Whether these findings in coronary bypass surgical prophylaxis can be extrapolated to recommendations for prevention of PVE and postoperative sternotomy infections in valve replacement surgery has not been adjudicated. Currently, the American Heart Association (AHA) recommends cefazolin-based regimens in cardiac valve surgery. It seems reasonable to conclude that the choice of which cephalosporin regimen to recommend for cardiac valve surgical prophylaxis should center around three factors: (1) susceptibility patterns of the particular hospital's microflora, especially among those strains commonly implicated in PVE and postoperative wound infections (eg, CNS; S aureus); (2) patient's history of penicillin and/or cephalosporin hypersensitivity (preferably confirmed by skin testing); and (3) calculated drug delivery costs (including both acquisition and administration costs).

One of the underemphasized "down-sides" to the use of cephalosporin prophylaxis in patients undergoing cardiac valve surgeries is the selection and perpetuation of antibiotic-resistant bacterial reservoirs within the hospital. As previously mentioned, most cases of PVE today are caused by methicillin-resistant CNS (about 80 to 90 percent). Archer and Armstrong clearly showed that patients receiving either nafcillin-rifampin or cefazolin prophylaxis for cardiac valve surgery had a significantly increased colonization rate with methicillin-resistant CNS as compared with non-antibiotic-treated cardiac patients in the coronary care unit; moreover, the use of rifampin in one of the prophylactic regimens led to a significant colonization rate with rifampin-resistant CNS. Kernodle et al have recently confirmed these observations. It thus appears that the use of perioperative cardiac valve surgical prophylaxis has been a double-edged sword, reducing the rate of PVE and postoperative wound infections in the individual patient on one hand, but helping to establish and perpetuate an antibiotic-resistant, resident CNS nosocomial flora responsible for most subsequent cases of PVE, on the other hand.

**Vancomycin-based Prophylaxis**

The issue of vancomycin-based prophylactic regimens for the prevention of PVE and sternotomy infections following prosthetic valve surgery remains controversial to date. The rationale for such approaches involves the preponderance of "methicillin-resistant" CNS isolates from bona fide cases of PVE, the frequent etiologic role of these strains in sternotomy wound infections as well as the relatively narrow microbiologic spectrum of activity of vancomycin (mainly against Gram-positive cocci, the most common cause of early PVE). At the present time, the potential for adverse events from the routine prophylactic use of vancomycin in cardiovascular surgery appears to outweigh the drug's potential benefits in this setting. For example, there are at least four separate recent reports documenting the selection of vancomycin-resistant Gram-positive cocci in the setting of vancomycin usage. These studies have included the prophylactic and/or therapeutic use of this agent in long-term peritoneal dialysis and hemodialysis, and in the setting of gut decontamination in neutropenic cancer patients. The selected vancomyc-
cin-resistant organisms have been CNS or enterococci (eg, *Enterococcus faecalis*, *faecium*, and *gallinarum*). Le Clerq et al.²⁶ confirmed that the mechanism of vancomycin resistance in their *E. faecium* isolates was plasmid mediated, raising the frightening potential for dissemination of this resistance factor to other bacteria now considered universally susceptible to vancomycin (eg, staphylococci; *Streptococcus viridans*).

In addition to the above adverse microbiologic consequences of vancomycin prophylaxis, several important systemic toxic reactions of this agent need to be emphasized. It has been appreciated for the last decade that the rapid intravenous infusion of this agent (<30 to 60 minutes) may result in the "red man" or "red neck" syndrome etiologically associated with massive histamine release and mast cell degranulation.²⁰ The syndrome features truncal rash, pruritus, and in some cases, hypotension and angioedema. Such reactions may be particularly disturbing when occurring in the intraoperative and perioperative periods and featuring profound hypotension in a patient under general anesthesia and possibly on cardiopulmonary bypass.²⁰ Recently, investigators have confirmed that this syndrome may be seen in patients in whom the drug is administered slowly and in whom histamine release is not the pathogenetic mechanism.³¹-³³

The current recommendation of the AHA is to reserve the prophylactic use of vancomycin in cardiothoracic surgery to patients allergic to cephalosporins, or in hospital units in which the endemic rate of nosocomial colonization or infection with methicillin-resistant staphylococci is a significant problem.²⁵ It should be noted that the initial prophylactic vancomycin dose should be at least 15 mg/kg; studies by Farber et al.²⁴ suggest that the commonly used regimen of 7 mg/kg (500-mg dose in adults) given preoperatively to patients undergoing cardiopulmonary bypass and open-heart surgery may provide serum levels that are not bactericidal for many CNS isolates.

Newer glycopeptide and lipopeptide antibiotics (eg, teicoplanin and daptomycin, respectively) show promise for cardiac surgical prophylaxis and are currently in clinical trials.

**Prevention of PVE During Bacteremia- Inducing Procedures**

Much of the current information concerning the relative merits of various prophylactic antibiotic regimens in preventing bacterial endocarditis emanates from the animal model of Durack and Petersdorf.²⁸ These investigators delineated that the most effective prophylactic regimens for preventing experimental streptococcal endocarditis were the synergistic combinations of cell wall active agents plus aminoglycosides (eg, penicillin or vancomycin plus streptomycin). Since the animal endocarditis model used in these studies involved an indwelling foreign body (catheter) akin to a prosthetic cardiac valve, it has seemed reasonable for the AHA to recommend similar antibiotic combination therapies for the optimal prevention of postprocedural PVE in humans. The only significant difference between findings in the animal model and recommendations by the AHA for preventing human postprocedural PVE involves the use of gentamicin instead of streptomycin for antienterococcal synergy; this is related to the frequent occurrence of high-level streptomycin resistance among clinical enterococcal isolates in many geographic areas.²⁶

It should be mentioned that the recent identification of enterococci exhibiting high-level gentamicin resistance (with or without plasmid-mediated penicillin resistance)²⁷ from diverse geographic locales may necessitate future changes in approach to antienterococcal prophylaxis for patients undergoing urological or gastrointestinal operations or diagnostic procedures.

For prosthetic valve recipients undergoing significant dental, oral, and other upper airway procedures, parenteral combination therapy regimens are recommended to provide maximal synergistic effect against the oral streptococci.²⁸

To our knowledge, there are no randomized, placebo-controlled trials that confirm the benefits of prophylactic antibiotics in preventing native valve endocarditis. Recently, however, Horstkotte et al.²⁸ in West Germany confirmed the beneficial effect of antibiotic prophylaxis for prosthetic valve recipients undergoing bacteremia-inducing diagnostic or therapeutic interventions. Among 287 such procedures in which antibiotic prophylaxis was provided, no case of postprocedural PVE was seen; in contrast, among 390 interventions in which no prophylactic antibiotic prophylaxis was given, eight cases of endocarditis were observed (p = 0.01).

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