Should antibiotic prophylaxis be used routinely in clean surgical procedures: A tentative yes

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Background. *The incidence of surgical site infection (SSI) after clean surgical procedure has traditionally been regarded as too low for routine antibiotic prophylaxis. But we now know that host factors may increase the risk of SSI to as high as 20%. We assessed the value of prophylactic cefotaxime in patients stratified for risk of SSI in a randomized double-blind trial.*
Methods. *Patients admitted for clean elective operations were enrolled, stratified for risk by National Nosocomial Infection Survey criteria, and randomized to receive intravenous cefotaxime 2 gm or placebo on call for operation. They were followed for 4 to 6 weeks for SSI diagnosed by Centers for Disease Control and Prevention criteria.*
Results. *Analysis of 775 patients showed that the 378 evaluable patients who received cefotaxime had 70% fewer SSIs than those who did not—Mantel-Haenszel risk ratio (MH-RR) 0.31; 95% confidence intervals (CI) 0.11 to 0.83. Benefit was clear in the 616 low risk patients—0.97% versus 3.9% SSI (MH-RR 0.25, CI 0.07 to 0.87, p = 0.018), but only a trend was seen in 136 high risk patients—2.8% versus 6.1% SSI (MH-RR 0.48, CI 0.09 to 2.5).*
Conclusions. *The results indicate clear benefit for routine antibiotic prophylaxis in clean surgical procedures. High risk patients need more study. (SURGERY 1995;118:742-7.)*

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THE VALUE OF prophylactic antibiotics is well established in clean-contaminated operations and in clean operations in which prostheses are implanted.[1,2] But prophylaxis is not generally recommended for most clean surgical procedures, because postoperative wound infections have been reported in fewer than 3% of operations.[3]

Recently this traditional approach has been challenged. Careful postoperative surveillance has shown that in this era of outpatient and short stay surgery about 50% of wound infections are diagnosed after the patient has been discharged from hospital.[4] Even in clean wounds the risk of infection varies with the patient risk from less than 1% to 16%.[5] We cannot assume, therefore, that wound infection rates after clean operative procedures are necessarily low.

In a double-blind trial Platt et al.[6] found that perioperative antibiotic prophylaxis with cefonicid was useful in herniorrhaphy and in certain types of breast surgery,[6] but their investigation showed no statistical proof of benefit at the surgical site. We therefore conducted a randomized double-blind placebo-controlled study in patients undergoing clean surgical procedures, stratified by risk of postoperative infection, to determine whether a preoperative antibiotic reduces postoperative surgical infection.

METHODS

Starting in April 1992 we enrolled patients admitted to the Queen Elizabeth Hospital Centre, Montreal, for clean general surgery procedures or for simple elective cholecystectomy in a study of antibiotic prophylaxis. Patients in whom prosthetic implantation was planned were not eligible to participate. The experimental protocol was approved by the hospital research committee, and written informed consent was obtained from each patient before enrollment. Patients were excluded if they had recently received antibiotic therapy or required antibiotics, if allergic to penicillin or cephalosporins, if pregnant, or if they refused consent.

Eligible patients were enrolled, and each underwent a routine history and physical examination and preoperative blood tests including a white blood cell and dif-

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Table I. Characteristics and procedures in patients in low risk group

Factor	*Antibiotic (n = 313)*	*Placebo (n = 312)*	*p Value*
Age (yr)*	53.5 ± 15	53.3 ± 14.7	
Gender (M/F)	154/159	144/168	
Body mass index (kg/m^2)*	26.5 ± 4.6	26.9 ± 5.2	
Blood lymphocytes $\times 10^{-9}$)*	1.937 ± 0.708	2.132 ± 1.786	
Duration of operation (min)*	61.9 ± 28.5	61.4 ± 32.1	
ASA score of 1	145	146	
ASA score of 2	152	159	
ASA score of 3	16	7	
Thyroid, head/neck	15		
Breast, axilla	49	47	
Biliary	82	91	
Other laparotomy	55	49	
Vascular	37	32	
Hernia	75	74	

*Mean ± standard deviation.

Table II. Characteristics and procedures in patients in high risk group

Factor	*Antibiotic (n = 72)*	*Placebo (n = 70)*	*p Value*
Age (yr)*	73.8 ± 8.9		
Gender (M/F)	35/37		
Body mass index (kg/m^2)*	27.5 ± 6.2		
Blood lymphocytes ($\times 10^{-9}$)*	1.780 ± 1.006		
Duration of operation (min)*	77.6 ± 47.8		
ASA score of 1	3		
ASA score of 2	23		
ASA score of 3	46		
Thyroid, head/neck	9		
Breast, axilla	6		
Biliary	24		
Other laparotomy	10		
Vascular	12		
Hernia	11		

*Mean ± standard deviation.

ferential count. They were then stratified to high or low risk groups by use of the criteria of the National Nosocomial Infection Surveillance system (NNIS).[7] This system uses three factors, the American Society of Anesthesiologists (ASA) score, the presence of contamination at the operation, and a procedure-related time cut-point (T-time), to indicate risk of infection. Patients with fewer than two factors present were designated as low risk and the remainder as high risk.

Low and high risk patients were randomly assigned separately by the pharmacist in blocks of four to receive intravenous cefotaxime (2 gm) or an identically labeled placebo. The antibiotic was mixed in 100 ml 5% dextrose in water and was infused rapidly on call for operation. No other antibiotics were permitted.

After operation, surveillance was performed by the infection control nurse in hospital and at 1 to 2 weeks and 4 to 6 weeks after operation. Neither the operating surgeon nor the infection control nurse had any knowledge of the drug assignments. The final surveillance interview was conducted by telephone. Each patient was asked a series of questions designed to identify any intervening complication. In addition, the infection control nurse obtained information regarding scheduled or unscheduled follow-up visits made by the patient.

The criteria used for diagnosis of surgical site infection were those designated by the Centers of Disease Control and Prevention.[8,9] By these criteria superficial incisional surgical site infection was diagnosed when pus drained from the wound, when any wound discharge was associated with local signs of inflammation or a positive culture, or when the surgeon diagnosed a wound infection. Postoperative organ-space infection was diagnosed on investigation of abdominal pain or fever by

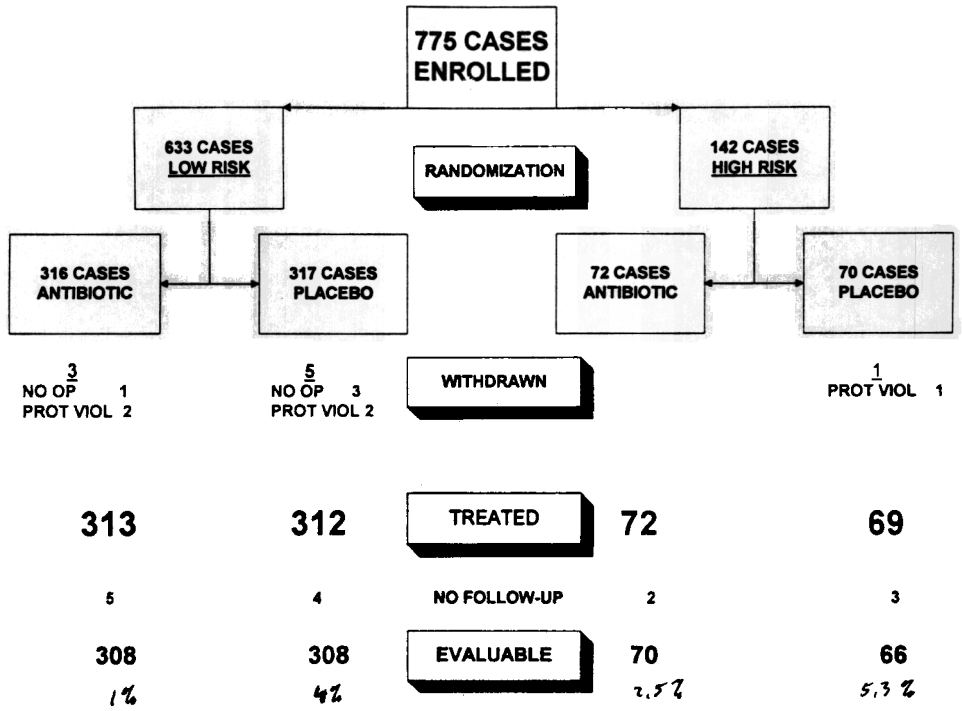

Fig. 1. Flow chart of patients studied. *NO OP*, No operation; *PROT VIOL*, protocol violated.

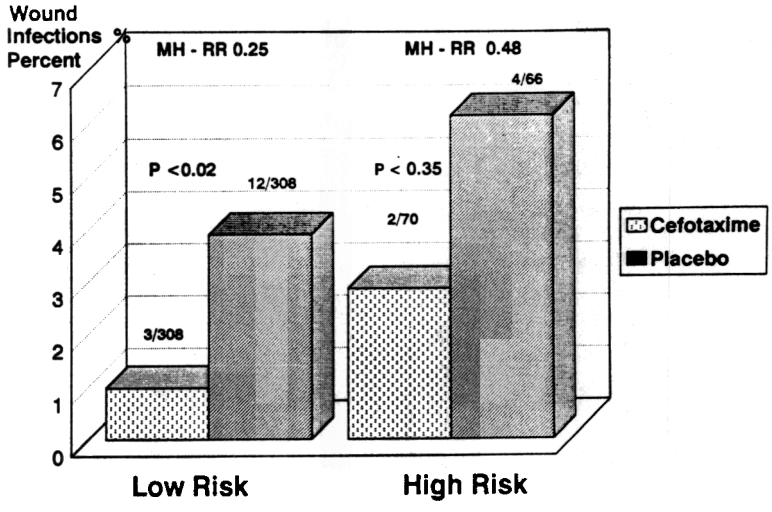

Fig. 2. Cefotaxime versus placebo in low and high risk clean operations. *MH-RR*, Mantel-Haenszel risk ratio.

means of abdominal ultrasonographic examination and treated by use of open or percutaneous drainage.

Demographic data, information about the surgical procedure, and the results of the routine preoperative white blood cell and differential counts were culled from hospital records. The data were entered along with surveillance reports into a computerized statistical package (SPSS Inc., Chicago, Ill.) for analysis. Patients were withdrawn from the study if no operation or a disqualifying operation was performed, if the protocol was violated, or if no follow-up was available.

Statistical evaluation was performed with Student's two-tailed t test to compare continuous variables and chi-squared analysis for discontinuous variables. After preliminary tests of homogeneity were performed, Mantel-Haenszel methods were used to compute the odds ratios and relative risk ratios and 95% confidence intervals.[10] A sample size of 800 was calculated to the give

80% power and a 35% to 40% reduction in the overall risk of infection from the expected baseline risk of 5%.

RESULTS

A total of 775 patients were enrolled. Six hundred thirty-three were stratified as low risk and 142 as high risk. By random assignment 316 low risk patients received antibiotic and 317 the placebo, and 72 high risk patients received the antibiotic and 70 patients a placebo. Nine patients were subsequently withdrawn before treatment and 14 for lack of follow-up, leaving a total of 750 evaluable patients (Fig. 1). Tables I and II compare the characteristics of the patient groups.

Surgical site infections developed in three patients who received the antibiotic and 16 given the placebo (Mantel-Haenszel risk ratio 0.31; 95% confidence intervals 0.11 to 0.83; $p = 0.013$). Among low risk patients five given the antibiotic and 12 treated with the placebo got surgical site infections (Mantel-Haenszel risk ratio 0.25; 95% confidence intervals 0.07 to 0.87; $p = 0.018$). A similar trend was found among high risk cases, but the result was not statistically significant (risk ratio 0.48; 95% confidence intervals 0.09 to 2.5; $p = 0.35$) (Fig. 2). The calculated odds ratios and their confidence intervals were almost identical to the risk ratios and confidence intervals.

The main difference in characteristics between low and high risk patients was in the ASA score ($p < 0.0001$). But high risk patients were also older than low risk (71.3 ± 10 years versus 53.4 ± 12 years, $p < 0.0001$), and their operative procedures lasted slightly longer than those of patients at low risk (75.7 ± 50 minutes versus 61.1 ± 30 minutes, $p < 0.001$). In patients given the placebo, a real increase in infections was seen in high risk patients (6.1% versus 3.8%, $p < 0.0001$).

DISCUSSION

The decision to use prophylactic antibiotics in nonimplant clean operations involves philosophical and scientific considerations. Many physicians already use antibiotics in these circumstances,[11, 12] and two recent randomized trials of prophylaxis found reductions in postoperative wound infections but neither achieved statistical significance.[6, 13] In the present study we have attempted further scientific evaluation of the problem. In so doing, we have addressed three questions.

Do patients benefit from antibiotic prophylaxis before clean operations? We have found a 70% reduction in surgical site infection. The infections were nearly all superficial incisional infections. Most occurred some time after the patients had been discharged from hospital but produced enough symptoms to affect their recovery. This result is consistent with those of previous randomized studies and is clearly of statistical significance. Moreover, because the trial encompassed a wider range of general surgery procedures than have been submitted to double-blind study previously, these results, achieved with a single dose of antibiotic, may be important in clinical care.

Do all patients benefit? We failed to find clear benefit in high risk patients, although a trend toward benefit was observed. But the number of high risk patients was too small for a definitive answer. We may, however, speculate that in high risk patients, host factors that favor infection may limit the value of the antibiotic. Further study of a larger group of high risk patients is warranted, because in this group the baseline infection rate at the surgical site was almost twice that in low risk patients.

Who benefits most from antibiotic prophylaxis? We have used NNIS criteria for differentiating low from high risk patients, because they lend themselves readily to prospective study. The earlier discriminant derived by Davidson et al.[14] and the more widely investigated index (SENIC risk index) defined by Haley et al.[5] in the Study on the Efficacy of Nosocomial Infection Control both require information that can only be obtained retrospectively. In the NNIS system the simple and somewhat subjectively derived ASA score seems to carry the greatest weight.[15] This is in keeping with our findings. Our low risk patients as defined by this system had the greatest gain from the antibiotic, a 75% reduction in surgical site infection.

The inclusion of simple elective cholecystectomy with traditional clean operations may be controversial, but it is well supported by previous studies.[16-18] In those studies both the frequency of infection and the organisms involved in superficial incisional surgical site infections after simple elective cholecystectomy were consistent with a skin derived infection, as occurs in clean operations, rather than a visceral source typical of high risk biliary surgery.

CONCLUSIONS

In this double-blind study of single-dose antibiotic prophylaxis in nearly 800 patients undergoing clean surgical operations, we have found a 75% reduction in surgical site infections in low risk patients as defined by NNIS criteria. A similar trend but without statistical significance was seen in high risk patients. Further study of these patients is suggested; for the present antibiotic prophylaxis can certainly be recommended for those at low risk.

REFERENCES

1. Condon RE, Wittmann DH. The use of antibiotics in general surgery. Curr Probl Surg 1991;28:803-907.
2. Abramowicz M, ed. Antimicrobial prophylaxis in surgery. The Medical Letter 1992;34:5-8.
3. Haley RW, Calver DH, White JW, et al. The nationwide nosoco-

mial infection rate: a new need for vital statistics. Am J Epidemiol 1985;121:159-67.
4. Brown RB, Bradley S, Opitz E, Cipriani D, Pieczarka R, Sands M. Surgical wound infections documented after hospital discharge. Am J Infect Control 1987;15:54-8.
5. Haley RW, Culver DH, Morgan WM, White JW, Emori TG, Hooton TM. Identifying patients at high risk of surgical wound infection: a simple multivariate index of patient susceptibility and wound contamination. Am J Epidemiol 1985;121:206-15.
6. Platt R, Zaleznik DF, Hopkins CC, et al. Perioperative antibiotic prophylaxis for herniorrhaphy and breast surgery. N Engl J Med 1990;322:153-60.
7. Culver DH, Horan TC, Gaynes RP, et al. Surgical wound infection rates by wound class, operative procedure, and patient risk index. Am J Med 1991;91(suppl 3B):152S-7S.
8. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definition of surgical wound infections. Infect Control Hosp Epidemiol 1992;13:606-8.
9. Consensus paper on the surveillance of surgical wound infections. Infect Control Hosp Epidemiol 1992;13:599-605.
10. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Br J Cancer 1976;34:585-612.
11. Platt R, Zucker JR, Zaleznik DF, et al. Prophylaxis against wound infection. J Infect Dis 1992;166:556-60.
12. Hopkins CC. Antibiotic prophylaxis in clean surgery: peripheral vascular surgery, noncardiovascular thoracic surgery, herniorrhaphy, and mastectomy. Rev Infect Dis 1991;13(suppl 10):S869-73.
13. Wagman LD, Tegtmeier B, Beatty JD, et al. A prospective randomized double-blind study of the use of antibiotics at the time of mastectomy. Surg Gynecol Obstet 1990;170:12-6.
14. Davidson AIG, Clark C, Smith G. Postoperative wound infection: a computer analysis. Br J Surg 1971;58:333-7.
15. Garibaldi RA, Cushing D, Lerer T. Risk factors for postoperative infection. Am J Med 1991;91(suppl 3B):158S-63S.
16. Lewis RT, Allan CM, Goodall RG, et al. The conduct of cholecystectomy: incision, drainage, bacteriology and postoperative complications. Can J Surg 1982;25:304-7.
17. Stone AM, Tucci VJ, Isenberg HD, Wise L. Wound infection acute versus chronic cholecystitis. Am J Surg 1977;133:285-8.
18. Lewis RT, Goodall RG, Marien B, Park M, Lloyd-Smith W, Wiegand FM. Biliary bacteria, antibiotic use, and wound infection in surgery of the gallbladder and common bile duct. Arch Surg 1987;122:44-7.

DISCUSSION

Dr. L. Beaty Pemberton (Kansas City, Mo.). You have shown us the efficacy of preoperative antibiotics in a group of patients with low risk and in clean operations. I personally welcome this further proof of the value of preoperative antibiotics if antibiotics are given before incision.

Although the surgical residents that I am in charge of know this information and can pass it on their examinations, they do seem to have a much lower concern for wound infections than I do, perhaps because I come from the age in which we didn't use preoperative antibiotics. In any event, I often have to remind them and ask them whether they have given the antibiotics in appropriate cases. Maybe this paper will add a little weight to convince them that wound infections actually do occur when they are the operating surgeon and that they can be minimized.

I have two questions for you. What was the cost of administering the 2 gm cefotaxime IV before operation? Second, do you have any estimates of how many patients in the high risk group it would take to continue your study and show that patients with antibiotics have a much lower number of wound infections compared with those without antibiotics? How many patients would it take to make this statistically significant?

Dr. Joseph S. Solomkin (Cincinnati, Ohio). On the basis of the Platt study, done in a somewhat different patient group, there has been interest in the provision of antibiotic prophylaxis to patients undergoing clean elective operations. I firmly believe the current study supports the view that it should not be used.

The first issue has to do with the meaning of the statistics, which I thought were very nicely presented as confidence intervals and risk ratios. On the basis of the confidence intervals presented, somewhere between two and about 15 infections were prevented in those 300 patients. These are described as being superficial wound infections. Apparently the benefit to be gained could be as small as two patients.

I would also question the use of a third-generation cephalosporin, which I think is an important weakness in this particular study. The particular agent chosen has a short half-life and also has relatively poor staphylococcal coverage in comparison with much cheaper drugs such as cefazolin.

The other important issue with the use of third-generation and even second-generation cephalosporins for surgical prophylaxis has to do with the increasingly important impact they have on the acquisition of β-lactamase–mediated resistance among hospital flora. Given the small number of infections prevented, I think this would be by itself an important reason not to use this particular regimen. I would therefore ask you to comment on the reasons for your selection of this agent.

I think the high risk group is well defined by both the SENIC and the NNIS data. I was therefore somewhat concerned that in the relatively small number of such patients, you saw a low infection rate. Please comment simply on whether you think this is a sample size problem or whether in fact there are intrinsic problems with the definition of high risk.

Dr. Christopher R. McHenry (Cleveland, Ohio). I wanted to raise one concern about the conclusion that antibiotics are of value in low risk clean operations. If I am interpreting your data correctly, 82 patients underwent cholecystectomy, which is not a clean but rather a clean-contaminated procedure. Approximately 15% of patients undergoing cholecystectomy will have contaminated bile and thus will benefit from antibiotic prophylaxis with a reduced risk of wound infection. Is your conclusion accurate given that 82 of the patients who were considered in your data underwent cholecystectomy?

Dr. John A. Weigelt (St. Paul, Minn.). I am worried that there are so many confounding issues, some of which have been discussed, and one that I hope is addressed in the article, that is, the duration of the operation. You had a very wide range of surgical procedures that have very different durations. Could you convince us that the time was not a major factor in the outcome of the infections?

Dr. Harry C. Sax (Rochester, N.Y.). I want to expand on Dr. McHenry's question. How many of these cholecystectomies were laparoscopic? Where were the infections? Were they at distant trocar sites or were they at the site where you brought the gallbladder through and may have spilled bile and stones?

Dr. Dietmar H. Wittmann (Milwaukee, Wis.). I have two points to raise. The first has to do with the patient mix, which indeed is a problem and diminishes the value of the study. Unfortunately, in many similar studies various procedures are lumped together because it is difficult to enroll a sufficient number with the same operation to show a significant difference. So it is difficult to draw conclusions as to the value of an antibiotic for a specific operation. I can contribute to the issue because I carried out a prospective, randomized study on 379 patients with a single clean neurosurgical operation comparing single-dose placebo versus single-dose cefamandole. In the placebo group there were three infections and none in the antibiotic group, a significant difference only if one accepts an error margin of 10%. Comparing the costs spent for antibiotics given for prophylaxis in one group and for treatment in both groups, however, revealed that expenses in the placebo group were significantly higher at a 5% error margin.

My second remark has to do with Dr. Solomkin's comment about the activity of cefotaxime against staphylococci. I recently reviewed the literature about this issue, and I must say that against current belief this antibiotic has good activity against staphylococci. Of more than 900 strains of staphylococcus recently published, more than 90% were sensitive to cefotaxime at tissue levels. This correlated well with the results of clinical studies.

Dr. Lewis (closing). Dr. Pemberton, I can't tell you specifically the cost of the antibiotic, but I will put that question together with Dr. Solomkin's question about the philosophical and financial benefit from preventing a few infections. Clearly, whether one elects to use an antibiotic in a clean case does depend on significant philosophical considerations. In this case we probably prevented approximately nine infections, comparing the antibiotic group with the low risk placebo group. One of these was a subphrenic abscess.

If one looks at the figures for the cost of even a superficial wound infection and if one considers the cost of the antibiotic at approximately $18/day or maybe $6.00 for single dose, I think we are way ahead if we use prophylaxis. But there are clearly philosophical considerations and considerations of generation of resistant organisms.

In the high risk group the number of patients that we would have to study is approximately 500.

The choice of cefotaxime was alluded to in my conclusions but only briefly. Cefotaxime is an antibiotic that we have studied in the past. We have studied its pharmacodynamics in relation to prophylaxis, looking at tissue and mucosal concentrations. It was because we had done this that we knew the antibiotic would last the 3 hours or so that would be required for the operations we were studying. It may not be the best antibiotic. But in the cases that we studied, which were operations in which there was a risk from large numbers of gram-positive organisms, cefotaxime proved to be a satisfactory antibiotic, perhaps because of the metabolites to which Dr. Wittmann has referred. But the purpose of the present study (and it was not actually supported by a drug company) was really to study the principle of routine prophylaxis rather than the specific antibiotic of choice.

With respect to the patients who underwent cholecystectomy, there is a notion, which I think comes from an historic perception rather than from the study of patients, that simple elective cholecystectomy carries a significant risk of infection from organisms in the bile. This has been disputed several times, and we ourselves have studied, without using antibiotic prophylaxis, 500 consecutive patients in whom simple elective cholecystectomy was performed with an infection rate of only 3%. We have examined this again in a randomized study and have found infections to be few and far between and caused predominantly by skin bacteria.

So I think it is true that after simple elective cholecystectomy, the wound infections that you see are more likely to be caused by skin organisms as in any clean operation rather than by bile-related organisms.