Efficacy of Cefazolin, Cefamandole, and Gentamicin as Prophylactic Agents in Cardiac Surgery

Results of a Prospective, Randomized, Double-blind Trial in 1030 Patients

ALLEN B. KAISER, M.D., MICHAEL R. PETRACEK, M.D., JOHN W. LEA IV, M.D., DOUGLAS S. KERNODLE, M.D., ALBERT C. ROACH, PHARM.D., WILLIAM C. ALFORD, JR., M.D., GEORGE R. BURRUS, M.D., DAVID M. GLASSFORD, JR., M.D., CLARENCE S. THOMAS, JR., M.D., and WILLIAM S. STONEY, M.D.

In an effort to develop an improved regimen of antibiotic prophylaxis in cardiac surgery, 1030 patients who were to have elective cardiothoracic surgery involving a median sternotomy were selected at random to receive cefamandole or cefazolin, with or without gentamicin, in a prospective double-blind study. Cefazolin was significantly less effective than cefamandole at both the sternal (1.8% *vs.* 0.4%, respectively, $p < 0.05$) and donor sites (1.3% *vs.* 0%, respectively, $p < 0.02$). Seven *Staphylococcus aureus* infections occurred among cefazolin recipients as compared with no such infections among the patients receiving cefamandole ($p < 0.01$). All five wound infections yielding fungi or gentamicin-resistant gram-negative rods occurred in patients who had received gentamicin as a second prophylactic agent. These data suggest that gentamicin has no role as a prophylactic antibiotic in cardiac surgery and that, compared with cefamandole, cefazolin offers unreliable prophylaxis against deep infection at both the sternal and donor sites.

From the Departments of Medicine and Surgery, Saint Thomas Hospital, and Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee

PROPHYLACTIC ANTIBIOTICS have proven effective in lowering wound infection rates after cardiac surgery,[1,2] and most cardiovascular surgeons routinely use one or more antibiotics during the perioperative period. However, despite administration of prophylactic antibiotics, infections in both the sternal and donor sites continue to occur in 1–5% of patients, and controversy exists regarding the optimal prophylactic regimen.[3–6]

Since 1978, more than 1000 median sternotomies have been performed each year at Saint Thomas Hospital. Perioperative cefazolin has been the mainstay of prophylaxis. The deep sternal wound and donor site infection rates have each averaged approximately 2% for the last 5 years. The pathogen spectrum has remained relatively constant over this period of time. *Staphylococcus aureus* has accounted for approximately 40% of pathogens in sternal wounds and coagulase-negative staphylococcus, 25%. Enteric gram-negative rods, fungi, and mixed pathogens have accounted for the remainder of the identifiable pathogens.

Since the early 1980s, several studies had indicated that cefamandole was the most active cephalosporin against coagulase-negative staphylococci *in vitro*.[7–9] The clinical relevance of this finding remains unknown. Because coagulase-negative staphylococci were known to be a common pathogen in sternal wound sites in our hospital, a prospective, randomized, blinded study comparing cefamandole with the most commonly used prophylactic antibiotic, cefazolin, was instituted in November 1984. Because cephalosporin-resistant pathogens accounted for approximately one-fifth of such infections, gentamicin was also included in this trial.

Materials and Methods

Antibiotic Regimens

Using block randomization, patients were assigned to one of four prophylactic regimens. Regimen A consisted of cefazolin, 2 g intravenously (I.V.) at induction of anesthesia, 1 g every 4 hours during operation, and 1 g every 6 hours after operation for 72 hours. Regimen B included cefazolin as outlined above, plus gentamicin

Reprint requests and correspondence: Allen B. Kaiser, M.D., P.O. Box 380, Saint Thomas Hospital, Nashville, TN 37202.

Submitted for publication: April 9, 1987.

1.5 mg/kg given I.V. at the induction of anesthesia. Regimen C was cefamandole, 2 g I.V. at induction of anesthesia, 1 g every 2 hours during operation, and 1 g every 4 hours after operation for 72 hours. Regimen D included cefamandole as above, except that gentamicin 1.5 mg/kg was given I.V. at the induction of anesthesia. No dose adjustments were made for renal failure. Placebo doses were not included. All randomization was performed by one investigator (A.C.R.). Drugs were dispensed in minibags labeled "Mancef" and marked with time for infusion.

Definition of Infection

Wounds were considered infected if (1) purulence was present; and (2) deep subcutaneous tissue (Class II infection), sternum (Class III infection), or posterior mediastinum (Class IV infection) was involved. Class I or superficial infections of the subcutaneous tissue of the sternum or donor site were not included. By definition, such infections appeared trivial upon inspection, and neither prolonged hospitalization nor altered outpatient management was required. Class I sternal infections were tabulated prospectively, however. When the code was broken at the close of the study, the Class I infections were noted to be evenly distributed among the four prophylactic regimens. One Class I infection occurred among regimen A recipients, three among regimen B recipients, two among regimen C recipients, and three among regimen D recipients.

At 3-month intervals, the attending surgeon, at least one other cardiac surgeon investigator, and one nonsurgeon member of the investigative team (A.B.K.) reviewed the clinical course of all patients with wounds exhibiting inflammation and/or drainage. An agreement was reached as to the presence or absence of infection and the depth of infection. Care was also taken at this time to exclude patients with secondary infections in the sternal area that may have developed as a complication of ischemic necrosis of the underlying tissue. One such patient, who was eventually identified as a regimen B recipient, met this criterion and was excluded. She was a 63-year-old patient with long-standing Raynaud's disease and was receiving steroid therapy; she experienced necrosis of the entire hemisternum associated with the use of the ipsilateral internal mammary artery for implantation. According to protocol design, after approximately 1000 patients had been studied, antibiotic regimens associated with infections were identified with a letter code by the pharmacist. At that time, in January 1986, a significant difference in treatment categories was noted. The code was subsequently broken, and the study ended.

Patient Selection

The study design was approved by the Saint Thomas Hospital Institutional Review Board. Written informed consent was obtained from all participants. All adult patients scheduled for elective median sternotomy incision who were free of infection and not receiving any therapeutic antibiotics were considered eligible for inclusion in the study. To remain in the study, patients had to adhere to the antibiotic protocol for at least 24 hours.

All patients showered or bathed with an antiseptic-containing soap the evening before operation. Shaving of the operative site(s) was performed in the holding area immediately before operation. The mediastinum was routinely irrigated with a kanamycin solution (1 g/L of saline) before closure.

Drug Levels

Early in the course of this study, an average of seven plasma specimens per patient were obtained from 25 patients during the operative period. Specimens were frozen at −20 C and shipped to Eli Lilly Laboratories for analysis. Gentamicin levels were analyzed by radioimmunoassay techniques. Cefamandole and cefazolin plasma levels were measured by bioassay. Antibiotic levels were plotted against time on semilog paper and the best straight line determined. The lowest intraoperative serum concentration of antibiotic (usually occurring immediately before antibiotic redosing) was estimated from this plot.

Cost Analysis

Seven of 11 patients with sternal wound infection and five of the six patients with donor site infection had evidence of infection develop after discharge and were re-admitted to Saint Thomas Hospital specifically for management of the infections. All re-admission hospital charges for these 12 patients were considered to be direct costs of infection. For the patients whose wound infections developed before discharge, the charges were considered to be secondary to infection only during the portion of the hospital stay that was clearly prolonged as a result of infection.

Risk Analysis

Demographic data on patients who had cardiac surgery at Saint Thomas Hospital are maintained by an in-office minicomputer. Host risk factors and intra-operative and postoperative complications are identified on work sheets by physician assistants. All such infor-

TABLE 1. *Sternal and Donor Site Infection Rates in Cardiothoracic Surgery: A Comparison of the Efficacy of Prophylactic Antibiotics*

Prophylactic Antibiotics	Patients Who Had Median Sternotomy	Sternal Wound Infections (%)	Patients Requiring Donor Site Incision*	Donor Site Infections (%)
Cefazolin	255	3 (1.2)	239	4 (1.7)
Cefazolin–gentamicin	253	6 (2.4)†	236	2 (0.8)
Cefamandole	259	2 (0.8)	246	0 (0)
Cefamandole–gentamicin	263	0 (0)†	242	0 (0)
Total	1030	11 (1.1)	963	6 (0.6)
All cefazolin	508	9 (1.8)‡	475	6 (1.3)†
All cefamandole	522	2 (0.4)‡	488	0 (0)†
Total	1030	11 (1.1)	963	6 (0.6)
With gentamicin	516	6 (1.2)	478	2 (0.4)
Without gentamicin	514	5 (1.0)	485	4 (0.8)
Total	1030	11 (1.1)	963	6 (0.6)

* Includes those patients who had coronary artery bypass and required a leg incision for the harvesting of saphenous vein.

† Difference in infection rates is significant at $p < 0.02$, Fisher's exact test.

‡ Difference in infection rates is significant at $p < 0.05$, Fisher's exact test.

mation is obtained at the time of hospitalization and entered prospectively into the computer program. These data were available for analysis for patients entered into the study. Age and the presence of diabetes mellitus, obesity, hypertension, use of internal mammary arteries in coronary artery bypass, perfusion time, and cross-clamp time were tabulated. All statistical tests for association of frequencies (contingency table analysis) were performed by chi square analysis or by Fisher's exact test when expected frequencies were less than five.

Results

Patient Demographics and Risk Factors

Of 1446 patients who had median sternotomy at Saint Thomas Hospital from November 1984 through January 1986, 1057 (73%) were entered into the study. Operations were subsequently canceled for 11 patients, and nine patients were removed from the study for failure to adhere to the antibiotic regimen for the first 24 hours. Seven patients scheduled for thoracic surgery not involving a median sternotomy were inadvertently entered into the study and were later removed. The 27 patients excluded from the study after entry were evenly distributed among the four prophylactic regimen groups.

A total of 1030 patients were therefore available for evaluation. Of these patients, 57 had median sternotomy for valve replacement only, 44 for valve replacement and coronary artery bypass, 919 for coronary artery bypass alone, and 10 for other cardiac surgical procedures. During this period of time, 389 patients had median sternotomy but were not considered for the study. Nine sternal wound infections determined retrospectively by routine nosocomial surveillance occurred among the patients who were not from the study, for an infection rate of 2.2%. Cefazolin was usually given as a prophylactic agent in these patients who were not from the study, although cefamandole and vancomycin, with or without gentamicin, were also used occasionally.

An analysis of infections by the seven participating surgeons demonstrated no significant difference in surgeon-specific infection rates. All risk factors were homogeneously distributed among the four treatment regimens, between patients receiving cefazolin *versus* cefamandole, and between patients receiving gentamicin *versus* no gentamicin. There were no cases of prosthetic valve endocarditis among the 101 patients who had valve replacement.

Efficacy of Prophylaxis

Sternal wound infections developed in 11 of the 1030 patients who had elective median sternotomy (Table 1). Donor site infections developed in six of 963 patients requiring a donor site incision. Patients receiving cefamandole–gentamicin had a significantly lower sternal wound infection rate than those receiving cefazolin–gentamicin (0% and 2.4%, respectively; $p < 0.02$). When infection rates for the regimens that included gentamicin are compared with rates for those that did not, the results are virtually identical (1.2% *vs.* 1.0%). When the results were analyzed by individual cephalosporins, patients receiving cefamandole with or without gentamicin had a significantly lower infection rate than patients receiving cefazolin with or without gentamicin at both the sternal (0.4% *vs.* 1.8%, $p < 0.05$) and donor sites (0% *vs.* 1.3%, $p < 0.02$).

TABLE 2. *Pathogens, Class of Infection, and Prophylaxis Regimen*

	Sternal Infections		Donor Site Infections	
Antibiotic Regimen	Patient No.*/ Class of Infection	Pathogen(s)†	Patient No./Class of Infection	Pathogen(s)
Cefazolin	1/III	*Staphylococcus aureus* (M, K)	12/II	*S. aureus;* CNS; enterococci
	2/III	*S. aureus*	13/II	*Escherichia coli;* enterococci
	3/II	CNS (M, K, G)	14/II	*S. aureus*
			15/II	*S. aureus; Proteus mirabilis*
Cefazolin/gentamicin	4/II	*S. aureus*	16/II	Pseudomonas (K, G); Proteus
	5/III	*S. aureus* Citrobacter (K, G)		Klebsiella
	6/II	CNS (M, K, G) Pseudomonas (K)	17/II	Pseudomonas (K, G)
	7/III	Pseudallesheria		
	8/IV	*Candida tropicalis*		
	9/II	*E. coli*		
Cefamandole	10/II	CNS (M, K, G)		
	11/II	(No growth)		

* All patients had coronary artery bypass surgery (CAB) except patients 5 (ventricular aneurysmectomy) and 7 (CAB plus aortic valve replacement).

† Resistance (if present) to cefazolin/cefamandole (K) is noted within parentheses. Coagulase-negative staphylococci (CNS) and *S. aureus* were also tested for resistance to methicillin (M); and gram-negative rods were tested to resistance to gentamicin (G). All *S. aureus* infections were resistant to penicillin. Susceptibility testing was performed by standard Kirby-Bauer sensitivity testing.

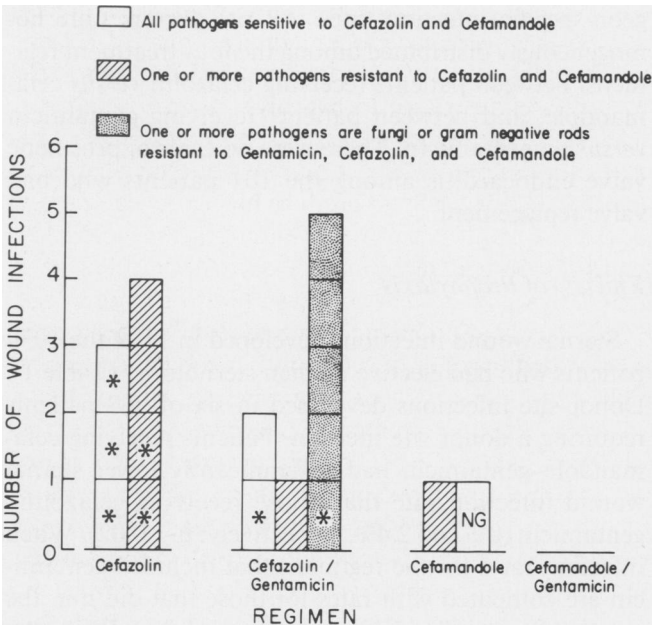

FIG. 1. Correlation of prophylactic antibiotics and antimicrobial resistance of pathogens. One infection in a cefamandole recipient yielded no growth (NG) on culture. All infections yielding *S. aureus* (denoted by an asterisk) occurred among cefazolin or cefazolin–gentamicin recipients. Resistance of fungi and gram-negative rods to cefazolin–cefamandole and gentamicin occurred only in cefazolin–gentamicin recipients. No infections occurred among cefamandole–gentamicin recipients.

Infecting Organism

All seven wound infections yielding *S. aureus* (four sternal and three donor sites) occurred in patients receiving cefazolin as a prophylactic agent (seven of 508 cefazolin recipients *vs.* none of 522 cefamandole recipients, $p < 0.01$). Coagulase-negative staphylococci as a single or co-infecting pathogen were identified in three sternal wound sites and one donor site. Three of these infections occurred in patients receiving cefazolin (Table 2). In five wound infections, all pathogens isolated were susceptible to both cefazolin and cefamandole (Fig. 1). All of these infections occurred in recipients of cefazolin or cefazolin–gentamicin (five of 508 cefazolin recipients *vs.* none of 522 cefamandole recipients, $p < 0.05$). Of five wound infections yielding gram-negative bacilli resistant to gentamicin (3) or fungi (2), all occurred in patients who had received gentamicin in addition to cefazolin as a prophylactic agent.

Pharmacokinetics

Intra-operative antibiotic levels were measured in 12 patients receiving cefazolin, 13 receiving cefamandole, and 14 receiving gentamicin. The mean trough levels of antibiotics during the bypass procedure averaged 39

μg/mL for cefazolin, 21 μg/mL for cefamandole, and 1.5 μg/mL for gentamicin. However, the trough levels ranged widely among patients. For cefazolin recipients, the lowest trough plasma concentration was 22 μg/mL. For the cefamandole recipients, the lowest trough concentration was 11 μg/mL, and for the gentamicin recipients, 0.7 μg/mL. By the close of the surgical procedure, gentamicin levels in gentamicin recipients were negligible.

Infection Complications and Costs

The excess costs of hospitalization attributable to infection are outlined in Table 3. Among the six patients with Class II infections of the sternal wound, two infections resulted in prolongation of hospitalization and three in re-admission to Saint Thomas Hospital. One patient was managed by repeated incision and drainage of the infection in the physician's office. All Class III and Class IV infections at the sternal site occurred among cefazolin or cefazolin–gentamicin recipients. Three patients with Class III infections of the sternum required re-admission to the hospital; the fourth patient's primary hospitalization was prolonged extensively. A Class IV infection developed in one patient during the initial hospitalization. This patient eventually died of multiple complications. Five of the six deep (Class II) infections occurring at the donor sites resulted in rehospitalization. The average cost of donor site infections was $8500, an amount similar to the $9000 cost of Class II infection at the sternal incision site. Physician fees and office charges related to both sternal and donor site infections were not determined.

TABLE 3. *Excess Cost of Hospitalization Attributable to Infection*

Depth of Infection (No. Patients)	Total Excess Costs ($)	Mean Excess Cost ($)
Sternal site		
Class II (6)*	53,500	8,900
Class III (4)	160,200	40,000
Class IV (1)	73,300	73,300
All sternal sites (11)	287,000	26,000
Donor site		
Class II (6)	51,000	8,500
All sites (17)	338,000	19,882

* Both infections associated with cefamandole prophylaxis were Class II infections.

Discussion

A primary goal of the design of this study was to evaluate the relative efficacy of cefamandole *versus* cefazolin in preventing infection resulting from coagulase-negative staphylococci. Although three of the four infections yielding coagulase-negative staphylococci occurred in cefazolin recipients, infections resulting from coagulase-negative staphylococci were too infrequent to allow conclusions to be drawn regarding the relative efficacy of these two cephalosporins. One can only speculate as to whether a significant advantage of cefamandole *versus* cefazolin could be demonstrated in a setting where coagulase-negative staphylococci were a more frequent cause of postsurgical wound infection.

Of great interest, however, was the finding that infections resulting from *S. aureus* were significantly less likely to occur among the cefamandole recipients. Even if the one infection resulting from a methicillin-resistant *S. aureus* in a cefazolin recipient is not included in the analysis, significantly more *S. aureus* infections occurred among cefazolin recipients than among cefamandole recipients ($p < 0.02$). Slama et al. also recently noted that cefazolin tended to be less effective in preventing *S. aureus* infection after cardiac surgery than either cefamandole or cefuroxime.[6] *In vitro* studies are not currently available that directly explain why cefamandole should prevent *S. aureus* infection more effectively than cefazolin. As early as 1973, however, failures of cefazolin in treating infection resulting from *S. aureus* have been reported.[10,11] Although the precise cause of this phenomenon remains unexplained, a number of investigators have noted that cefazolin appeared to be more vulnerable to hydrolysis by the beta-lactamase of certain *S. aureus* strains than either cefamandole or cephalothin.[12–16] Cefamandole has also been shown experimentally to produce higher concentrations than either cefazolin or cephalothin in fibrin clots.[17,18] Clinically, prophylactic use of cefamandole has been shown to result in high concentrations of antibiotic in atrial muscle and cardiac valve tissues.[19] Whether the inferior performance of cefazolin is related to its vulnerability to *S. aureus* beta-lactamase, to inferior tissue levels, or to other factors is unknown. Whatever the reason(s), data are accumulating to suggest that cefazolin may not be as reliable as other cephalosporins in prophylaxis of wound infection in cardiac surgery.

One conclusion of our study was that gentamicin, when given as a single preoperative dose, offered no protection from infection resulting from cephalosporin–resistant pathogens. Although gentamicin combined with cefamandole was the most effective of the four prophylactic regimens, an analysis of infection rates of the various antibiotic combinations (Table 2) suggests that it was the use of cefamandole *per se,* not cefamandole plus gentamicin, that best explained the observed

differences in infection rates. Another interpretation of the apparent lack of gentamicin effectiveness may be related to the use of kanamycin irrigation in all patients. Although there are inadequate data to settle the issue, topical kanamycin may, in fact, be as efficacious as systemically administered gentamicin, thereby blunting any possible demonstration of the latter's efficacy.

However, it was of considerable interest to note that all infections resulting from cephalosporin-resistant (Patient 6) or cephalosporin and gentamicin-resistant (Patients 5, 16, and 17) gram-negative enteric pathogens occurred in patients receiving gentamicin as a second prophylactic agent. Moreover, both fungal infections occurred in gentamicin recipients (Patients 7 and 8). This failure/adverse effect of gentamicin was disappointing but not completely unexpected. Gentamicin has yet to be proven effective as a prophylactic agent in prospective clinical trials in clean surgery.[20] Furthermore, a previous study in cardiac surgery suggested that the routine use of gentamicin prophylaxis can be associated with a marked increase in gentamicin resistance within the hospital environment.[21] Given the fact that plasma levels were uniformly low in all patients at the close of operation, an observation noted previously,[22] it may be that prophylactic efficacy cannot be realized unless frequent doses of this agent are given. The threat of ototoxicity or nephrotoxicity associated with repeated doses must, however, serve as a caution, if not a deterrent, in designing prospective clinical trials involving frequent doses of gentamicin.

Because failure of prophylaxis in cardiothoracic surgery has been related to inadequate serum levels at the close of prolonged procedures,[4,23] we administered intraoperative doses of cefamandole and cefazolin so that adequate levels of these cephalosporins would be maintained throughout the surgical procedure. The results of our cephalosporin serum assays obtained during cardiopulmonary bypass were consistent with the findings of others.[24–27] Based upon these data, cefazolin dosing intervals might safely be lengthened to 6 or 8 hours. However, pending collection of additional data, frequent doses of cefamandole (every 2 hours) should be used during bypass if predictably high levels are to be achieved throughout the surgical procedure.

In May 1986, cardiac surgeons at Saint Thomas Hospital changed from the predominant use of cefazolin to cefamandole. Subsequent to this change, only eight deep sternal wound infections have developed among 1131 patients (infection rate, 0.7%). Five deep donor site infections have also occurred during this time. *S. aureus* has been isolated from four of these 13 infections. These follow-up data suggest that cefamandole continues to be preferred to cefazolin for prophylaxis of cardiac surgery in our hospital.

In view of these results, single-dose gentamicin, as an adjunct to cephalosporin prophylaxis, probably has no place in routine prophylaxis in cardiac surgery. Efficacy has not been demonstrated, and there is a suggestion that the use of gentamicin prophylactically may encourage the emergence of resistant organisms. Whether multiple dosing of gentamicin or the use of other broad-spectrum antibiotics would be effective in preventing gram-negative rod infection is unknown. The apparent failure of cefazolin in preventing wound infection, especially infection resulting from *S. aureus,* has important implications in view of the widespread current use of this antibiotic. Cefazolin has clearly demonstrated its effectiveness as a prophylactic agent in a wide variety of clean and clean-contaminated surgical procedures.[20] Nevertheless, this study and the recent study by Slama et al.[6] have now demonstrated its inferiority to other cephalosporins in prophylaxis of wound infections in cardiac surgery.

References

1. Fong IW, Baker CB, McKee DC. The value of prophylactic antibiotics in aorta-coronary bypass operations: a double-blind randomized trial. J Thorac Cardiovasc Surg 1979; 78:908–913.
2. Penketh ARL, Wansbrough-Jones MH, Wright E, et al. Antibiotic prophylaxis for coronary artery bypass graft surgery. Lancet 1985; 1:1500.
3. Beam TR, Bhayana JN, Raab TA, et al. Failure of antimicrobial prophylaxis in open heart surgery (abstract). Clinical Research 1981; 29:726A.
4. Platt R, Munoz A, Stella J, et al. Antibiotic prophylaxis for cardiovascular surgery: efficacy with coronary artery bypass. Ann Intern Med 1984; 101:770–774.
5. Antibiotic cover for cardiac surgery. Lancet 1985; 2:701–702.
6. Slama TG, Sklar SJ, Misinski J, Fess SW. Randomized comparison of cefamandole, cefazolin, and cefuroxime prophylaxis in open-heart surgery. Antimicrob Agents Chemother 1986; 29:744–747.
7. Kagan BM, Slotnick IJ, Choto RG. *In vitro* susceptibility of hospital isolates to cefamandole. Current Therapeutic Research 1980; 28:498–503.
8. Williams TW Jr, Smith NJ, Wright S. *In vitro* evaluation of vancomycin (VA), cefamandole (MA), cefazolin (CZ), cefuroxime (CXM), and Cefonicid (CID) against methicillin resistant *Staphylococcus epidermidis.* ASM Annual Meeting, March 1986, No. 67 (abstract).
9. Menzies RE, Cornere BM, MacCulloch D. Cephalosporin susceptibility of methicillin-resistant, coagulase-negative staphylococci. Antimicrob Agents Chemother 1987; 31:42–45.
10. Quinn EL, Pohlod D, Madhavan T, et al. Clinical experiences with cefazolin and other cephalosporins in bacterial endocarditis. J Infect Dis 1973; 128:S386–S391.
11. Bryant RE, Alford RH. Unsuccessful treatment of staphylococcal endocarditis with cefazolin. JAMA 1977; 237:569–570.
12. Sabath LD, Garner C, Wilcos C, Finland M. Effect of inoculum and of beta-lactamase on the anti-staphylococcal activity of thirteen penicillins and cephalosporins. Antimicrob Agents Chemother 1975; 8:344–349.

13. Farrar WE, Gramling PK. Antistaphylococcal activity and beta-lactamase resistance of newer cephalosporins. J Infect Dis 1976; 133:691–695.
14. Fong IW, Engelking ER, Kirby WMM. Relative inactivation by *Staphylococcus aureus* of eight cephalosporin antibiotics. Antimicrob Agents Chemother 1976; 9:939–944.
15. Chapman SW, Steigbigel RT. Staphylococcal beta-lactamase and efficacy of beta-lactamase antibiotics: *in vitro* and *in vivo* evaluation. J Infect Dis 1983; 147:1078–1089.
16. Regamey C, Libke RD, Engelking ER, et al. Inactivation of cefazolin, cephaloridine, and cephalothin by methicillin-sensitive and methicillin-resistant strains of *Staphylococcus aureus.* J Infect Dis 1975; 132:291–294.
17. Bergeron MG, Nguyen BM, Trottier S, Gauvreau L. Penetration of cefamandole, cephalothin, and desacetylcephalothin into fibrin clots. Antimicrob Agents Chemother 1977; 12:682–687.
18. Weinstein AJ, Fieker D, Hall G. Cefamandole-aminoglycoside therapy of experimental enterococcal endocarditis. J Antimicrob Chemother 1983; 11:61–67.
19. Archer Gl, Polk RE, Duma RJ, Lower R. Comparison of cephalothin and cefamandole prophylaxis during insertion of prosthetic heart valves. Antimicrob Agents Chemother 1978; 13:924–929.
20. Kaiser AB. Drug therapy: antimicrobial prophylaxis in surgery. N Engl J Med 1986; 315:1129–1138.
21. Roberts NJ Jr, Douglas RG Jr. Gentamicin use and *Pseudomonas* and *Serratia* resistance: effect of a surgical prophylaxis regimen. Antimicrob Agents Chemother 1978; 13:214–220.
22. Daschner FD, Eschenbruch E, Metz B, et al. Penetration of gentamicin into heart valves, subcutaneous and muscular tissue of patients undergoing open heart surgery. J Cardiovasc Surg 1981; 22:581–584.
23. Goldmann DA, Hopkins CC, Karchmer AW. Cephalothin prophylaxis in cardiac valve surgery: a prospective, double-blind comparison of two-day and six-day regimen. J Thorac Cardiovasc Surg 1977; 73:470–479.
24. Akl B, Richardson G. Serum cefazolin levels during cardiopulmonary bypass. Ann Thorac Surg 1980; 29:109–112.
25. Bryan CS, Smith CW Jr, Sutton JP, et al. Comparison of cefamandole and cefazolin during cardiopulmonary bypass. J Thorac Cardiovasc Surg 1983; 86:222–225.
26. Klepetko W, Georgopoulos A, Graninger W, et al. Perioperative cefamandole prevention in aortocoronary bypass operations: the course of serum levels in extracorporeal circulation. Langenbecks Arch Chir 1984; 362:237–243.
27. Polk RE, Archer Gl, Lower R. Cefamandole kinetics during cardiopulmonary bypass. Clin Pharmacol Ther 1978; 23:473–480.