The Timing of Surgical Antimicrobial Prophylaxis

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Objective: To obtain precise information on the optimal time window for surgical antimicrobial prophylaxis.

Summary Background Data: Although perioperative antimicrobial prophylaxis is a well-established strategy for reducing the risk of surgical site infections (SSI), the optimal timing for this procedure has yet to be precisely determined. Under today's recommendations, antibiotics may be administered within the final 2 hours before skin incision, ideally as close to incision time as possible.

Methods: In this prospective observational cohort study at Basel University Hospital we analyzed the incidence of SSI by the timing of antimicrobial prophylaxis in a consecutive series of 3836 surgical procedures. Surgical wounds and resulting infections were assessed to Centers for Disease Control and Prevention standards. Antimicrobial prophylaxis consisted in single-shot administration of 1.5 g of cefuroxime (plus 500 mg of metronidazole in colorectal surgery).

Results: The overall SSI rate was 4.7% (180 of 3836). In 49% of all procedures antimicrobial prophylaxis was administered within the final half hour. Multivariable logistic regression analyses showed a significant increase in the odds of SSI when antimicrobial prophylaxis was administered less than 30 minutes (crude odds ratio = 2.01; adjusted odds ratio = 1.95; 95% confidence interval, 1.4–2.8; $P < 0.001$) and 120 to 60 minutes (crude odds ratio = 1.75; adjusted odds ratio = 1.74; 95% confidence interval, 1.0–2.9; $P = 0.035$) as compared with the reference interval of 59 to 30 minutes before incision.

Conclusions: When cefuroxime is used as a prophylactic antibiotic, administration 59 to 30 minutes before incision is more effective than administration during the last half hour.

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Surgical site infection (SSI), at least the third most common type of nosocomial infection, increases morbidity and mortality, lengthening hospital stay 2-fold on average.[1] The introduction of routine antimicrobial prophylaxis was a breakthrough in the prevention of SSI in nonclean surgical interventions and implant surgery.[2] The antibiotic used should cover the pathogens commonly found in most surgical interventions. Today, single-shot administration of first- or second-generation cephalosporin is the state-of-the-art procedure in routine antimicrobial prophylaxis.[3] Because anaerobic activity is limited in most cephalosporins, treatment is supplemented with metronidazole where indicated. As early as 1961, Burke[4] showed the timing of antimicrobial prophylaxis to be crucial in animals. The Classen et al's landmark study[5] confirmed that in humans, the antimicrobial agent should be administered within 2 hours before skin incision. The guidelines for the prophylactic administration of antibiotics consisting of single-shot administration of cefuroxime (a second-generation cephalosporin), combined with metronidazole in colorectal surgery, are based on this time window at Basel University Hospital. Other authors[6,7] have suggested that the optimal window for surgical prophylaxis is less than 60 or even less than 30 minutes before skin incision, or have simply advised performing antimicrobial prophylaxis immediately before starting the operation. Such recommendations are not backed by evidence gathered in large clinical trials. The guidelines in place in many countries contain no more than a general recommendation to conduct antimicrobial prophylaxis 60 minutes or less before surgery.[2,8] For reasons of logistics, the administration of antibiotics less than 30 minutes before incision is a routine practice at Basel University Hospital. However, there is little evidence in the literature to show that tissue levels of cefuroxime can reach the minimum inhibitory concentration at incision required to prevent SSI by commonly expected bacteria within a few minutes. Therefore, the administration of prophylactic antibiotics within the final half hour before skin incision may not suffice for optimal prevention of SSI. The present prospective observational study was conducted to obtain more precise information on the optimal window for antimicrobial prophylaxis. Specifically, we tested the hypothesis that the risk of SSI was lower when cefuroxime (plus metronidazole in colorectal surgery) was applied between 2 hours and 30 minutes before surgery than when administered in the final half hour before surgery.

METHODS

Patients and Procedures

All consecutive surgery performed in the Visceral, Vascular, and Traumatology Divisions of the General Surgery Department at Basel University Hospital were registered in this prospective study. It was approved by the human subject committee and was part of a broader quality improvement program in the years 2000 and 2001, which was supported by the hospital executive board. As an observational study, it was exempted from the written informed consent requirement. The study was designed to include all consecutive procedures between January 1, 2000, and December 31, 2001. Operations involving no incision (closed reductions of joint dislocations, for instance) or a hospital stay of less than 24 hours were excluded, along with procedures classified as dirty-infected and interventions in which antimicrobial agents were administered for more than 24 hours after incision for therapeutic purposes. Likewise excluded were all procedures not adhering to in-house guidelines for the prophylactic administration of antimicrobial agents within 2 hours before skin incision.

We prospectively collected in-hospital data on a standardized case report form. The variables recorded included age, sex, underlying disease, additional diagnoses, American Society of Anesthesiologists (ASA) score, type of procedure, surgical team members, wound class, duration of surgery, length of hospital stay, intensive care before and after the operation, and so forth (for a total of 82 variables).

Outcome-of-Interest and Main Predictor Variable

The outcome-of-interest in this study was SSI occurrence as defined by the Centers for Disease Control and Prevention.[1] According to the nosocomial infection surveillance system in place in the authors' clinical practice since 1999, the resident surgeon completed a prospective nosocomial infection surveillance form for each patient, recording type of nosocomial infection and SSI, date of diagnosis, and treatment. Each form was subsequently reviewed and signed by a fellow surgeon.

Three approaches were adopted for postdischarge monitoring, with a minimum duration of 30 days for nonimplant surgery and 1 year for implant operations. The first 2 procedures were consecutively applied in all patients. In the first, forms and supplementary documents were sent to the primary care practitioners performing postsurgery clinical controls. These materials included a description of the quality control strategy followed. Up to 2 reminders were mailed, stressing the need to fully ascertain the presence of SSI. The professionals involved were paid a small fee for each completed form as consideration for their effort. Second, patients' electronic charts were screened to detect readmissions and outpatient clinic visits. Because all traumatology patients are scheduled for routine outpatient appointments, the surveillance forms for this series of patients were predominantly completed on the occasion of such routine visits. Finally, patients for whom outpatient follow-up data were missed by the first 2 approaches were interviewed by physicians of the study team by telephone. For this purpose we used a standardized questionnaire, which allowed systematic evaluation of wound healing and acquisition of missing information. In case of suspicious findings, attending primary care practitioners identified in the interview were contacted.

All cases showing evidence of SSI were validated by a board-certified infectious disease specialist based on a comprehensive review of patient history, initial microbiology results, and outcome >1 year after surgery. The data were recorded using an electronically readable form created by Cardiff TELEForm Software (Cardiff TELEForm Desktop V 8.0, 2002, Verity Inc., Sunnyvale, CA).[9]

The primary predictor variable was antimicrobial prophylaxis timing. Application of perioperative antimicrobial prophylaxis was indicated, according to Centers for Disease Control and Prevention guidelines on surgical wound classification,[1] as follows: class I (clean) involving a nonabsorbable implant or breast surgery; all class II (clean-contaminated) procedures; and class III (contaminated) procedures when the source of infection was surgically removed in its entirety, obviating the need for antibiotic therapy.

Antimicrobial prophylaxis was administered by the anesthetic team to all patients via single-shot, intravenous infusion of 1.5 g of cefuroxime in 20 mL of sodium chloride solution over 2 to 5 minutes and was combined with metronidazole (500 mg, intravenous, 5 minutes) in colorectal patients. In patients presenting with renal failure, however, dosage was adapted to calculated clearance and in osteosynthesis operations, 0.75 g of cefuroxime was injected 8 and 16 hours after the first application. The time in exact minutes that the infusion of antibiotics ended was prospectively recorded by the anesthesiologist or anesthetic nurse responsible and entered into the computerized anesthesia chart. Colorectal patients received no intraluminal antibiotics. Before elective left hemicolon and rectum surgery, patients underwent mechanical bowel preparation.

Covariates and Database

A total of 82 variables were entered for each surgical procedure on a 4-page Cardiff TELEForm data sheet. The TELEForm information on all the surgical procedures analyzed in this study was reviewed and completed as necessary with data from the respective medical histories. Each completed form was cross-checked by a second member of the research team.

We used Cardiff TeleForm Desktop V 8.0 software to scan both these inpatient data sheets and the outpatient surveillance forms and export the data to an Excel file (Windows Microsoft Excel 2003, Microsoft Corp.). Data were cleaned for scanning errors before statistical analysis.

Statistical Analysis

For the analysis of the relationship between the timing of antibiotic prophylaxis and SSI occurrence we divided time into intervals. Cutoffs of 120 and 0 minutes before surgery were established on the ground of the findings by Classen et al.[5] To formally test our a priori hypothesis, we divided this period into 2 intervals 120 to 30 and 29 to 0 minutes before skin incision. To obtain more precise information on the

optimal window for antimicrobial prophylaxis, we increased the timing categories to 3 (120–60, 59–30, 29–0 minutes before skin incision). Finally, the period between 74 and 0 minutes before incision was divided into 15-minutes intervals. In light of the small number of surgeries with timing between 120 and 75 minutes before incision, this time interval was not further subdivided. Risk was calculated by dividing the number of operations involving subsequent SSI in a given timing category by the total number of operations in that category. The odds of SSI were calculated by dividing the number of SSI by the number of surgical procedures without SSI, and odds ratios were used to describe and model the association between risk of SSI and timing category. The time interval with the lowest observed risk of SSI was defined as the reference group. Account was taken of factors that could potentially confound the association between timing of antibiotic prophylaxis and the likelihood of contracting SSI by fitting multivariable logistic regression models and obtaining adjusted odds ratios and 95% confidence intervals for the odds ratios. The decision on which variables to include in the regression model was based on their potential role as SSI risk factors or on indications of differences in distribution across timing. First, all relevant SSI risk factors evaluated in this study were incorporated, which included all variables showing significant maldistribution across the various timing categories (ASA score in groups I–IV, division of surgical specialty—visceral, vascular, trauma—wound classification, smoking status, diabetes, lowest intraoperative body temperature, and T time surpassed, which referred to the 75th percentile in hours of the duration of surgery as defined in the National Nosocomial Infections Surveillance system[10]). Second, supplemental variables were included in the model based on a larger understanding of their relevance as SSI risk factors gained from the literature on this topic (sex, age by 10-year intervals, body mass index, preoperative in-hospital antibiotic therapy, immunosuppression, including steroids).[11–14]

Indicator variables were included in the logistic regression model for the levels of categorical variables and model comparisons were based on likelihood ratio tests.

χ^2 statistics and the corresponding P values were calculated to assess the homogeneity of the distribution of characteristics by timing interval. All P values were 2-sided and not adjusted for multiple testing. P values lower than 0.05 were considered to be statistically significant. All analyses were conducted using Stata 9.2 (Stata Statistical Software; Stata Corp., College Station, TX).

RESULTS

Between January 1, 2000, and December 31, 2001, a total of 6540 consecutive invasive procedures were performed on inpatients. Prospective in-hospital data were recorded in 96.1% (6283 of 6540) and a long-term follow-up data set was built for 91.1% (5721 of 6283 procedures). Of those 5721 procedures, 83.3% (4768 of 5721) were followed up by a physician, whereas in only 16.7% of procedures (953 of 5721) were the patients contacted by telephone. Antimicrobial prophylaxis was applied in 4265 of the 6283 procedures.

Antibiotics were administered within 2 hours before incision in 3836 of 4265 procedures; in 362 procedures the antibiotic prophylaxis was administered after incision and in 67 procedures >120 minutes before incision. These 3836 procedures met our inclusion criteria and were performed in 3313 patients who had a median hospital stay of 10 days (interquartile range, 6–17 days). Of the 3836 procedures, 2756 (71.8%) had class I wounds (clean), 660 (17.2%) class II wounds (clean-contaminated), and 420 (10.9%) class III wounds (contaminated).

In this series of 3836 procedures, a total of 180 SSI were detected (4.69%): in 109 instances in the hospital and in 71 instances after discharge. Of these 180 infections, 30.6% were classified as superficial SSI, 29.4% as deep SSI, and 40% as organ/space SSI.

Data on baseline characteristics by surgical procedure and subsequent SSI are given in Table 1. Table 2 shows that the distribution of some characteristics such as ASA score and surpassed T time differed across the timing categories for the prophylactic administration of antibiotics. All variables exhibiting significant differences in distribution were entered in the multivariable logistic regression model. The 3 types of SSI (superficial, deep, organ/space) were similarly distributed over timing categories ($P = 0.462$).

The model testing our a priori hypothesis showed a significant increase in the odds of SSI when prophylaxis was applied in the final half hour, which concerned 49% of all procedures in this series, compared with procedures in which prophylaxis was administered between 2 hours and 30 minutes before surgery (crude odds ratio = 1.71; adjusted odds ratio = 1.66; 95% confidence interval, 1.2–2.3; $P = 0.002$).

In additional analyses, we increased the timing categories to 3 (120–60, 59–30, 29–0 minutes before skin incision; Fig. 1). They showed a significant increase in the odds of SSI when the antibiotics were applied less than 30 minutes (crude odds ratio = 2.01; adjusted odds ratio = 1.95; 95% confidence interval, 1.4–2.8; $P < 0.001$) and 120 to 60 minutes (crude odds ratio = 1.75; adjusted odds ratio = 1.74; 95% confidence interval, 1.0–2.9; $P = 0.035$) as compared with the reference interval of 59 to 30 minutes before surgery.

Finally, our most detailed model gave the following results: Although antibiotic prophylaxis was applied in most patients between 44 and 0 minutes before surgical incision, the lowest rate of SSI was recorded when the antibiotics were administered between 74 and 30 minutes before surgery (Fig. 2). Risk of SSI varied significantly over timing categories ($P < 0.001$, Table 1) and univariable logistic regression analysis showed that when antibiotic prophylaxis was applied 29 to 15 (unadjusted odds ratio = 2.96; 95% confidence interval, 1.6–5.5; $P = 0.001$) and 14 to 0 (unadjusted odds ratio = 1.99; 95% confidence interval, 1.0–3.8; $P = 0.041$) or 120 to 75 minutes before incision (unadjusted odds ratio = 3.25; 95% confidence interval, 1.5–7.1; $P = 0.003$), the odds of contracting SSI were significantly higher than when the antibiotics were administered between 59 and 45 minutes before surgery. The overall heterogeneity of SSI risk with timing category remained statistically significant after adjust-

TABLE 1. Summary of Characteristics by Surgical Procedure and Presence of Surgical Site Infection

Characteristics	No. Surgical Procedures	No. SSI	SSI (%)	*P*
Total	3836	180	4.69	
Timing of prophylactic antibiotic use (minutes before incision)				<0.001
0–14	831	39	4.69	
15–29	1054	72	6.83	
30–44	991	33	3.33	
45–59	496	12	2.42	
60–74	263	9	3.42	
75–120	201	15	7.46	
Sex				0.377
Male	1944	97	4.99	
Female	1892	83	4.39	
Age				0.505
0–29	316	8	2.53	
30–39	397	18	4.53	
40–49	516	27	5.23	
50–59	575	25	4.35	
60–69	681	32	4.7	
70–79	728	35	4.81	
80–89	511	31	6.07	
≥90	112	4	3.57	
ASA score				0.001
1	526	13	2.47	
2	1859	74	3.98	
3	1311	84	6.41	
4	140	9	6.43	
NNIS				<0.001
0	1674	47	2.81	
1	1601	72	4.5	
2	505	50	9.9	
3	56	11	19.64	
Division of surgical specialty				<0.001
Visceral surgery	1448	78	5.39	
Traumatology	1802	61	3.39	
Vascular surgery	586	41	7	
Wound classification				<0.001
I	2756	96	3.48	
II	660	46	6.97	
III	420	38	9.05	
Smoking status				<0.001
Never	2135	80	3.75	
Previous or current smoker	1550	97	6.26	
Unknown	151	3	1.99	
Diabetes				0.001
No	3508	152	4.33	
Yes	328	28	8.54	
Immunosuppressive drugs				0.401
No	3699	172	4.65	
Yes	128	8	6.25	
Unknown	9	0	0	
BMI (kg/m^2)				0.077
<18	139	6	4.32	
≥18–25	1654	71	4.29	
>25–30	1063	50	4.7	
>30	417	31	7.43	
Unknown	563	22	3.91	
Preoperative albumin (g/L)				0.033
1–35	1118	67	5.99	
>35–52	1814	83	4.58	
>52	24	0	0	
Unknown	880	30	3.41	
Lowest intraoperative body temperature				<0.001
<35°C	169	15	8.88	
35.0°C–35.9°C	594	37	6.23	
36.0°C–36.9°C	423	28	6.62	
≥37°C	2650	100	3.77	
Preoperative in-hospital antibiotic therapy				0.594
Yes	247	14	5.67	
No	3579	166	4.64	
Unknown	10	0	0	
Emergency procedure				0.4
Yes	1108	47	4.24	
No	2728	133	4.88	
T time*				<0.001
Exceeded	908	74	8.15	
Not exceeded	2928	106	3.62	

*T time, 75th percentile (in hours) of the duration of surgery as defined in the NNIS system.[10]

SSI indicates surgical site infection; ASA, American Society of Anesthesiologists; NNIS, National Nosocomial Infections Surveillance System; BMI, body mass index.

ing for 12 confounders in multivariable analyses (*P* value from likelihood ratio test = 0.0002; Fig. 3).

DISCUSSION

This prospective study provides observational evidence of a possible need to refine existing recommendations on the timing of surgical antimicrobial prophylaxis. To our knowledge, this is the largest study conducted on this issue in which a single drug was administered for less than 24 hours. Classen et al's landmark study[5] suggested a time frame of up to 2 hours before incision, whereas the National Surgical Infection Prevention Project recommends administering antimicrobial agents as close to incision time as possible to obtain low SSI rates[15]; similar criteria are set out in European guidelines.[16,17] The present results call these recommendations into question. The Classen et al's study,[5] for instance, was conducted when it was standard practice to administer antibiotics to all patients for at least 24 hours, which was extended to ≥48 hours in more than 80% of the cases. Moreover, the antibiotics administered had widely varying half-lives. Consequently, the Classen et al time window may not be appropriate for optimal prevention of SSI after surgery as practiced today with single-shot regimes. In addition, antimicrobial

TABLE 2. Percentage Distribution of Time Intervals During Which Antibiotic Prophylaxis Was Administered, by Characteristics of Surgical Procedures (Intervals Measured in Minutes Before Initiation of Surgery)

		Time Intervals (min)						
Characteristics	**N**	**−120 to −75**	**−74 to −60**	**−59 to −45**	**−44 to −30**	**−29 to −15**	**−14 to 0**	***P***
Total	3836	5.2	6.9	12.9	25.8	27.5	21.7	0.462
SSI								
Superficial	55	1.8	3.6	5.5	23.6	41.8	23.6	
Deep	53	13.2	7.5	3.8	15.1	43.4	17.0	
Organ/space	72	9.7	4.2	9.7	16.7	36.1	23.6	
Sex								0.282
Male	1944	5.9	6.7	12.2	25.4	27.4	22.4	
Female	1892	4.5	7.0	13.6	26.3	27.6	20.9	
Age								0.586
0–29	316	5.4	6.0	13.6	20.3	30.1	24.7	
30–39	397	5.8	6.3	10.3	28.0	30.2	19.4	
40–49	516	4.8	7.0	13.6	25.4	28.5	20.7	
50–59	575	4.5	5.6	12.0	30.4	25.6	21.9	
60–69	681	5.6	6.6	12.6	25.6	25.8	23.8	
70–79	728	5.5	7.8	13.3	25.1	25.8	22.4	
80–89	511	5.3	7.4	14.9	24.1	28.6	19.8	
≥90	112	4.5	9.8	12.5	26.8	31.3	15.2	
ASA score								<0.001
1	526	5.7	6.3	14.6	28.7	27.6	17.1	
2	1859	4.7	7.3	12.9	26.8	28.6	19.7	
3	1311	5.8	6.7	12.7	23.7	26.5	24.6	
4	140	5.7	5.0	10.0	21.4	20.7	37.1	
NNIS								0.22
0	1674	4.8	6.5	13.4	27.0	28.4	20.0	
1	1601	5.5	7.6	13.2	25.0	26.9	21.7	
2	505	5.7	5.7	10.9	24.8	26.1	26.7	
3	56	7.1	7.1	7.1	25.0	28.6	25.0	
Division of surgical specialty								<0.001
Visceral surgery	1448	5.6	5.9	10.4	22.2	29.6	26.3	
Traumatology	1802	5.3	8.2	16.3	30.6	25.6	14.1	
Vascular surgery	586	4.3	5.3	9.0	20.1	27.8	33.4	
Wound classification								<0.001
I	2756	5.4	7.2	14.6	27.0	26.3	19.5	
II	660	5.5	6.2	9.4	22.9	29.5	26.5	
III	420	3.6	5.5	7.6	23.1	32.1	28.1	
Smoking status								0.342
Never	2135	5.3	7.4	12.7	26.2	28.1	20.3	
Previous or current smoker	1550	5.4	6.3	13.4	25.4	26.6	23.0	
Unknown	151	2.6	4.6	11.9	25.8	27.8	27.2	
Diabetes								0.04
No	3508	5.4	6.8	13.1	26.2	27.6	20.9	
Oral antidiabetics	225	3.6	6.7	12.0	23.1	24.9	29.8	
Insulin	103	2.9	9.7	8.7	19.4	30.1	29.1	
Immunosuppressive drugs								0.721
No	3699	5.2	6.9	12.9	26.0	27.5	21.5	
Yes	128	6.3	7.0	13.3	21.9	25.0	26.6	
Unknown	9	0.0	0.0	0.0	22.2	44.4	33.3	
BMI (kg/m^2)								0.733
<18	139	7.9	5.8	12.9	25.9	25.9	21.6	
≥18–25	1654	5.3	7.3	12.8	25.2	28.2	21.2	
>25–30	1063	5.7	6.1	11.5	27.0	26.7	23.0	
>30	417	4.6	7.4	13.4	27.6	25.4	21.6	
Unknown	563	4.1	6.7	15.6	24.3	28.6	20.6	

(*Continued*)

TABLE 2. (*Continued*)

Characteristics	N	Time Intervals (min)						*P*
		−120 to −75	−74 to −60	−59 to −45	−44 to −30	−29 to −15	−14 to 0	
Preoperative albumin (g/L)								0.302
1–35	1118	5.8	6.9	13.5	24.7	25.1	24.0	
>35–52	1814	4.9	7.4	12.6	26.1	28.9	20.0	
>52	24	4.2	4.2	8.3	16.7	33.3	33.3	
Unknown	880	5.2	5.7	13.0	27.0	27.3	21.8	
Lowest intraoperative body temperature								0.709
<35°C	169	8.3	7.7	10.7	24.9	26.0	22.5	
35.0°C–35.9°C	594	5.1	7.1	15.7	23.2	27.9	21.0	
36.0°C–36.9°C	423	4.3	6.4	12.5	28.1	27.4	21.3	
≥37°C	2650	5.2	6.8	12.5	26.1	27.5	21.8	
Preoperative in-hospital antibiotic therapy								0.656
Yes	247	6.5	6.5	10.9	24.7	26.7	24.7	
No	3579	5.2	6.9	13.0	26.0	27.5	21.4	
Unknown	10	0.0	0.0	30.0	10.0	30.0	30.0	
Emergency procedure								0.14
Yes	1108	5.0	6.9	11.6	24.2	30.2	22.1	
No	2728	5.4	6.9	13.5	26.5	26.4	21.5	
T time*								0.007
Exceeded	908	6.5	8.1	13.4	28.0	25.4	18.5	
Not exceeded	2928	4.8	6.5	12.8	25.2	28.1	22.6	

*T time, 75th percentile (in hours) of the duration of surgery as defined in the NNIS system.[10]
SSI indicates surgical site infection; ASA, American Society of Anesthesiologists; NNIS, National Nosocomial Infections Surveillance System; BMI, body mass index.

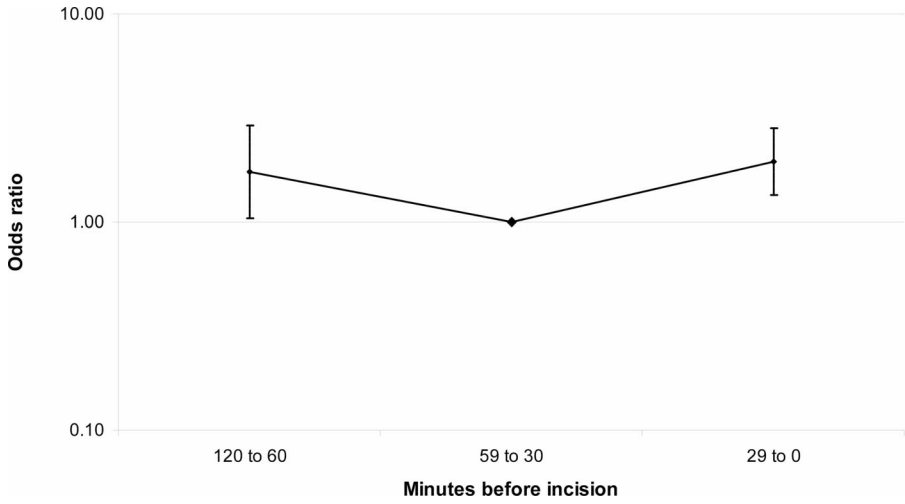

FIGURE 1. Risk-adjusted odds ratios and 95% confidence intervals for surgical site infection versus timing of antimicrobial prophylaxis divided into 3 time intervals. Association of timing of antibiotic prophylaxis and the odds of SSI obtained with multivariable logistic regression analysis, which included wound classification, ASA score in groups I to IV, division of surgical specialty (visceral, vascular, trauma), lowest intraoperative body temperature, body mass index, preoperative antibiotic therapy, smoking status, diabetes, immunosuppression, T time surpassed,[10] sex, and age by 10-year intervals. The −59 to −30 minutes timing category was defined as the reference group. By comparison, the odds of SSI rose significantly when the antibiotics were applied less than 30 minutes (adjusted odds ratio = 1.95; 95% confidence interval, 1.4–2.8; $P < 0.001$) and 120 to 60 minutes before surgery (adjusted odds ratio = 1.74; 95% confidence interval, 1.04–2.93; $P = 0.035$).

prophylaxis timing should ensure that serum and tissue drug levels at the beginning of the operation exceed the minimum inhibitory concentration for organisms likely to be present in the surgical environment. Different authors[18–20] have reported attaining appropriate tissue levels of cefuroxime anywhere from 20 to 90 minutes after intravenous application. Very little is known about cefuroxime levels at earlier times. Administering surgical antimicrobial prophylaxis as close to

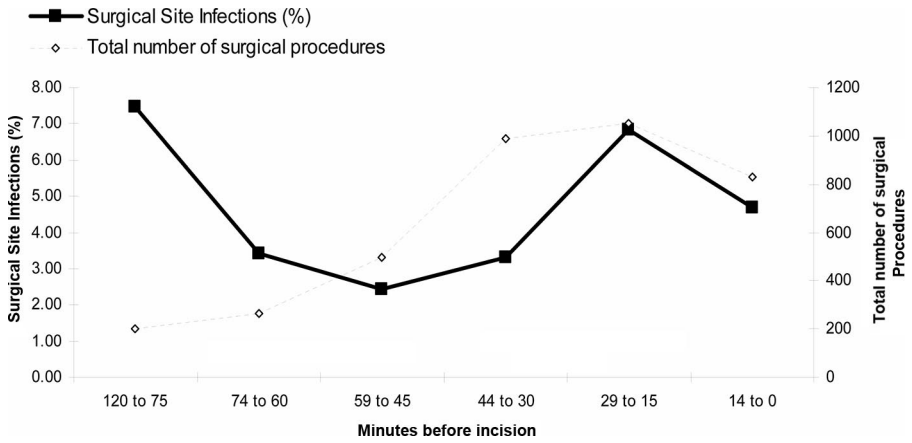

FIGURE 2. Surgical site infection rate and total number of surgical procedures performed versus timing of the prophylactic administration of antibiotics. The risk of SSI was calculated by dividing the number of operations involving subsequent SSI in a given timing category—in minutes before surgical incision—by the total number of operations in that category. Although antibiotic prophylaxis was applied in most patients between 44 and 0 minutes before surgical incision, the lowest rate of SSI was recorded when the antibiotics were administered between 74 and 30 minutes before surgery.

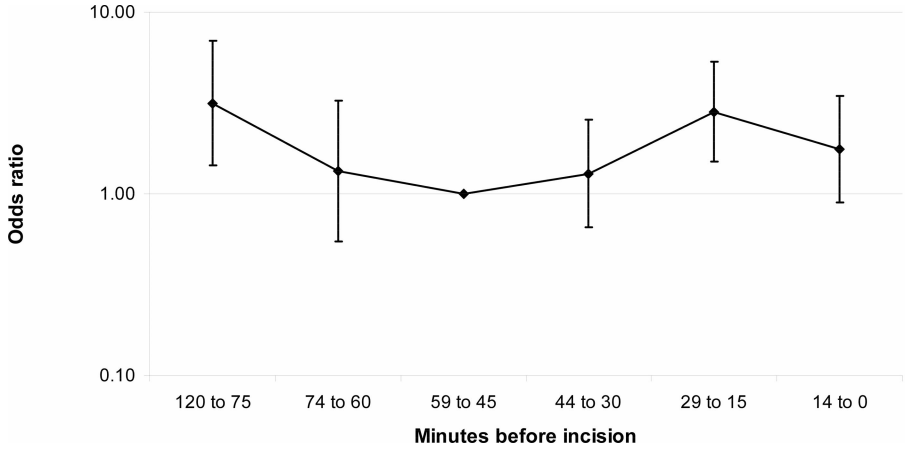

FIGURE 3. Risk-adjusted odds ratios and 95% confidence intervals for surgical site infection versus timing of antimicrobial prophylaxis divided into 6 time intervals. Association of timing of antibiotic prophylaxis and the odds of SSI obtained with multivariable logistic regression analysis, which included wound classification, ASA score in groups I to IV, division of surgical specialty (visceral, vascular, trauma), lowest intraoperative body temperature, body mass index, preoperative antibiotic therapy, smoking status, diabetes, immunosuppression, T time surpassed,[16] sex, and age by 10-year intervals. The −59 to −45 minutes timing category was defined as the reference group. By comparison, the odds of SSI rose significantly when antimicrobial prophylaxis was administered 29 to 15 minutes (risk-adjusted odds ratio = 2.82; 95% confidence interval, 1.5–5.3; $P = 0.001$) or 120 to 75 minutes before skin incision (risk-adjusted odds ratio = 3.16; 95% confidence interval, 1.4–7.0; $P = 0.005$), and the odds was 1.75 times higher when applied within the last 14 minutes (95% confidence interval, 0.9–3.4; $P = 0.103$).

the incision time as possible may not suffice to guarantee appropriate tissue levels at the surgical site in today's—primarily elderly—surgical patients.

Two recent studies of other antimicrobial agents with different pharmacokinetics support the findings reported here that surgical antimicrobial prophylaxis should not be administered as close to incision time as possible.[21,22] In one, the administration of vancomycin 16 to 60 minutes before incision in coronary artery bypass surgery was associated with the lowest risk of SSI.[21] A rapid increase in the volume of distribution of vancomycin at the initiation of cardiopulmonary bypass, exacerbated in patients with decreased circulation to the surgical site such as patients with diabetes or patients with arteriosclerosis, was considered potentially responsible for the increased risk of SSI if surgery was initiated within 15 minutes of the vancomycin infusion. In another study, the rate of SSI was lower when the antibiotic was administered >1 hour versus ≤1 hour before surgery.[22] As this difference was based on only 17 SSI, it was indicative of a trend but not statistically significant. Finally, previous studies have been too small for the precise analysis of narrow timing categories. In the present study, by contrast, the sample size was large enough to analyze the data by 15-minute intervals in the 74 minutes preceding incision.

Based on pharmacologic arguments one would expect a dose-response relationship in that the risk of SSI would increase with decreasing time to incision when antibiotic prophylaxis is given. However, when we analyzed separately the time intervals 29 to 15 and 14 to 0 minutes before surgery, we did not observe a clear dose-response relationship. Methodological factors (eg, the fact that we were not able to control for all relevant risk factors in the multivariable analysis or chance fluctuations) and biologic factors might be responsible for this relationship. The latter could arise if during a procedure the tissue antibiotic level falls below the minimum inhibitory concentration for organisms likely to be present in the surgical environment, subsequent to which host defenses are unable to prevent further growth.

Another point to be addressed is the finding of the higher SSI incidence if the antibiotics are given in the time interval 120 to 75 minutes before incision. Two explanations seem possible. Either the antibiotic tissue levels are already too low at time of incision, which we believe is the first vulnerable phase because of the transfer of residual resident skin flora into the surgical site, or the antibiotic tissue levels are too low during a later phase of the surgical intervention lying between incision and the 4 hours duration when prophylaxis is meant to be readministered. This has a clinical implication; if the latter hypothesis would be true the time interval to motivate redosing (now set at 4 hours) should eventually not start at the moment of the incision but rather at the time point of prior administration of the prophylaxis.

This study was subject to several limitations: most importantly, it was not a randomized clinical trial, but a prospective cohort study exploring a consecutive series of surgical procedures. The fact that prophylaxis may be administered later in more severely ill patients because of greater complexity in connection with anesthesia, for instance, may introduce an inherent bias. Indeed, the distribution of some patient and procedure characteristics, such as ASA score, division of surgical specialty, wound class, diabetes, and T time, differed significantly across timing categories for the prophylactic administration of antibiotics. Yet the distribution of other characteristics and the 3 types of SSI did not differ significantly across timing categories. Consequently, to obtain adjusted results, all characteristics that were not homogeneously distributed over the different timing categories, along with other potentially confounding SSI risk factors, were entered in the multivariable statistical analysis. However, residual confounding of results by unmeasured variables can never be ruled out entirely in observational studies.

A second limitation was that postdischarge monitoring was not conducted by outpatient clinics following a standard protocol to examine patients. Because high inpatient and outpatient follow-up rates (96.1% and 91.1%, respectively) could be achieved, we think that the 3-step assessment procedure was able to ascertain the large majority of SSI occurring before and after hospital discharge and that under ascertainment was unlikely to have biased the results on the association with timing.

Another issue is the generalizability of our findings. The emergence of cefuroxime-resistant strains, most commonly methicillin-resistant *Staphylococcus aureus* may lower the effectiveness of antimicrobial prophylaxis. A recent trial clearly showed that routine antimicrobial prophylaxis fails when the most frequent pathogens are not covered.[23] The absence of methicillin-resistant *S. aureus* in the SSI identified in the present study, however, reduced the likelihood of any such confounding variable. In turn, it remains unclear whether the results of this study can be generalized to hospitals with a substantial problem with methicillin-resistant *S. aureus* hospital-acquired infections. Furthermore, the optimal time window for surgical antimicrobial prophylaxis reported here may not be generalizable to all antimicrobial agents.

Implementing a refined optimal time window for the prophylactic administration of antibiotics in clinical practice will probably be difficult. In some hospitals the present broad recommendation that calls for administration less than 1 hour before incision is followed under 70% of the time, despite the existence of major quality improvement programs.[8] Refinement may conceivably increase the likelihood of noncompliance. Nonetheless, the aim should be to apply prophylaxis at the optimal time, despite practical and logistic difficulties.

In conclusion, when cefuroxime is used as a prophylactic antibiotic, administration 59 to 30 minutes before incision is more effective than administration during the last half hour.

Because of the observational nature of the evidence presented, corroboration of our findings is encouraged.

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