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THE TIMING OF PROPHYLACTIC ADMINISTRATION OF ANTIBIOTICS AND THE RISK OF SURGICAL-WOUND INFECTION

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Abstract *Background.* Randomized, controlled trials have shown that prophylactic antibiotics are effective in preventing surgical-wound infections. However, it is uncertain how the timing of antibiotic administration affects the risk of surgical-wound infection in actual clinical practice.

Methods. We prospectively monitored the timing of antibiotic prophylaxis and studied the occurrence of surgical-wound infections in 2847 patients undergoing elective clean or "clean–contaminated" surgical procedures at a large community hospital. The administration of antibiotics 2 to 24 hours before the surgical incision was defined as early; that during the 2 hours before the incision, as preoperative; that during the 3 hours after the incision, as perioperative; and that more than 3 but less than 24 hours after the incision, as postoperative.

Results. Of the 1708 patients who received the prophylactic antibiotics preoperatively, 10 (0.6 percent) subsequently had surgical-wound infections. Of the 282 patients who received the antibiotics perioperatively, 4 (1.4 percent) had such infections ($P = 0.12$; relative risk as compared with the preoperatively treated group, 2.4; 95 percent confidence interval, 0.9 to 7.9). Of 488 patients who received the antibiotics postoperatively, 16 (3.3 percent) had wound infections ($P<0.0001$; relative risk, 5.8; 95 percent confidence interval, 2.6 to 12.3). Finally, of 369 patients who had antibiotics administered early, 14 (3.8 percent) had wound infections ($P<0.0001$; relative risk, 6.7; 95 percent confidence interval, 2.9 to 14.7). Stepwise logistic-regression analysis confirmed that the administration of antibiotics in the preoperative period was associated with the lowest risk of surgical-wound infection.

Conclusions. In surgical practice there is considerable variation in the timing of the prophylactic administration of antibiotics, and administration in the two hours before surgery reduces the risk of wound infection. (N Engl J Med 1992;326:281-6.)

THE widespread use of antimicrobial agents for prophylaxis has altered surgical practice markedly in the past 20 years and now represents one of the most frequent uses of antibiotics in hospitals, accounting for as many as half of all antibiotics prescribed.[1-5] Surgical antimicrobial prophylaxis has been shown in many randomized clinical trials to reduce the incidence of postoperative wound infections.[6-9] Currently, such prophylaxis is recommended at the time of many "clean–contaminated" and some clean operations (usually those involving the implantation of a prosthetic device).[10] In actual practice, however, we found that prophylactic antimicrobial agents are often not administered at the optimal time to ensure their presence in effective concentrations throughout the operative period.[11] No study has examined how variations in the timing of prophylaxis affect the occurrence of surgical-wound infections in actual clinical practice.

It is increasingly recognized that to assess the quality of care, investigators must examine the linkage between the processes of care and patients' outcomes. Donabedian has proposed that "in order to make valid assessments of the quality of care, it is necessary to know in detail what kinds of care can be expected to produce what kinds of results."[12] Research into outcomes with observational methods can answer questions about the effectiveness of care or particular practice patterns that cannot be examined in randomized clinical trials. Large numbers of patients, as well as practitioners, can be included in such studies. These methods tend to maximize the opportunities for investigators to delineate the scope and effects of particular medical practices.[13] We used prospective observational methods to study the effect of practice patterns associated with antimicrobial prophylaxis on the subsequent occurrence of surgical-wound infections at our hospital.

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Methods

The LDS Hospital is a 540-bed teaching hospital affiliated with the University of Utah School of Medicine in Salt Lake City. More than 30,000 surgical procedures are performed each year, including many specialized procedures such as organ transplantation. Surgery involving pediatric patients is not performed at LDS Hospital. The present study was performed with the HELP hospital-information system (Health Evaluation through Logical Processing), which was developed to gather hospital-related data that has been described in detail elsewhere.[14] This system closely tracks practice patterns associated with the use of prophylactic antibiotics in surgical patients by recording all orders for antibiotic drugs, the exact time of drug administration, the duration of antibiotic use, and the time the prophylactic agent was discontinued. In addition, the system tracks all aspects of surgical procedures, including scheduling, the type of operation performed, the specific surgeon, the duration of surgery, the wound classification, surgical complications, and exact times of the first incision and the final closure. Thus, it records the exact time of antibiotic administration with respect to that of the initial surgical incision. The criteria used for the diagnosis of surgical-wound infections were the algorithms used for this purpose in the Study on the Efficacy of Nosocomial Infection Control.[15] Furthermore, this definition was included in the computer-based surveillance system used at our hospital to detect all hospital-acquired infections, including surgical-wound infections, and described elsewhere.[16] This system has been in continuous clinical operation for more than nine years, including the time of the study.

All inpatients who underwent scheduled elective surgery from May through November in either 1985 or 1986 (a combined period of 12 months) were followed from the time of admission to the time of discharge. Patients were excluded from the study if they underwent surgery more than 48 hours after admission to the hospital, if they did not receive antibiotics, if treatment with antibiotics was begun more than 24 hours before or after surgery, if patients had any preexisting infection, if they underwent a surgical procedure for which antibiotic prophylaxis is not recommended, or if they had more than one operation during the same hospitalization. On each day of the study, a clinical pharmacist reviewed the medical records of the patients who had undergone surgery within the previous 24 hours, to verify the exact time of the start of antimicrobial prophylaxis with respect to the surgical incision; the pharmacist then monitored the duration of prophylaxis for at least 48 hours. The medical charts of any patient in whom a surgical-wound infection developed were reviewed by an infection-control practitioner and an infectious-disease physician.

After each operation, the surgeon was required to assign a specific classification to the surgical wound, using a standard classification system described elsewhere.[16] In brief, dirty and contaminated wounds were considered to be those with gross contamination or spillage in the operative field, whereas clean–contaminated wounds were those that involved the surgical transection of a nonsterile mucocutaneous surface. All other procedures were considered to be clean. If unexpected problems were discovered at the time of surgery, surgeons were instructed to indicate them in the wound classification. All operations classified as clean or clean–contaminated were included in the study, and all operations classified as contaminated or dirty were excluded from the study. An infectious-disease physician surveyed 250 randomly selected charts to assess the accuracy of the wound-classification system and found no discrepancies.

Patients were assigned to groups on the basis of the relation between the time of their first dose of prophylactic antibiotics and the time of the initial surgical incision. Antibiotic administration was considered early if it occurred 2 to 24 hours before the incision, preoperative if it occurred 0 to 2 hours before the incision, perioperative if it occurred within 3 hours after the incision, and postoperative if it occurred more than 3 hours after the incision but less than 24 hours after surgery.

Specimens were obtained for culture from all surgical wounds with evidence of infection, and all isolates recovered were identified by standardized methods of subculturing. Organisms were identified with use of the API identification system (Analytab Products, Plainview, N.Y.). Antimicrobial-susceptibility testing was performed with the Microscan Microbroth Dilution System (Baxter Health Care, W. Sacramento, Calif.), and for anaerobes the broth-elution method with antimicrobial disks was used.

Statistical Analysis

The chi-square test was used to compare rates of wound infection according to the timing of antibiotic prophylaxis. A Wilcoxon test was used to compare infection rates according to the hour of antibiotic prophylaxis in relation to the time of surgical incision. Results were expressed as relative risks and 95 percent confidence intervals, with the group receiving preoperative antibiotic prophylaxis used as the reference group. Since the patients in this study were not randomly assigned to the various timing groups, we developed a logistic-regression model to predict surgical-wound infection while controlling for other factors that might be confounded with timing.[17] Our strategy was to find the best model without regard to timing and then to test whether the inclusion of timing added significant predictive power. Eleven sets of independent variables, including known risk factors for surgical-wound infection, were considered: the patient's age, sex, hospital service, attending physician, underlying disease, nursing service, surgeon, types of surgery, duration of surgery, postoperative procedures, and timing of antibiotic administration. The use of these variables presented the possibility of two problems: the presence of a nonmonotonic relation in the case of continuous variables (age and duration of surgery), and the presence of a large number of indicators for the evaluation of risk.

Four steps were taken to reduce the impact of these potential problems on the logistic model. First, the continuous variables (age and duration of surgery) were categorized by grouping patients into deciles quantified by dummy variables, so that any nonmonotonic relations between the infection rate and these variables could be assessed. Second, the number of categories in the variables for underlying diseases and types of surgery was reduced by combining similar categories. For example, underlying diseases were classified according to the integer part of the relevant code in the *International Classification of Diseases, Ninth Revision, Clinical Modification,* which resulted in 202 different classes of disease, and groups of similar diseases were further combined by an infectious-disease physician blinded to the rates of infection in the categories. The result was 176 categories of underlying disease and 105 categories of type of surgery. Third, the number of categories in a variable set was further reduced by classifying all categories containing fewer than 10 patients as "other." For example, 45 of the 176 classes of underlying disease included 10 or more patients, and the patients in the remaining 131 categories were classified as having "other" diseases. Finally, each variable set defined in accordance with the first three steps was considered for further analysis if it achieved a significance of $P<0.05$ in the overall-set logistic regression of surgical-wound infection,[18] with the exception of the categories of age and sex, which were retained because they are fundamental to epidemiologic studies. To reduce the number of categories, each significant variable set was tested separately in a forward stepwise logistic regression, with the indicators considered in the final analysis for which there was a significance level of $P<0.10$ for the differential association with surgical-wound infection.

Results

Study Population

Of the 6959 patients who underwent elective surgery during the study period, 2847 patients satisfied the criteria for inclusion in the study. Three hundred forty-six types of surgical procedures were performed; the most common, representing 55 percent of the total, were total abdominal hysterectomy (10 percent), cholecystectomy with intraoperative cholangiography (9 percent), bowel resection (8 percent), vaginal hysterectomy (7 percent), gastric bypass for morbid obesity with cholecystectomy (6 percent), total knee arthroplasty (6 percent), total hip arthroplasty (5 percent), and gastric bypass for morbid obesity without cholecystectomy (4 percent). The patients ranged in age from 11 to 97 years (mean, 53). There were 1758 women and 1089 men. The average length of hospitalization was 7.6 days; 55 patients died during their hospitalization. There were 1359 clean operations and 1488 clean–contaminated operations.

Timing of Antibiotic Administration

Of the 2847 patients qualifying for the study, 1708 (60 percent) had antibiotics administered preoperatively (0 to 2 hours before the initial surgical incision) (Table 1). The remaining patients received antimicrobial prophylaxis as follows: 282 patients had perioperative antibiotic administration (within 3 hours after the incision), 488 patients had postoperative antibiotic administration (more than 3 hours after incision), and 369 patients received antibiotics early (2 to 24 hours before the incision). Four intravenous antibiotics accounted for 84 percent of all the antibiotics used: cefazolin (56 percent), cefonicid (12 percent), cefoxitin (10 percent), and cefamandole (6 percent). None of these antibiotics were overrepresented in any of the timing groups. All the patients received prophylaxis for a minimum of 24 hours after surgery, and more than 80 percent received it for at least 48 hours. No difference in the duration of antibiotic prophylaxis was detected among the various timing groups.

Surgical-Wound Infections

In the 2847 surgical patients in our study, 44 surgical-wound infections were detected (1.5 percent) (Table 1). There was no significant difference between the two study years in the overall rates of such infections. Among the 1708 patients who received preoperative antibiotics, surgical-wound infections developed subsequently in 10 (0.6 percent). Among the 282 patients who received perioperative antibiotics, surgical-wound infections developed in 4 (1.4 percent) (P = 0.12; relative risk, 2.4; 95 percent confidence interval, 0.9 to 7.9). Among the 488 patients who received postoperative antibiotics, surgical-wound infections developed in 16 (3.3 percent) (P<0.0001; relative risk, 5.8; 95 percent confidence interval, 2.6 to 12.3). Finally, there were 14 surgical-wound infections (3.8 percent) among the 369 patients who received antibiotics early (P<0.0001; relative risk, 6.7; 95 percent confidence interval, 2.9 to 14.7). Among the 1359 clean surgical procedures, there were 16 wound infections (1.2 percent), and among the 1488 clean–contaminated operations there were 28 such infections (1.9 percent). This difference was not significant (P = 0.17).

Table 1. Temporal Relation between the Administration of Prophylactic Antibiotics and Rates of Surgical-Wound Infection.

Time of Administration*	No. of Patients	No. (%) of Infections	Relative Risk (95% CI)	Odds Ratio† (95% CI)
Early	369	14 (3.8)‡	6.7 (2.9–14.7)	4.3§ (1.8–10.4)
Preoperative	1708	10 (0.59)	1.0	
Perioperative	282	4 (1.4)¶	2.4 (0.9–7.9)	2.1‖ (0.6–7.4)
Postoperative	488	16 (3.3)‡	5.8‡ (2.6–12.3)	5.8** (2.4–13.8)
All	2847	44 (1.5)	—	—

*For the administration of antibiotics, "early" denotes 2 to 24 hours before the incision, "preoperative" 0 to 2 hours before the incision, "perioperative" within 3 hours after the incision, and "postoperative" more than 3 hours after the incision.

†As determined by logistic-regression analysis.

‡P<0.0001 as compared with the preoperative group (all P values were determined by logistic-regression analysis).

§P = 0.001.

¶P = 0.12 as compared with the preoperative group.

‖P = 0.23.

**P = 0.0001.

For the period that extended from 2 hours before to 10 hours after surgery, we stratified the rate of surgical-wound infections according to the hour of antibiotic administration in relation to the time of the surgical incision (Fig. 1). The group of patients who received early antibiotics was not included in this analysis. The lowest rate of surgical-wound infection occurred in the patients who received antibiotics from 0 to 2 hours before surgery. The trend toward higher rates of infection with each successive hour that antibiotic administration was delayed after the surgical incision was significant (z score, 2.00; P<0.05 by the Wilcoxon test).

Bacteriology

Forty-three bacterial isolates were recovered from 41 of the 44 surgical-wound infections that occurred in the course of the study. Three infections were not cultured, and two infections each yielded two organisms. *Staphylococcus aureus* accounted for seven isolates, *Bacteroides fragilis* for six, gram-negative rods for six (species of enteric bacilli were not further identified), *Enterobacter cloacae* for five, enterococcus for five, *Klebsiella pneumoniae* for two, *Pseudomonas aeruginosa* for two, *Escherichia coli* for two, and other organisms for the remaining eight. Gram-negative organisms were encountered in wound infections more frequently after clean–contaminated operations than after clean operations, but the difference was not significant.

Susceptibility to Prophylactic Agents

Of the 43 isolates from the 41 surgical-wound infections, 25 (58 percent) were resistant to the antimicrobial agent used, 15 (35 percent) were susceptible to the agent used, and 3 (7 percent) were not tested for susceptibility to the agent used. When we studied the isolates according to the timing of antibiotic prophylaxis, 9 of 12 recovered from the early group (75 percent), 8 of 14 from the preoperative group (57 percent), 3 of 4 from the perioperative group (75 percent), and 5 of 13 from the postoperative group (39 percent) were resistant to the prophylactic agent used. However, none of the differences between timing groups in the rate of such resistance reached statistical significance.

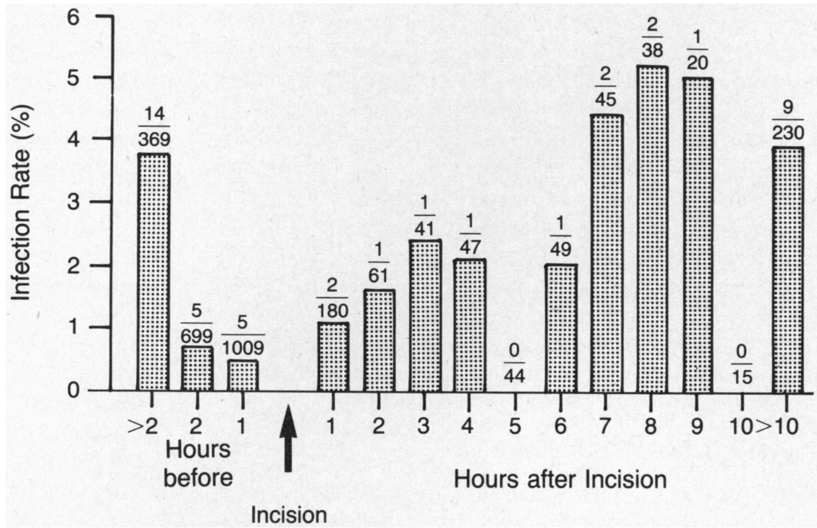

Figure 1. Rates of Surgical-Wound Infection Corresponding to the Temporal Relation between Antibiotic Administration and the Start of Surgery.

The number of infections and the number of patients for each hourly interval appear as the numerator and denominator, respectively, of the fraction for that interval. The trend toward higher rates of infection for each hour that antibiotic administration was delayed after the surgical incision was significant (z score, = 2.00; P<0.05 by the Wilcoxon test).

Logistic Regression Analysis

The results of the logistic regression analysis are presented in Table 1. Of the 11 original sets of variables tested, only 5 were significant at the 0.05 level: underlying disease, nursing service, type of surgery, duration of surgery, and timing of the first dose of prophylactic antibiotics. Age, sex, surgeon, and postsurgical procedures were not statistically significant. The 106 categories contained in the five significant variable sets were reduced to 24 indicators by a stepwise selection procedure (with P<0.1 as the criterion for selection) within each set and were further reduced to 15 (P<0.1) when all the indicators were included in a single model. Subsequently, age and sex were included in the model, and finally the timing of prophylaxis. In the final model, sex and six of the nine age-group deciles were not significant (P>0.10). Of the remaining three age groups, those for patients 41 through 47 and 66 through 70 years old were significant (P≤0.05), and that for patients 71 through 75 years old was borderline (P = 0.06). The odds ratios indicate that the relation of age to rates of surgical-wound infection was nonmonotonic. After we controlled for all these variables, the results for two timing groups were significant in relation to the preoperative group. Postoperative antibiotic administration had the strongest relation to infection (odds ratio = 5.8; 95 percent confidence interval, 2.4 to 13.8; P = 0.0001), and early antibiotic administration the next strongest relation (odds ratio = 4.3; 95 percent confidence interval, 1.8 to 10.4; P = 0.001). Perioperative antibiotic administration was not significantly different from preoperative administration with respect to the development of surgical-wound infection (odds ratio = 2.1; 95 percent confidence interval, 0.6 to 7.4; P = 0.23).

Discussion

Early trials of prophylactic antimicrobial agents often failed to show efficacy in preventing surgical-wound infections because the antibiotics were given after surgery was completed. Using a guinea pig model of subcutaneous *S. aureus* infection, Burke demonstrated that administering antibiotics before or shortly after the inoculation of skin with *S. aureus* reduced the size of the ensuing skin lesion markedly and that with each delay of an hour in antibiotic administration, the resulting lesion became larger until the third hour. By the fourth hour, the lesion was the same size as in untreated control animals.[19] This work was corroborated by Shapiro et al., who used the guinea pig model for studies with *B. fragilis*.[20] The clinical validity of these observations was established by Polk and Lopez-Mayor in a study of perioperative and postoperative administration of cephaloridine in which there was a significantly lower rate of surgical-wound infection in patients who received the drug perioperatively.[21] These results were further supported in a trial by Stone et al., who also found the lowest rate of surgical-wound infection in patients receiving preoperative antibiotics and showed that the rates of wound infection in patients given antibiotics one to four hours after the start of surgery were significantly higher than those in patients with preoperative administration and were the same as those in patients receiving no prophylaxis.[22]

The relation between the timing of antibiotic prophylaxis in clinical practice and the occurrence of surgical-wound infections has not been well studied, although several clinical trials have suggested an association. We found that the use of antibiotics within the two-hour period before an operation was associated with the lowest rate of surgical-wound infection, and logistic-regression analysis also supported the conclusion that antibiotic administration during this period was inversely associated with the occurrence of such infections. Patients who received antibiotic prophylaxis more than three hours after the initial incision had a wound-infection rate of 3.3 percent, more than five times the rate in those who received antibiotics within two hours of surgery ($P<0.0001$). Patients who received an antibiotic within three hours after the incision had an infection rate of 1.4 percent, almost three times the rate in the preoperative timing group ($P = 0.12$). These differences suggest that there is an increased risk of surgical-wound infection even if the antibiotic is administered shortly after the surgical incision is made. In our study, the rate of wound infection was higher with each hour that passed after the surgical incision, supporting the observation that the risk of infection increases with each hour after the incision until antimicrobial prophylaxis is administered.

The patients who received their antibiotics more than two hours before surgery also had a high rate of wound infection. Our criteria for entry into the study limited it to patients who were undergoing elective surgery. Patients admitted to the hospital more than 48 hours before surgery and patients who had any evidence of infection before surgery were excluded. In a randomized study of antibiotic prophylaxis, Stone et al. also observed a trend toward higher rates of surgical-wound infection in patients in whom antimicrobial prophylaxis was started 12 hours before surgery.[22]

The logistic-regression analysis revealed several factors associated with the development of surgical-wound infections. Few age categories were significantly associated with such infection, and the relation was nonmonotonic. Two longer intervals for the duration of surgery were associated with increased rates of infection; surgical-wound classification was not significantly associated, however, probably because our study included only clean and clean–contaminated surgical wounds. Admission to specific hospital services (general surgery, general internal medicine, or cardiovascular surgery) was associated with surgical-wound infection. In addition, certain underlying diseases (arthropathies, acute and chronic forms of ischemic heart disease, and intestinal symptoms usually requiring surgery) were also associated with an increased risk of surgical-wound infection. This observation probably reflects a group of patients who are more severely ill and at higher risk for postoperative complications. After we controlled for all these variables, early and postoperative administration of prophylactic antibiotics was still significantly associated with an increased rate of infection, indicating that the timing of antibiotic administration is critical in preventing surgical-wound infections in routine clinical practice.

Risk factors that have been linked to surgical-wound infections include operative factors such as the type and length of surgery, operative technique, surgeon's skill, preoperative preparation of the surgical site, and factors in the host such as advanced age, the presence of diabetes, cancer, obesity, or malnutrition. Improvements in the management of many of these problems have contributed to the overall decline in the rate of surgical-wound infections.[23-28] Because of the low rate of surgical-wound infection in patients who have undergone clean or clean–contaminated surgery, interventional studies to reduce the incidence of such infections further often lack statistical power to detect significant differences. Indeed, our study, which had a surgical-wound infection rate of 1.5 percent, required nearly 3000 patients for a statistically significant difference in the infection rate to be detectable among groups of patients receiving antibiotics at different times. Further randomized clinical studies in this area will need very large samples to detect significant differences in outcomes. Given the cost and logistical difficulties of mounting such studies, it appears unlikely that they will be performed. Furthermore, randomized clinical trials do not provide data on the way clinicians use interventions in actual practice.[29] Ellwood noted that "outcomes management lacks the purposeful randomization of a clinical trial, but . . . generates information about the results of the seemingly natural variations in practice style."[30] If all the antibiotics in this study had been administered appropriately, an estimated 27 wound infections could have been prevented.

Assessing the effectiveness of a particular clinical intervention requires a system of intense surveillance that is able to provide monitoring, analysis of variations, assessment of interventions, feedback, and education.[31] Information from such investigations, reported to clinicians, allows them to alter their practice patterns and continually improve the quality of patient care. Indeed, the information obtained in this study was reported to our physicians and has altered practice patterns. In the first six months of 1991, 96 percent of all prophylactic antibiotics administered to surgical patients at LDS Hospital were given during the two hours before the surgical incision.

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