Antibiotic Prophylaxis in Vascular Surgery

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Preoperative and intraoperative antibiotic prophylaxis of infection in peripheral vascular surgery has been widely used although controlled studies have been lacking. A randomized, prospective, double-blind study of cefazolin versus placebo during 565 arterial reconstructive operations was performed at this hospital from February 1976 through August 1977. Among the 462 patients undergoing surgery of the abdominal aorta and lower extremity vasculature, there was a highly significant difference in the infection rates: 6.8% for placebo recipients versus 0.9% for cefazolin recipients ($p < .001$). Of the 18 infections, four involved vascular grafts and all four graft infections occurred in the placebo group. Over 8% of abdominal wounds of patients receiving placebo became infected versus 1.2% of cefazolin patients ($p < .05$). Groin wounds were infected infrequently, 1.1% for placebo patients versus none for cefazolin patients. No infections occurred among 103 brachiocephalic procedures. Skin antisepsis was analyzed retrospectively. Infection rates were significantly higher ($p < .01$) following hexachlorophene-ethanol versus a povidone-iodine skin preparation. Adverse effects of cefazolin were carefully monitored: no rash, phlebitis, or emergence of resistant strains was observed. A brief perioperative course of cefazolin and povidone-iodine skin antisepsis are recommended in vascular reconstructive surgery of the abdominal aorta and lower extremity vasculature.

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THE EFFICACY OF PERIOPERATIVE antimicrobial prophylaxis of wound infections following peripheral vascular surgery has been widely debated. Controlled studies have been lacking, in part because, as pointed out by Szilagyi, the low wound infection rate associated with peripheral vascular surgery would require a study of very large size to achieve statistically significant results.[16] In the absence of such controlled studies, proponents of pre-, peri-, and postoperative antimicrobial prophylaxis have emphasized the high morbidity and mortality associated with graft infections,[7] and the success of prophylaxis in uncontrolled reports,[10] and the reproducible efficacy of antimicrobials in experimental studies.[1,13,19] Opponents of unrestricted prophylaxis point out that the relatively low infection rate in peripheral vascular surgery does not justify the needless exposure of the vast majority of patients to potentially toxic antimicrobials.[16] Additionally, results from occasional clinical studies have suggested that prophylactic antimicrobials may not be efficacious in peripheral vascular surgery.[6] Thus, Simmons and Stoley commented vigorously that "the prophylactic use of antibiotics should undergo the greatest scrutiny since this common use (especially in surgery) is supported by very few appropriately designed, randomized, controlled clinical trials.[15]

In an effort to resolve this important issue, a prospective, randomized, double-blind study evaluating the efficacy of cefazolin versus placebo in preventing infections in peripheral vascular surgery was performed.

Methods

Selection of Patients

The study was conducted at this institution from February 1976 through August 1977. All patients scheduled to undergo vascular surgery were considered eligible for participation in the study if: 1) elective abdominal aortic or peripheral vascular surgery was performed; 2) no preoperative area of "wet gangrene" or cellulitis was present; 3) there was no history of severe penicillin allergy (anaphylaxis, wheezing or exfoliative dermatitis) or of cephalosporin allergy; 4) no preoperative antimicrobials had been administered; 5) written informed consent was obtained. Two patients did not enter the study because of refusal to participate; one patient was excluded because of a history of a severe penicillin reaction; and only 18 patients (3% of the total) were inadvertently omitted from the study. During the 19 month evaluation 565 patients completed the study. Antimicrobials were given within 24 hours postoperatively in seven patients

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inadvertently during additional emergency surgery. All seven patients had received their preoperative and appropriate intraoperative cefazolin or placebo; they were continued in the study; no wound infections occurred in these patients.

Midway through the study no wound complications had occurred among 103 patients undergoing carotid artery or brachial artery surgery. Thus, patients undergoing brachiocephalic procedures were no longer included in the study after February 1977.

The Administration of Antimicrobials

On the day prior to surgery the hospital pharmacist (ACR) assigned each patient to receive either intravenous placebo (normal saline) or antimicrobial (cefazolin in normal saline) using a table of random numbers. All medications were specifically designed as "placef" (placebo-cefazolin) and given a code number. The medications were indistinguishable by gross inspection. All involved nurses were given instruction in the logistics of the study. One hundred ml of saline with or without 1 g of cefazolin was given with the on-call medications and postoperatively every six hours for four doses. During surgery of greater than four hours duration an additional 100 ml of saline with or without 500 mg of cefazolin was given. The code was not revealed on any of the patients until all decisions regarding the status of the wound had been concluded.

Evaluation of the Patients

Each patient was inspected daily specifically for signs of phlebitis, rash, fever, and wound infection. The vast majority of patients were seen by the attending surgeons at least once following hospital discharge and late wound complications were reported.

Wound infections were categorized according to depth of involvement: superficial (Class I), subcutaneous tissue (Class II), and graft (Class III) as previously described by Szilagyi et al.[16] Wounds were considered to be infected when purulence (in the absence of prior ischemic necrosis) was noted or when rupture of the graft occurred in the presence of purulence and/or positive cultures. Each instance of possible infection was evaluated by at least three of the authors prior to assignment to the infected or non-infected category.

Monitors

Two physicians not directly involved in the study served as study monitors. They were apprised of the results of the study at intervals and participated in the decision to terminate the study in August 1977.

Analysis of Results

Every procedure was recorded on a marginal punch card for sorting and tabulation. All statistical analyses were performed using Fisher's Exact Test.

Results

Wound infection rates in the 462 patients undergoing surgery of the abdominal aorta and/or lower extremity vasculature are shown in Table 1. There was a highly significant difference in the infection rates among the 237 placebo recipients (6.8%) when compared with the 225 cefazolin recipients (0.9%) ($p < .001$). The two infections in the cefazolin group were Class II infections. It was striking that all four graft infections (Class III) occurred in the placebo group. Two of these patients died and two underwent above-the-knee amputations.

Bacterial pathogens were isolated from the wound and/or bloodstream of 17 of the 18 infected patients (Table 2). One purulent Class I infection was not cultured. Cefazolin-sensitive coagulase-positive staphylococci predominated, isolated in pure culture from nine infections or in association with a cefazolin-resistant *E. coli* (one patient) or with anaerobic bacilli (one patient). In the remaining six patients gram-negative bacilli (pseudomonas, *E. coli*, klebsiella, and enterobacter) were isolated either in pure culture or mixed with enterococci or coagulase-negative staphylococci. Five infections due to cefazolin-resistant organisms occurred, and gram-negative bacilli accounted for the resistance in each instance.

TABLE 1. *Wound Infections Among Patients Receiving Cefazolin or Placebo Prophylaxis*†

Prophylaxis	Number of Infections	Number of Patients	Per Cent Infected	Number of Infections by Category		
				Class I	Class II	Class III
Cefazolin	2	225	0.9%*	0	2	0
Placebo	16	237	6.8%*	4	8	4
Total	18	462	3.9%			

* The difference is significant at $p < .001$. † Brachiocephalic procedures are not included.

The cefazolin prophylaxis did not predispose to cefazolin resistance (Fig. 1). Wound infections harboring cefazolin-resistant pathogens were no more frequent in the patients receiving cefazolin prophylaxis than in patients receiving placebo. The most striking finding however was the total absence of cefazolin-sensitive pathogens in patients receiving perioperative cefazolin. This difference (12 infections among 237 placebo recipients versus no infections among 225 cefazolin recipients) in the isolation of cefazolin-sensitive strains was highly significant ($p < .0005$) and accounted for the overall difference in the study.

Infection rates were analyzed by surgical procedure and site of the skin incision (Tables 3 and 4). As noted in Table 3, there were no infections among 103 brachiocephalic procedures. The highest infection rate occurred following abdominal aortic resection (7.8%) and one Class III infection developed. Procedures involving a bypass of the femoral artery and lower extremity vasculature were associated with a 4.8% infection rate and three Class III infections occurred. Compared to the placebo group, cefazolin prophylaxis was associated with a significantly lower infection rate ($p < .01$) for the femoral-lower leg bypass procedures.

As noted in Table 4 abdominal sites were involved in 184 procedures and infection occurred in 4.9%. Significantly higher infection rates ($p < .05$) were observed in the placebo group undergoing abdominal incisions than among comparable patients given cefazolin prophylaxis. Only 0.6% of groin sites became infected; however, both infections at this site occurred among placebo recipients.

Adverse reactions. Potentially adverse effects of cefazolin were evaluated prospectively (double-blind) by daily observation for rash and phlebitis. The postoperative intravenous infusion had to be discontinued prematurely in two patients because of a truncal rash and in two patients because of severe intravenous related phlebitis. All four of these patients were found to have received placebo when the code was subsequently broken; phlebitis and rash did not occur among the patients given cefazolin.

TABLE 2. *Bacterial Pathogens Isolated from Wound Infections*

Pathogen	Number of Pathogens by Category of Infection			Total Number of Pathogens
	I	II	III	
Staphylococcus aureus (coagulase positive)	3	5	1	9
Mixed: staphylococci and gram-negative bacilli		1	1	2
Gram-negative enteric bacilli		2	2*	4
Mixed: enteric bacilli and gram-positive cocci		2		2
No culture	1			1
Total	4	10	4	18

* One patient developed a urinary tract infection and sepsis due to a cefazolin-sensitive *E. coli* 48 hours after graft implantation; graft dehiscence occurred 13 days postoperatively; cultures obtained on the seropurulent fluid at the time of re-exploration while the patient was on antimicrobials were sterile.

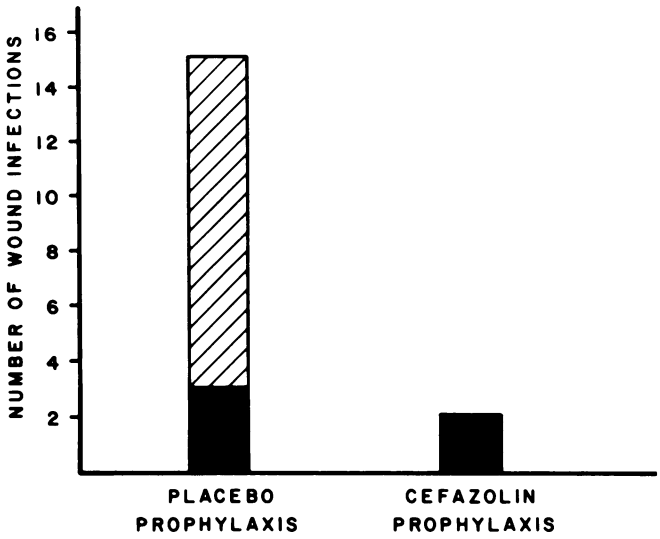

FIG. 1. Cefazolin sensitivity of pathogens isolated from 17 wound infections. One Class I infection was not cultured. A wound infection was considered to be cefazolin-sensitive if all isolates were sensitive to cefazolin. A wound infection was considered to be cefazolin-resistant if any isolate was resistant to cefazolin. Striped area: cenazolin-sensitive infection. Solid area: cefazolin-resistant infection.

Preoperative antiseptic skin preparation. Midway through the study it was noted that a number of patients had received a hexachlorophene-ethanol skin preparation as contrasted with a povidone-iodine-containing skin preparation used in the majority of the patients (Table 5). The hexachlorophene had been used as an initial scrub followed by an ethanol scrub; seven infections followed (10.3%). The patients who received either povidone-iodine alone or hexachlorophene-povidone-iodine experienced only a 2.8% infection rate ($p < .01$). During the second half of the study all patients received a povidone-iodine preparation and no additional subsets of high infection were identified.

The infection rate among patients who had received the hexachlorophene-ethanol skin preparation and systemic placebo prophylaxis was extremely high (18.9%). The marked protection afforded by cefazolin in these patients (no infections in 31 patients, $p < .01$) suggests that the efficacy of systemic prophylaxis is more pronounced with higher infection rates.

TABLE 3. *Occurrence of Infection by Surgical Procedure and Prophylactic Regimen*

Surgical Procedure	Total Procedures Infection/Procedures (%)	Prophylactic Regimen	
		Cefazolin Infection/Procedures (%)	Placebo Infection/Procedures (%)
Brachiocephalic	0/103	0/ 55	0/ 48
Abdominal aortic resection*	7/ 90 (7.8)	1/ 39 (2.6)	6/ 51 (11.8)
Aortofemoral bypass†	1/ 94 (1.1)	0/ 47	1/ 47 (2.1)
Femoral-lower leg bypass	10/208 (4.8)	1/105 (1.0)	9/103 (8.7)
Femoral artery surgery‡	0/ 56	0/ 27	0/ 29
Popliteal artery surgery	0/ 14	0/ 7	0/ 7

* Includes renal artery reconstruction. † Includes six patients with aorto-femoral-popliteal bypass. ‡ Includes femorofemoral bypass and femoral endarterectomy.

The efficacy of cefazolin versus placebo in preventing wound infection was reevaluated for the 394 patients receiving a povidone-iodine-containing skin preparation. Only two of 194 patients (1.0%) receiving cefazolin developed a wound infection versus 9 of 200 patients (4.5%) receiving placebo. A significant difference ($p < .05$) in infection rate between the cefazolin and placebo groups was again observed.

Discussion

Peripheral vascular surgery is associated with low infection rates but differs from many surgical procedures with low infection rates in that the morbidity of infection is extremely high.[7,8,16] This fact was amply demonstrated in this study by the two amputations and two deaths among the four patients with graft infections. However, indiscriminate use of antimicrobials could not be condoned as over 95% of patients undergoing peripheral vascular surgery would be needlessly exposed to potential side-effects of antimicrobials: allergic reactions, phlebitis, and the selection of resistant flora. Thus, despite the low rate of infection, a properly controlled prospective study was warranted.

The major considerations of the study were in regard to the efficacy and adverse effects of cefazolin. The results were conclusive: wound infections occurred significantly less often following perioperative cefazolin prophylaxis and no adverse effects (phlebitis, rash, antimicrobial resistance) were related to the 24–36 hours of cefazolin use.

All four of the Class III infections (graft involvement) occurred in the placebo group. Although the difference in the rate of Class III infections between the cefazolin and placebo groups was not statistically significant ($p = .062$), a consistent trend of more infections in the placebo group was observed with the Class I and Class II infections. Given the significant difference in infection rates when the wounds were considered together, the authors and monitors were unwilling to continue the study in order to accrue additional Class III infections to prove the point statistically.

Several unexpected results were encountered. First, the low rate of infection associated with groin incisions was contrary to previous reports.[3,16] Meticulous care of the groin area has been emphasized for years and probably accounted for this low infection rate.

The high infection rate associated with hexachlorophene-ethanol skin preparation was striking. This high infection rate was not limited to a particular site of infection or particular class of involvement. The efficacy of the hexachlorophene scrub was probably impaired by the short contact with the skin. Additionally, ethanol is known to inactivate hexachlorophene.[17] Although ethanol is rapidly cidal for most micro-organisms, it leaves no residual activity and resident flora may soon reappear on the skin's surface.[11] The hexachlorophene-ethanol preparation thus has theoretical flaws and, as demonstrated by the study, was associated with a higher rate of infection than the povidone-iodine skin preparation. In a previous study comparing hexachlorophene skin preparations (without ethanol) versus povidone-iodine, the infection rates

TABLE 4. *Occurrence of Infection by Site of Incision and Prophylactic Regimen*

Site of Incision	Total Incisions Infection/Incisions (%)	Prophylactic Regimen	
		Cefazolin Infection/Incisions (%)	Placebo Infection/Incisions (%)
Abdominal incision	9/184 (4.9)	1/ 86 (1.2)	8/ 98 (8.2)
Groin incision	2/358 (0.6)	0/179	2/179 (1.1)
Leg incision	7/228 (3.1)	1/117 (0.9)	6/111 (5.4)

TABLE 5. *Occurrence of Infection by Antiseptic Skin Preparation and Systemic Prophylactic Regimen*

Antiseptic Skin Preparation	Total Patients Infection/Patients (%)	Systemic Prophylaxis	
		Cefazolin Infection/Patients (%)	Placebo Infection/Patients (%)
Hexachlorophene-ethanol	7/ 68 (10.3)	0/ 31	7/ 37 (18.9)
Povidone-iodine	11/394 (2.8)	2/194 (1.0)	9/200 (4.5)

following hexachlorophene antisepsis were slightly higher, but the difference did not achieve statistical significance.[4]

The lack of emergence of resistant strains associated with the cefazolin therapy was most gratifying. The importance of a *short* course of prophylactic antibiotic to minimize the emergence of resistant strains has been emphasized in the literature.[5] Prophylactic antimicrobials given for as long as five days definitely have been associated with the emergence of resistant strains.[14] Since the presence of antimicrobials in the tissue at the time of surgery appears to be the most important aspect of prophylaxis,[2] the postoperative cefazolin was limited to four doses.

Staphylococcus aureus has been reported as the most common pathogen in wound infections complicating peripheral vascular surgery;[18] this finding was verified in our study. The efficacy of cephalosporins against staphylococci and the relatively low incidence of toxic and allergic reactions associated with their use prompted our selection of this class of antimicrobial. Cefazolin was chosen from among the cephalosporins because its use results in high sustained serum levels and renal toxicity has been virtually nonexistent.[12] It would appear from our study that the primary effect of cefazolin prophylaxis was to prevent all potential infections due to cefazolin-sensitive pathogens.

Questions regarding prophylactic antimicrobial therapy still remain, not only for vascular surgery but also for other surgical procedures. It is not settled as to how low the infection rate must fall before the risk of prophylactic antimicrobials outweigh their benefit. In patients receiving placebo the infection rates following abdominal aortic and lower extremity vascular surgery were 11.8% and 8.7%, respectively, and antimicrobial prophylaxis was clearly warranted. However, infections following elective head and neck vascular procedures have not been recognized at our institution in years and no infections were seen during the first half of the study. Thus we do not routinely use prophylactic antimicrobial therapy for head and neck surgery. A spectrum of infection rates is observed for other types of clean surgery and rates may vary among institutions. Only careful active surveillance of surgical wounds will identify problem areas for future study and amelioration.

In summary: 1) Cefazolin begun preoperatively and continued for a brief course of therapy was significantly more effective than placebo in preventing wound infections. 2) Brachiocephalic procedures were not associated with any infections regardless of prophylaxis. 3) Despite previous reports, groin wounds were infrequently infected (0.6%). 4) The povidone-iodine skin preparation was associated with significantly fewer infections than the hexachlorophene-ethanol preparation. 5) Graft infections occurred infrequently (0.9%), but when present, they were much more likely to occur without cefazolin prophylaxis. 6) The prophylactic use of cefazolin and povidone-iodine was associated with no side effects and cefazolin-resistance did not emerge. The prophylactic use of cefazolin and povidone-iodine is recommended in vascular reconstructive surgery.

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Discussion

Dr. Wiley F. Barker (Los Angeles, California): I certainly want to compliment Drs. Mulherin and Dale and their associates for presenting the objective data to justify what many of us have been doing on the basis of their prior advice several years ago, with good apparent results, but most of us haven't had the documentation.

I would like to submit the data which Mr. H. H. G. Eastcott, of St. Mary's London, provided me with last week when I showed him the abstract.

In 1976, St. Mary's Hospital had the first readout of a computerized analysis of about seven prior years of work on abdominal aortic aneurysm grafting. Their practice had been established as follows. On the basis of the concept that a patient who had pathogens growing in his nasopharynx would be more at risk for infection, they had obtained cultures of the nose and throat, before operation. Those patients with positive cultures for pathogens received appropriate antibiotics on the regimen that Dr. Dale and his associates have suggested; namely, given at the time of on-call medication. Other patients received none.

(Slide) As you will see, there were five graft infections in the patient group that seemed to be less at risk, whereas there were no graft infections in the 76 from which pathogens were grown. Whether this is really a justifiable assumption or not, I'm not totally sure.

Since this data came out in 1976, St. Mary's has gone to the treatment of all patients on the regimen outlined by Dr. Dale, using floxicillin. They now have 139 patients in their treated series, and have had only one instance of an infected graft; the patient is thought to have been already infected at the time of operation, as the patient was moribund, with a leaking aneurysm, in established renal failure.

I have one question for Dr. Dale and his associates. I did not clearly understand whether graft infections were counted separately from the graft and wound infections which may have occurred together. Can you clarify that finally in your discussion?

Dr. Robert Edward Condon (Wood, Wisconsin): This certainly has been a controversial subject. Prior to this morning's presentation, I think it's fair to say that there was a small body of experimental evidence which supported the concept of antibiotic prophylaxis in connection with vascular grafting procedures, but the only prospectively organized, blinded, controlled trial which had been conducted in this area was the report of Evans and Pollack, which included a small subset of vascular patients in a much larger clinical study. The numbers were small, and the infection rates were low. Those authors, when comparing cephaloridine with placebo, were unable to demonstrate that there was any significant difference between treated and nontreated patients.

So I think it's not only Dr. Barker, but many others of us, who are grateful to Dr. Dale and his colleagues for bringing forward this morning this well-designed, prospective, blinded, well-controlled clinical trial.

But I would like to raise one issue. The infection rate in the placebo group over all was about 6%. Surprisingly, many of those infections involved, not the groin wound, but the abdominal wound where the infection rate was about 8%. Even if you eliminate patients who got the ineffective hexachlorophene/alcohol prep, the overall infection rate is still about 4% in the placebo group.

These infection rates seem to me to be a little bit high for clean elective surgery, and since the conclusion of the study supporting the administration of prophylactic antibiotics really depends primarily on the infection rate in the control group, I'd appreciate it if Dr. Mulherin or Dr. Dale could give us some further information about the infection rate in the placebo group, in comparison with their previous experience.

Is the infection rate experienced in this study representative of their previous experience with vascular procedures, or is it some kind of an unusual phenomenon, related only to the study, and perhaps not truly representative of the infection risk in patients undergoing vascular grafts?

Dr. Emerick Szilagyi (Detroit, Michigan): Antimicrobial prophylaxis in vascular surgery is a nearly universal practice, and although originally its use was purely empirical, and although it is still often abused, there is a respectable body of evidence in support of its rational, selective employment. The ultimate proof of its value—that is, a randomized, prospective, double-blind evaluation—has, however, been missing. The report we have just heard is an account of the first attempt to provide this proof, a circumstance that clearly shows its great importance.

I had the opportunity to read the text of this report, for which I am grateful to the authors, and in reading it I could not help but ask myself the question: Has it, in fact, succeeded in providing the definitive assessment of the value of these drugs, an assessment we have so keenly been looking for?

There is no question that the study was devised on sound statistical principles, conducted with great care and reported with candor. Nevertheless, the report has features that have aroused some concern with respect to its ultimate meaning.

Time allows only the briefest indication of the more readily visible problems of this type. I find it regrettable that the authors included in the overall statistical treatment of the results the trivial degrees of infection. What one is exclusively interested in is the incidence of infectious involvement of the prosthetic implant. Inclusion of the minor infectious complications diluted the statistical material, and, in addition, introduced a potential source of numerical error, since noninfectious healing complications are often impossible to distinguish from primary infection.