

The Society of Thoracic Surgeons Practice Guideline Series: Antibiotic Prophylaxis in Cardiac Surgery, Part II: Antibiotic Choice*

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I. Overview

The importance of prophylactic antibiotics for cardiac surgery has been clearly demonstrated in a number of placebo-controlled studies completed nearly 30 years ago [1–4]. Surgical site infections (SSIs) and particularly sternal and mediastinal infections have implications for significantly increasing both morbidity and mortality, as well as their associated costs in both man-hours and dollars spent [5, 6].

Part I of this evidence-based guideline series (*The Society of Thoracic Surgeons Practice Guideline Series: Antibiotic Prophylaxis in Cardiac Surgery, Part I: Duration*, published in the January 2006 issue of the *Annals of Thoracic Surgery*) recommended that the duration for routine postoperative administration of prophylactic antibiotics be no longer than 48 hours [7]. This initial Guideline did not define the choice of antibiotic to be recommended, its dose, or frequency of administration. Those subjects are the basis for this report.

II. Choice of Primary Prophylactic Antibiotic

Cephalosporin or Glycopeptide

CLASS I RECOMMENDATION. A β -lactam antibiotic is indicated as a single antibiotic of choice for standard cardiac surgical prophylaxis in populations that do not have a high incidence of methicillin-resistant *Staphylococcus aureus* (MRSA [Level of Evidence A; see Appendix]).

There are numerous publications concerned with the optimal prophylactic antibiotic recommended for cardiac surgery, but many of these protocols are comparing not only two or more antibiotic regimens but also two different dosing programs, for example, single dose versus multidose, which was addressed in the previous Guideline. This second published Guideline will address addi-

tional publications in so far as they compare different antibiotic regimens involving comparable duration of multidose antibiotic administration.

The most pertinent report appeared in 2004 [8] and was a very complete meta-analysis of seven randomized trials, comparing the incidence of SSIs in patients receiving either glycopeptide prophylaxis (vancomycin or teicoplanin) or a β -lactam. Five of the seven trials used a multidose regimen and two invoked, in one of their trial groups, the single preoperative administration of a long-acting agent. In both of these latter reports, the single-dose agent was either less effective or not significantly different from the multidose antibiotic [9, 10]. In this international, multi-institutional meta-analysis involving 5,761 patients, β -lactams were at least as effective as glycopeptides for the overall prevention of SSIs. However, only one institution defined their site as having a high incidence of MRSA (more than 2.5 new cases of MRSA infection or colonization per 100 admissions) [11], and that may limit the degree to which these findings can be generalized to current practice in which MRSA is much more prevalent. Notwithstanding this caveat, it appeared that prophylaxis with glycopeptides such as vancomycin was less effective in preventing infection by methicillin-sensitive organisms, while such prophylaxis was more effective in preventing infection by methicillin-resistant organisms [8].

Distinguishing Between Cephalosporins

CLASS IIA RECOMMENDATION. Based on availability and cost, it is reasonable to use cefazolin (a first-generation agent) as the cephalosporin for standard cardiac surgical prophylaxis in view of the fact that most randomized trials could not discriminate between cephalosporins (Level of Evidence B).

The next issue to be addressed concerns the choice of a β -lactam, remembering that there are first- through fourth-generation agents presently available, which have differing half-lives, pharmacodynamics, and pharmacokinetics. It can be stated as fact that the later generation cephalosporins have better gram-negative and less gram-positive coverage. In that our predominant organism for cardiac surgical infections is a *Staphylococcus* sp,

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the earlier generation cephalosporins are likely to be preferred for prophylaxis. In fact, published data would support that conclusion [12].

In 1987, a randomized trial of more than 1,000 cardiac surgical patients was reported comparing multidose cefazolin, a first-generation cephalosporin, with multidose cefamandole, a second-generation cephalosporin, and found cefamandole to have a lower sternal infection rate [13]. This study, however, introduced a second agent, gentamicin, as an additional single-dose prophylactic drug, in half the patients in each cephalosporin group. That led to the comparative analysis being less than clear cut in defining an optimal cephalosporin. A more definitive randomized double-blind study comparing individual cephalosporins in 1,641 patients from Johns Hopkins Hospital between 1987 and 1990 was reported in 1993 [14]. The incidence of all surgical site infections was 8.4% with cefamandole prophylaxis, 8.4% cefazolin, and 9.0% with cefuroxime (clearly not significant). The relative incidence comparing cephalosporins and differentiating between deep and superficial infection was also not significantly different between the groups (specifically, deep sternal infection = 0.6% cefamandole, 1% cefazolin, and 1.5% cefuroxime). A 1992 meta-analysis [15] cited in the Hopkins report includes some with inherent flaws but still supports the conclusion that there is no cephalosporin regimen that is clearly superior in affecting a lower infection rate.

III. Issues Surrounding Staphylococcal Infection

Reasons for Concern in Cardiac Surgical Patients

Surgical site infections of the sternal wound and underlying mediastinum occur in 0.4% to 4% of cardiac surgical procedures, with more than 50% due to *S aureus* or coagulase-negative *S epidermidis* [16-22]. These infections have profound short- and long-term implications. In-hospital mortality rates of 10% to more than 20% have commonly been reported, and a 10-year follow-up study of such patients by the Northern New England Cardiovascular Disease Study Group demonstrated a marked negative impact not only on acute but also on long-term survival [23]. Hollenbeak and colleagues [24] found a 1-year mortality rate of 22% for coronary artery bypass graft surgery (CABG) patients with deep chest surgical site infections versus 0.6% for uninfected patients ($p = 0.0001$). Deep chest infection resulted in 20 additional hospital days per patient ($p = 0.0001$) and added an average of \$18,938 in hospital costs. Patients who died as a result of their infection incurred average costs that were \$60,547 more than infected patients who lived.

The choice of a prophylactic antibiotic has become increasingly controversial with the emergence of MRSA and methicillin-resistant coagulase-negative *Staphylococcus* (MRCNS). According to the National Nosocomial Infection Surveillance System Report, the median percentage of MRSA isolates from intensive care unit (ICU) and non-ICU patients in hospitals surveyed exceeded 40%, and the median percentage of MRCNS isolates exceeded

65% [25]. It has been estimated that colonization with methicillin-resistant organisms, often asymptomatic, occurs in 4% to 8% of ICU patients, 0.18% to 7.2% of inpatients, and 1.3% to 2% of persons in the community [26]. In one urban hospital, the incidence of MRSA among newly admitted patients was 7.3%, which is higher than the 1.3% to 5.3% prevalence in previous reports [27]. This alarming incidence of colonization has led to a strong recommendation for active surveillance at the time of hospital admission [27, 28]. At least one third of MRSA-colonized patients will have a healthcare-related MRSA infection, which is nearly 10 times the risk of noncolonized patients [26, 28]. In a study by Lin and associates [19] at a hospital with a high incidence of MRSA, 65% of post-sternotomy staphylococcal infections were due to methicillin-resistant organisms [19].

Some studies suggest that patients with post-sternotomy MRSA/MRCNS infections have a less favorable prognosis compared with those having methicillin-sensitive (MSSA) organisms. For example, in the study of Mekontso-Dessap and colleagues [22], overall mortality was 53.3% for MRSA post-sternotomy infections versus 19.2% for MSSA infections, with corresponding 3-year actuarial survival rates of 26% versus 79%. Methicillin-resistant *S aureus* was the only independent predictor of overall mortality, and MRSA infections had a higher incidence of mediastinitis-related death and treatment failure compared with MSSA. In a study of SSIs composed of largely cardiac and orthopedic procedures, Engemann and associates [5] found a mortality rate of 20.7% for MRSA versus 6.7% for MSSA, and most deaths in the cardiac group were due to post-sternotomy mediastinitis. The costs directly attributable to methicillin resistance were \$13,901 per case of staphylococcal infection.

Potential (Nonallergic) Indications for Primary or Adjuvant Glycopeptide (Vancomycin) Prophylaxis

CLASS IIB RECOMMENDATION. In the setting of either a presumed or known staphylococcal colonization, the institutional presence of a "high incidence" of MRSA, patients susceptible to colonization (hospitalized longer than 3 days, transfer from other inpatient facility, already receiving antibiotics), or an operation for a patient having prosthetic valve or vascular graft insertion, it would be reasonable to combine the β -lactam (cefazolin) with a glycopeptide (vancomycin) for prophylaxis, with the restriction to limit vancomycin to only one or two doses (Level of Evidence C).

The progressive emergence of methicillin-resistant staphylococcal organisms within hospitals and the community, as well as the possibly more serious course of such infections in the cardiac surgery patient, has led some to recommend more aggressive use of prophylactic vancomycin, even for patients with no history of penicillin or cephalosporin allergy [29]. For example, it is argued that patients having surgery in institutions with a high incidence of methicillin resistance would be better served by receiving vancomycin, although it is unclear as to what constitutes a high incidence [6, 30]. Other potential candidates for vancomycin prophylaxis might include

patients who are at higher risk for preoperative MRSA colonization, patients at higher risk for post-sternotomy infection in general, and patients with specific risk factors for MRSA post-sternotomy infection [31]. Active surveillance of admitted patients for staphylococcal colonization is desirable [28, 32], but results for cardiac surgery patients would generally not be available at the time of surgery except in those institutions where rapid polymerase chain reaction (PCR) testing is available. Finally, it has been suggested, but not generally accepted, that because of the devastating consequences of prosthetic valve or vascular graft infection with methicillin-resistant organisms, these patients should also routinely receive vancomycin [12, 29].

There are observational [33] and randomized trial data [12] supporting the use of vancomycin prophylaxis for cardiac surgery, as well as the results of a sophisticated decision analytic model [6]. Using the best available clinical and microbiological data from the literature, Zanetti and colleagues [6, 30] estimated that routine vancomycin use in a cohort of 10,000 CABG patients would result in 29 fewer deep chest infections, 58 fewer superficial infections, 3 fewer deaths, lower direct medical costs over 3 months, and a net \$1,170,000 cost saving compared with routine cefazolin. Sensitivity analysis indicated that cephazolin was more effective or less costly only when MRSA represented fewer than 3% of all staphylococcal isolates in a hospital, which would be unusual in contemporary practice. Based on 366,000 CABG procedures annually in the United States, this model predicts that vancomycin use would result in 110 fewer deaths, prevent 3,184 SSIs, and potentially save \$43 million.

One of the most serious objections to increased use of vancomycin prophylaxis is concern about the emergence of resistant strains of *Staphylococcus* and *Enterococcus* organisms [34, 35]. This consideration has prompted the publication of restrictive guidelines for the use of vancomycin or teicoplanin (both glycopeptides), which include a specific recommendation by the CDC against the routine use of vancomycin for prophylaxis (36). However, it should be noted that antibiotic resistance may also develop with β -lactam antimicrobials. Furthermore, the duration of vancomycin administration as a primary or adjuvant prophylactic agent, as opposed to its use for established post-sternotomy infections, must also be considered. In terms of the emergence of drug-resistant organisms, which is worse—using short-duration prophylactic vancomycin in a larger number of patients, possibly preventing some clinical infections due to methicillin-resistant organisms; or using a cephalosporin after which a serious SSI is more likely to involve MRSA or MRCNS, thus committing such patients to weeks or months of continuous vancomycin therapy [6, 29, 30]? This is a central question that as yet has not been resolved and would require research not likely to be performed. Thus, this particular question cannot be addressed by randomized trials.

Unless there is demonstrated penicillin or β -lactam allergy (see Section V, “Allergy to Penicillin”), it would

appear most reasonable to employ a cephalosporin as the primary prophylactic agent for the usual 24 to 48 hours, and only to use vancomycin selectively as an adjuvant agent, typically a single dose preoperatively (together with the first dose of cephalosporin) with at most one additional dose in valve or vascular implant patients or in all patients in highly selected environments (eg, where MRSA colonization is likely or documented or where there is a high prevalence of MRSA isolates from infections). This should provide a reasonable compromise between the goal of providing the broadest spectrum prophylaxis at the time when it is likely to be most effective, and the competing desire to restrict usage of vancomycin in order to minimize the emergence of resistant organisms.

Vancomycin as the Sole Prophylactic Antibiotic

CLASS IIB RECOMMENDATION. Because vancomycin is an agent that has no effect on gram-negative flora, its usefulness as an exclusive agent in cardiac surgical prophylaxis is not recommended (Level of Evidence C).

DISCUSSION. For situations in which vancomycin is believed to be indicated as prophylaxis for cardiac surgery, for example, β -lactam allergy, should it be used as a single agent or combined with another antimicrobial? Overall, vancomycin has a narrower antimicrobial spectrum, inferior tissue and bone penetration, less desirable pharmacokinetics, and slower bactericidal killing compared with cephalosporins [5, 8, 16, 30, 37]; and the incidence of SSI due to methicillin-sensitive organisms has been higher when only vancomycin has been employed for prophylaxis [8, 11]. Additionally, since some hospitals report both deep surgical site infections and blood stream infections after cardiac surgery from gram-negative organisms [38], it is recommended that an aminoglycoside be added for one preoperative and at most one additional postoperative dose to act as a specific gram-negative agent when vancomycin is indicated to be the primary prophylactic agent.

Mupirocin for Preoperative Therapy to Eliminate Staphylococcal Nasal Colonization

CLASS I RECOMMENDATION. Routine mupirocin administration is recommended for all patients undergoing cardiac surgical procedures in the absence of a documented negative testing for staphylococcal colonization (Level of Evidence A).

DISCUSSION. Mupirocin is a patient self-administered topical antibiotic that is highly effective in eradicating nasal *S aureus*, including methicillin-resistant strains of *Staphylococcus*. It is a naturally occurring antibiotic produced by a fermentation of *Pseudomonas* bacteria mixed in a non-irritating paraffin composition. Its specific mechanism of action is to bind to isoleucyl-transfer RNA synthetase and disrupt cell function [39]. It is reportedly more than 90% effective in eradicating nasal colonization of *Staphylococcus* for as long as 1 year [40]. Short-term therapy (a 5-day course) has been shown to be highly effective [41]. Correlation of nasal or hand colonization and infection in the same patient by the same phage type of *Staphylococcus*

has been shown to be near 90% [42]. Recent reports of both randomized and nonrandomized trials in cardiac surgical patients, one a meta-analysis, supports its routine use in prophylaxis [43-45].

Resistance to mupirocin ointment has become a concern for infectious disease specialists, but such resistance is largely found after prolonged treatment periods when used to treat either large open wounds or dermatitis. There have been no reports of high-level drug resistant strains developing after a short course of treatment such as proposed for preoperative prophylaxis despite 4 years of surveillance in one hospital using this approach routinely in both orthopedic and vascular surgery [46]. In fact, many, if not most, cardiac surgical programs have instituted a routine protocol for intranasal mupirocin beginning at least the day before operation (sooner, if elective operation) and continuing for 2 to 5 days after surgery. Recently, a PCR rapid analysis for *Staphylococcus* sp has become available in some hospitals, with additional institutions gaining access to the technology on a regular basis. A report has just been published [47] for a PCR-based mupirocin study performed at the Cleveland Clinic. In this study, screening for nasal carriage of *S aureus* (both MRSA and MSSA) was routinely performed before cardiac surgery. There were 6,334 patients screened over 21 months, and 1,342 were found to have colonization (21%), which is the identical incidence reported in a second study as well [45]. The administration of mupirocin was reserved for these colonized patients, and while the mupirocin use in the cardiac surgical population declined significantly (by nearly 80%), there was no demonstrable difference between carriers and noncarriers in the overall incidence of infection or in the incidence of infection caused by *S aureus*. It was concluded that the effect of mupirocin on colonized patients resulted in appropriately reducing the Staphylococcal infection incidence to nullify the influence of colonization.

Because, inherently, one would not recommend use of any agent that is not useful for treatment, limiting mupirocin prophylaxis to colonized patients would appear to be a sensible approach. However, access to the PCR test is required. Because mupirocin is self-administered, the patient must be informed about the need for the treatment and the technique of insertion. In the absence of access to PCR testing, routine prophylaxis with mupirocin is recommended.

IV. Guidelines for Appropriate Dosing of Prophylactic Antibiotics

RECOMMENDATIONS

1. In patients for whom cefazolin is the appropriate prophylactic antibiotic for cardiac surgery, administration within 60 minutes of the skin incision is indicated (Class I, Level of Evidence A). The preoperative prophylactic dose of cefazolin for a patient of greater than 60 kg body weight is recommended to be 2 g (Class I, Level of Evidence B).
2. When the surgical incision remains open in the operating room, to patients with normal renal function, a second dose of 1 g should be administered every 3 to 4 hours. If it is apparent that cardiopulmonary bypass will be discontinued within 4 hours, it is appropriate to delay until perfusion is complete to maximize effective blood levels (Class I, Level of Evidence B).
3. In patients for whom vancomycin is an appropriate prophylactic antibiotic for cardiac surgery, a dose of 1 to 1.5 g or a weight-adjusted dose of 15 mg/kg administered intravenously slowly over 1 hour, with completion within 1 hour of the skin incision, is recommended (Class I, Level of Evidence A). A second dose of vancomycin of 7.5 mg/kg may be considered during cardiopulmonary bypass, although its usefulness is not well established (Class IIb, Level of Evidence C).
4. For patients who receive an aminoglycoside (usually gentamicin, 4 mg/kg) in addition to vancomycin before cardiac surgery, the initial dose should be administered within 1 hour of the skin incision (Class I, Level of Evidence C). Redosing an aminoglycoside during cardiopulmonary bypass is not indicated and may be harmful (Class III, Level of Evidence C).

There is a considerable body of evidence supporting the need for the timely administration of preoperative antibiotics, which means administration within 1 hour of the skin incision [48, 49]. These data accrue from numerous animal and clinical studies and are broadly applicable to all procedures for which prophylactic antibiotics are administered [50, 51]. In spite of the relative paucity of controlled randomized or large-scale retrospective studies to address this issue specifically in cardiac surgery, the timing of the administration of the prophylactic antibiotic is quite important to the cardiac surgical community. Cardiopulmonary bypass (CPB) is a technique that is nearly exclusively used by cardiac surgeons, and it has profound effects on the volume of distribution, and elimination kinetics of a variety of drugs including the commonly used prophylactic antibiotics such as cephalosporins, vancomycin, and aminoglycosides [52-56]. Certain drugs, including opiates, nitrates and vancomycin also have been shown to be sequestered in the components of the heart lung machine, decreasing biological availability both during and after the completion of CPB [52, 55]. Therefore, appropriate perioperative dosing of antibiotics during cardiac surgery presents unique challenges, particularly since tissue levels, specifically in bone and sternal fat, are likely more relevant than the more commonly measured serum concentrations. In fact, cefazolin tissue concentrations during surgery are clearly correlated with body weight (increased body mass index correlates with decreased tissue levels) such that therapeutic tissue levels may not be achieved in the morbidly obese patient even with 2 g administered for prophylaxis [57].

Several studies have investigated intraoperative vancomycin [54–56], cephalosporin [53, 58], and aminoglycoside [54, 59] pharmacokinetics. After a single preoperative dose of vancomycin, typically administered over 1 hour, immediately before the skin incision serum concentrations averaged 18 to 66 mg/L after a dose of either 1 g or a weight-adjusted dose of 15 mg/kg [54–56]. All of these studies also documented an 11% to 41% abrupt decrease in serum vancomycin concentration after the initiation of cardiopulmonary bypass due primarily to dilution in direct proportion to the pump prime volume. During cardiopulmonary bypass, there is a progressive decline in serum concentrations due to a combination of renal clearance and sequestration in the heart lung machine [54–56]. After a single preoperative dose, the serum level in each of the reported studies remains above the minimal inhibitory concentration (MIC) for 90% of both methicillin-sensitive and methicillin-resistant *S aureus* (1 mg/L) and coagulase-negative *Staphylococcus* (2 mg/L) throughout the procedure with an average bypass time of approximately 1 to 2 hours [54–56]. There is incomplete recovery of serum levels after bypass, however, owing to vancomycin sequestration in the heart-lung machine, alterations in protein binding, and persistent changes in the volume of distribution after bypass. Similarly, studies have shown that aminoglycosides [54], first- and second-generation cephalosporins [53, 58] have a similar (as much as 50%) reduction in serum concentration after the initiation of CPB.

As a result of the reduction in the levels of cefazolin and vancomycin immediately after and during CPB, two studies evaluated the efficacy of administering a second dose of cefazolin or a second dose of vancomycin after the initiation of cardiopulmonary bypass [15, 58]. Both studies found that with the second dosing regimen, the serum levels were above the MIC for both *S aureus* and coagulase-negative *Staphylococci* throughout the procedure. The two-dose regimen of vancomycin resulted in higher serum levels but no significant difference in sternal bone, fat, myocardial, or pericardial tissue levels [15].

It is now firmly established with good documentation from both clinical and experimental studies that readministration of a prophylactic antibiotic during surgery should be within two half-lives of the antibiotic, exclusive of any influence of the effects of cardiopulmonary bypass [48, 60]. Cefazolin has a half-life of approximately 1.8 hours, and therefore it is recommended that there should be additional dosing during surgery every 3 to 4 hours when an operation is proceeding with an open wound beyond that period. The major consideration for defining the appropriate pharmacodynamics of antimicrobials is to maintain the serum level of any antibiotic used above the MIC for the infecting pathogens, presumed in cardiac surgery to be *Staphylococcus* sp, while the operative wound remains open. This typically dictates readministration approximately every two serum half-lives of each antibiotic considered appropriate [61].

V. Guidelines for Prophylactic Antibiotics in Special Circumstances

Allergy to Penicillin

RECOMMENDATIONS

1. In patients with a history of an immunoglobulin-E (IgE)-mediated reaction to penicillin or cephalosporin (anaphylaxis, hives, or angioedema), vancomycin should be given preoperatively and for no more than 48 hours. Alternatively, skin testing may be performed in these patients and, if negative, a cephalosporin regimen administered (Class I, Level of Evidence A).
2. For patients with a history of a non-IgE mediated reaction to penicillin (such as a simple rash) or an unclear history either vancomycin or a cephalosporin is recommended for prophylaxis with the understanding that these patients have a low incidence of significant allergic reactions to cephalosporins (Class I, Level of Evidence B).
3. The addition of an aminoglycoside or other gram-negative bacterial coverage to a vancomycin antibiotic regimen may be reasonable, but its efficacy is not well established (Class IIb, Level of Evidence C).

In patients with a history suggestive of an IgE-mediated reaction to penicillin (anaphylaxis, hives, or angioedema), indiscriminate use of a cephalosporin for surgical prophylaxis in cardiovascular surgery is not advised [62]. Early studies established a cross-reactivity rate between penicillin and cephalosporins at approximately 20% [63]. More recent data including those cephalosporins in current clinical use suggests a cross-reactivity rate of less than 2% [64].

As many as 20% of the general population are labeled penicillin-allergic. Fewer than half of these will have a history suggesting an IgE-mediated reaction to penicillin. Of these, fewer than 20% will have a positive penicillin skin-test [65]. Those patients with nonsuggestive or unknown histories have a penicillin skin-test positivity rate of less than 2% [66]. Among all patients labeled penicillin-allergic, the frequency of serious reactions to cephalosporin administration is less than 1% [64].

With regard to choice of alternative prophylaxis in the presence of allergy, vancomycin appears to be best owing to its gram-positive coverage and, particularly, coverage of methicillin-resistant *S aureus*. There are concerns over lack of gram-negative coverage with vancomycin relative to cephalosporins. For this reason, an aminoglycoside, usually gentamicin, should be added. It must be recognized, however, that gentamicin is associated with nephrotoxicity and ototoxicity, and excretion is delayed after cardiopulmonary bypass [67]. Therefore, a single dose, or at most two doses, of no more than 4 mg/kg is recommended [67]. There is no study directly comparing vancomycin and vancomycin plus an aminoglycoside. A single study from 1987 compared gentamicin plus a β -lactam with the latter alone and found no benefit to the combination therapy, compounded by the appearance of resistant gram-negative organisms only in patients receiving gentamicin [13].

The use of vancomycin as an alternative to cephalosporins is not entirely benign. Vancomycin commonly causes histamine release and cutaneous reactions when administered too rapidly. It is also associated with nephrotoxicity when used in combination with other nephrotoxins and can rarely cause anaphylaxis [64, 68]. In one study [69], 116 patients (106 adults and 10 children) undergoing cardiac surgery procedures were given vancomycin. Thirty-one patients (27%) had an adverse reaction including hypotension (25%). Maculopapular edema was seen in 6% and was associated with hypotension (Red Man's syndrome) in 5 patients and bronchospasm in 1 patient.

One group used mathematical modeling to predict the most cost-effective strategy for antimicrobial prophylaxis of cardiovascular surgery patients labeled penicillin-allergic [62]. The strategy of giving vancomycin to all patients labeled with a penicillin allergy was found to be the most expensive but was associated with the lowest rate of serious allergic reaction. Giving cefazolin to all such patients was the cheapest, but it was associated with the highest rate of allergic reaction. While giving vancomycin to patients with positive skin tests improved cost effectiveness, it was thought to be impractical on a routine preoperative basis. Therefore, this group adopted a policy of using vancomycin in place of cephalosporins in patients with a history suggesting a previous IgE-mediated reaction to penicillin.

An aminoglycoside is often added to vancomycin for cardiac surgery in penicillin-allergic patients owing to its enhanced gram-negative coverage as well as its coverage of methicillin-sensitive *S aureus*. However, in a 1987 study from St. Thomas Hospital in Nashville, the only patients with resistant gram-negative sternal infections were those who received gentamicin along with either cefazolin or cefamandole [13].

Specific Issues Regarding Gram-Negative Infections

RECOMMENDATIONS

1. For institutions with an outbreak of gram-negative deep wound infections due to a specific pathogen, it is reasonable to employ a first-generation cephalosporin for routine prophylaxis (≤ 48 hours) supplemented with an appropriate antibiotic to which the offending organisms are sensitive (Class IIa, Level of Evidence C).
2. In patients with renal dysfunction requiring gram-negative prophylaxis to supplement a cephalosporin or vancomycin as the primary antibiotic, it is reasonable to use either one dose of an aminoglycoside or an antibiotic such as levofloxacin with a low incidence of renal toxicity (Class IIa, Level of Evidence C).

Topical Application of Antibiotics

CLASS IIB RECOMMENDATION. Topical antibiotics may be considered for antibiotic prophylaxis in cardiac surgery (Level of Evidence B).

Some cardiac surgeons have used topical antibiotics, usually vancomycin or gentamicin, applied to the cut sternal edges. There is some appeal to this concept given

concerns over antibiotic penetration into this area and resultant infection with *S aureus*. As in the case of intravenous vancomycin, there is concern over the promotion of resistant organisms.

A review of the literature on the use of topical vancomycin revealed a single randomized controlled trial from 1989 comparing patients treated with either vancomycin-thrombin-powdered gelatin paste (223 patients) versus treatment with thrombin-powdered gelatin paste alone (193 patients) [70]. This group from the University of Massachusetts reported a sternal infection rate of 0.45% (1 patient) in the treatment group and 3.5% (7 patients) in the control group ($p = 0.02$). Multivariate testing was performed. The use of topical vancomycin and shorter operative times predicted reduced infection rates. Another reported study of 4 patients in whom serum levels were measured after topical application without systemic administration found levels of vancomycin in 1 patient as high as 4.4 mg/L 3 to 4 hours after topical application of 1 g vancomycin powder to the sternum, which is significantly lower than would be seen with systemic administration (18 to 66 mg/L) [71].

The topical application of gentamicin has also been studied. In a randomized trial of 2,000 cardiac surgery patients, Friberg and coworkers [72] compared prophylaxis with intravenous isoxazoly-penicillin alone versus this drug plus topical application of collagen-gentamicin sponges at sternotomy closure. The topical antibiotic group had an incidence of wound infection at 4.3% and the control group, at 9% ($p < 0.001$). The same author examined serum versus local wound fluid concentrations of gentamicin in 101 patients receiving topical gentamicin during cardiac surgery and found extremely high concentrations (median 304 mg/L) in local wound fluid but very low serum concentrations (peak median 2.05 mg/L) [72].

Eklund and associates [73] recently reported a randomized controlled trial comparing topical gentamicin-collagen implants ($n = 272$) and no topical antibiotics ($n = 270$) during coronary artery bypass graft surgery. Both study groups received standard intravenous prophylaxis consisting of cefuroxime (85%) or cefuroxime and vancomycin (14%). The sternal wound infection rate was 4.0% in the topical gentamicin group and 5.9% in the control group. Deep mediastinal infections were seen in 1.1% of the topical antibiotic group and 1.9% in the control group. The authors concluded that a slight reduction in infection was seen but that the population was too small to draw a definitive conclusion. While the use of topical antibiotics is controversial and they are not used by most cardiac surgeons, the existing studies demonstrate a reduction in the wound infection rate. More study is warranted before topical antibiotics can be recommended as standard prophylaxis.

Summary Conclusions

The primary prophylactic antibiotic for adult cardiac surgery is recommended to be a first-generation cephalosporin, which is usually cefazolin. The most frequent organism cultured in cardiac SSI is *Staphylococcus*, and colonization is considered the major factor in wound

contamination. For this reason, until rapid screening tests for *S aureus* colonization are widely available, mupirocin is recommended as a routine prophylactic measure. In patients considered at high risk for a staphylococcal infection, vancomycin (one preoperative with or without one additional dose) may be reasonable as an adjuvant agent to the cephalosporin. For patients who are considered β -lactam or penicillin allergic, vancomycin is recommended as the primary prophylactic antibiotic with additional gram-negative coverage. Topical antibiotics may be useful, but the evidence to support their efficacy is limited to three randomized trials.

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Appendix

Classification of Recommendations

Class I. Conditions for which there is evidence or general agreement, or both, that a given procedure is useful and effective.

Class II. Conditions for which there is conflicting evidence or a divergence of opinion, or both, about the usefulness/efficacy of a procedure.

Class IIa. Weight of evidence favors usefulness/efficacy.

Class IIb. Usefulness/efficacy is less well established by evidence.

Class III. Conditions for which there is evidence or general agreement, or both, that the procedure is not useful/effective.

Level of Evidence

Level A. Data derived from multiple randomized clinical trials.

Level B. Data derived from a single randomized trial or from nonrandomized trials.

Level C. Consensus expert opinion.