Antibiotic Prophylaxis and the Risk of Surgical Site Infections following Total Hip Arthroplasty: Timely Administration Is the Most Important Factor

Marjo E. E. van Kasteren,[1,2] Judith Manniën,[3] Alewijn Ott,[4] Bart-Jan Kullberg,[1,2] Annette S. de Boer,[3] and Inge C. Gyssens[4,5]

[1]Department of Internal Medicine, Radboud University Nijmegen Medical Centre, and [2]Nijmegen University Centre for Infectious Diseases, Nijmegen, [3]National Institute for Public Health and the Environment, Bilthoven, and Departments of [4]Medical Microbiology and Infectious Diseases and [5]Internal Medicine, Section of Infectious Diseases, Erasmus University Medical Center, Rotterdam, The Netherlands

(See the editorial commentary by Dellinger on pages 928–30)

Background. Surgical site infections (SSIs) following total hip arthroplasty can lead to prolonged hospitalization, increased morbidity and mortality, and high costs. This article analyzes the effect of various parameters of surgical antibiotic prophylaxis on the risk of SSI following total hip arthroplasty.

Methods. Data about SSI and potential prophylaxis-, patient-, and procedure-related risk factors were prospectively collected for 1922 patients who underwent elective total hip arthroplasty in 11 hospitals that participated in the Dutch intervention project, Surgical Prophylaxis and Surveillance. Multivariate logistic regression analysis was performed to correct for random variation among hospitals.

Results. SSIs (superficial and deep) occurred in 50 patients (2.6%). The highest odds ratios for SSI were found in patients who received prophylaxis after incision (2.8, 95% confidence interval [CI], 0.9–8.6; $P = .07$), had an American Society of Anesthesiology score that was >2 (2.8, 95% CI, 0.8–9.2; $P = .09$), and experienced a duration of surgery that was >75th percentile (2.5; 95% CI, 1.1–5.8; $P = .04$). Prolonged prophylaxis after the end of surgery and the use of antibiotic-impregnated cement did not contribute to fewer SSIs in this study.

Conclusions. This study suggests that intervention programs in search of amendable factors to prevent SSI should focus on timely administration of antibiotic prophylaxis.

Surgical site infection (SSI) following total hip arthroplasty (THA) can lead to prolonged hospitalization, increased morbidity and mortality, and high costs [1, 2]. The health and economic burdens of SSI are not restricted to patients' hospital stays [3]. Deep-implant SSI following THA is almost always diagnosed after discharge. Deep-implant SSIs following THA occur infrequently (0.3%–1.3%) [4–6] but can lead to severe incapacitation [7]. Known risk factors for SSI are related to the environment, surgeon, and patient [8]. Some of these factors are amenable to intervention (e.g., conditions in the operating room). Other factors, such as advanced age and diabetes mellitus, are intrinsic patient risks and cannot be modified [9]. Antimicrobial prophylaxis contributes to the reduction in incidence of SSI and is standard practice for THA. Specific recommendations are available regarding the choice of the antibiotic, duration of prophylaxis, and timing of the first dose [8, 10–12]. The cephalosporins cefazolin and cefuroxime are considered to have equal prophylactic efficacy. Available evidence suggests that administration of the first dose as near to the incision time as possible will achieve a decreased likelihood of SSI. However, controversy exists regarding the optimal duration of prophylaxis in connection with THA. The US advisory statement recommends that antimicrobial prophylaxis be administered within 1 h before incision and discontinued within 24 h after the end of the operation [12]. However, European guidelines recommend a single dose within 30 min before the incision [11, 13]. In

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Reprints or correspondence: Dr. Marjo E. E. van Kasteren, Dept. of Medicine, Radboud University Nijmegen Medical Centre, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands (M.v.Kasteren@elisabeth.nl).

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addition, despite the potential benefits of antibiotic-impregnated bone cement for joint arthroplasty, controversies remain regarding its use [12].

Most studies that have analyzed risk factors for SSI following THA have mainly focused on patient, procedure, or hospital characteristics [4, 14–16]. However, prospective studies of the contribution of the qualitative aspects of surgical prophylaxis to the prevention of SSI following THA are scarce. We conducted a prospective, multisite intervention study (the Surgical Prophylaxis and Surveillance [CHIPS] project) to research the quality of surgical prophylaxis in The Netherlands and documented patient outcome by surveillance of SSI [17–19]. This project aimed at narrowing the spectrum, shortening the duration, and optimizing the time of administration of prophylactic antibiotics without increasing the incidence of SSI by implementing the national guidelines for surgical prophylaxis. These guidelines, developed by the Dutch Working Party on Antibiotic Policy, recommend intravenous single-dose cefazolin administered within 30 min before the first incision for THA [13]. Here, we explore the contribution of the parameters of the prophylaxis process to the incidence of SSI for the population undergoing THA, with an emphasis on the timing of administration of prophylaxis.

METHODS

During 2000–2002, 11 of the 13 Dutch hospitals of the CHIPS project provided data on elective, primary THA before and after the implementation of the national guidelines for surgical prophylaxis. Procedures for revision of a hip prosthesis were excluded.

Data collection. All hospitals participated in the national SSI surveillance network PREZIES (Preventie van Ziekenhuisinfecties door Surveillance). Data about the surgical procedure, potential SSI risk factors, and infections for patients who developed SSI were collected according to the PREZIES protocol [20], using the criteria of the US Centers for Disease Control and Prevention [21]. Local infection-control professionals prospectively collected the data and identified cases of SSI. SSIs following THA were categorized as superficial (involving skin or subcutaneous tissue) or deep (involving fascia, muscle, and joint space). Postdischarge surveillance was performed for all patients. Surgeons were requested to describe clinical symptoms and whether a patient had developed an SSI on a registration card that was added to the outpatient medical record. The records were reviewed by the local infection-control professional at 30 days and 1 year after discharge [15]. Data about the quality of prophylaxis were collected from medical, anesthetic, and nursing records and medication charts. The method of prophylaxis data collection and validation are described elsewhere [17]. The choice of the antibiotic, number of doses, time of administration of the first dose and subsequent doses, use of antibiotic-impregnated bone cement, time of induction of anesthesia, and time of incision and closure of the wound were recorded.

Prophylaxis-, patient-, and procedure-related risk factors. Duration of prophylaxis was divided into 3 categories: single-dose (1 or, in case of prolonged surgery, more doses, as recommended by the national guidelines), 24 h (postoperative dosing for 24 h), and >24 h (postoperative dosing for >24 h). Timing of administration of prophylaxis was assessed as the interval (in minutes) between the administration of the first dose and the incision. If prophylaxis was administered by intravenous infusion, the point at which one-half of the infusate had been administered was noted as the time of administration. Timing of administration was divided into 4 categories: within 30 min before incision (as recommended by the national guidelines), 31–60 min before incision, >60 min before incision, and during or after incision. The use of antibiotic-impregnated bone cement was considered a potential confounder of the effect of systemic prophylaxis.

The selection of potential patient- and procedure-related risk factors for SSI included in the national PREZIES surveillance was based on the literature to allow comparison with data generated by surveillance systems of other countries and was limited by feasibility [20, 22]. The factors included sex, age, physical condition of the patient (according to the American Society of Anesthesiology [ASA] score [23]), wound class, duration of surgery of >75th percentile, National Nosocomial Infections Surveillance score [24], and duration of preoperative hospital stay (table 1). The annual volume of surgery and the teaching status of the hospital, which were recently described as important risk factors for THA [15], were also considered as possible confounders. Data about the quality of prophylaxis were linked to the PREZIES SSI database by matching date of birth, admission, and surgery.

The CHIPS prophylaxis database contained 2031 consecutive patients who underwent elective primary THA. Linkage with the SSI database was successful for 1999 procedures. For 1922 patients (96%), the data on the timing of antibiotic administration were complete. This data set was considered appropriate for analysis. Missing data for ASA score ($n = 19$), duration of surgical procedure ($n = 7$), and duration of surgical prophylaxis ($n = 32$) were adjusted using the missing value indicator method [25].

Statistical analysis. Statistical analysis was performed using SAS Software, release 9.1 (SAS Institute). The correlation between antibiotic prophylaxis parameters and potential patient and procedure related risk factors for SSI was tested univariately with the χ^2 test or Student's t test. Pearson's correlation coefficient was used to assess the correlation between the annual number of arthroplasties performed per hospital and the incidence of SSI. Multivariable regression analysis was performed

Table 1. Univariate analysis: association of selected variables with surgical site infection (SSI) following total hip arthroplasty.

Variable	Patients who experienced an SSI (n = 50)	Patients who did not experience an SSI (n = 1872)	OR (95% CI)	P[a]
Antibiotic prophylaxis variables				
Duration of prophylaxis				
Single dose[b]	16 (33)	633 (34)	Reference	
Multiple postoperative doses for ⩽24 h	26 (54)	782 (42)	1.4 (0.7–2.5)	.29
Multiple postoperative doses for >24 h	6 (13)	427 (23)	0.6 (0.2–1.4)	.22
Timing of administration of first dose				
>60 min before incision	5 (10)	110 (6)	2.0 (0.8–5.4)	.16
31–60 min before incision	14 (28)	524 (28)	1.2 (0.6–2.3)	.60
1–30 min before incision	25 (50)	1118 (60)	Reference	
During or after incision	6 (12)	120 (6)	2.2 (0.9–5.6)	.08
Use of antibiotic-impregnated bone cement	25 (50)	732 (39)	1.5 (0.9–2.7)	.14
Patient- and procedure-related variables				
Age, mean years ± SD[c]	72 ± 10	68 ± 11	1.5 (1.1–2.0)	.014
Female sex	40 (80)	1278 (68)	1.9 (0.9–3.7)	.08
ASA score [23][d]				
1	8 (16)	507 (27)	Reference	
2	29 (59)	1130 (61)	1.6 (0.7–3.6)	.23
3+	12 (24)	217 (12)	3.5 (1.4–8.7)	.007
NNIS surgical wound infection risk index [24] score[e]				
0	22 (46)	1267 (69)	Reference	
1	20 (42)	516 (28)	2.2 (1.2–4.1)	.010
2	6 (13)	65 (4)	5.3 (2.1–13.6)	<.001
Duration of preoperative hospital stay, days				
0–1	47 (94)	1766 (94)	Reference	
⩾2	3 (6)	106 (6)	1.1 (0.3–3.5)	.92
Duration of surgery of >75th percentile	20 (41)	435 (23)	2.3 (1.3–4.1)	.006

NOTE. Data are no. (%) of patients, unless otherwise indicated. ASA, American Society of Anesthesiology; NNIS, National Nosocomial Infection Surveillance.

[a] Univariate analysis by χ^2 and Student's t test.

[b] Zero postoperative doses.

[c] Per 10-year increase.

[d] One, healthy; 2, mild systemic disorder; ⩾3, severe systemic disorder.

[e] Includes the following elements: ASA score, wound contamination class, and duration of surgery.

to account for these possibly confounding risk factors. According to our hypothesis, the variables duration and timing of prophylaxis and the use of antibiotic-impregnated bone cement were forced into the multivariable model. The patient- and procedure-related risk factors for SSI, with a threshold of statistical significance of $P < .1$ in crude analyses, were included in the model. The National Nosocomial Infections Surveillance score was not included in the multivariate analysis because all procedures were clean (value, 0), and its other components (the ASA score and duration of surgery of >75th percentile) were already included in the model.

In the present multicenter study, patients were clustered by hospital. This level of hierarchy can introduce additional sources of variability and correlation (e.g., by hospital-specific treatment policies, risk factors, and the diagnostic accuracy of the infection-control professional). Therefore, a random coefficient model (procedure NLMIXED in SAS) was used to adjust the risk estimates for random variation among hospitals. In this model, both fixed and random effects can be entered nonlinearly. This model is basically a logistic regression model, supplemented with an extra term in the equation for the random effects associated with differences in infection risk among hospitals. Because regular logistic regression models do not take into account interhospital variability, they might overestimate the contribution of patient- and prophylaxis-related factors.

The final multivariate model was used to calculate the predicted probability of developing an SSI for each patient. These probabilities were averaged separately for patients with and for those without an SSI. The mean predicted probability for patients with an SSI was divided by the mean predicted probability for patients without an SSI. This ratio represents a measure of the goodness of fit of the model, with a ratio of 1 indicating

that the risk factors in the model do not contribute to the prediction of developing an SSI. Adjusted ORs were expressed with 95% CIs. $P < .05$ was considered to be statistically significant.

RESULTS

All 11 hospitals had operating rooms with laminar air–flow conditions. Drains were routinely used in all hospitals. The annual number of THAs per hospital varied from 47 to 249. Of the 1922 patients included in the analysis, 69% were female, with a mean age (±SD) of 68.8 ± 10.8 years. The ASA score was >2 for 12% of patients. The mean duration of preoperative stay (±SD) was 1.2 ± 2.1 days, the mean duration of the procedure (±SD) was 78.6 ± 35.3 min, and the mean duration of postoperative stay (±SD) was 8.8 ± 5.6 days. All patients received antimicrobial prophylaxis. The antibiotics that were administered were classified according to the Dutch Working Party on Antibiotic Policy guidelines as effective with a narrow spectrum (cefazolin [$n = 947$], flucloxacillin [$n = 48$], and erythromycin [$n = 8$] or clindamycin [$n = 1$] in cases of allergy) or with a broader spectrum (cefamandole [$n = 39$], cefuroxime [$n = 873$], amoxicillin plus netilmicin [$n = 1$], and clindamycin plus gentamicin [$n = 1$]). No antibiotic with a very short half-life (e.g., cephalothin; half-life, 0.5 h) was used. For the 2 patients receiving >1 prophylactic antibiotic, the combination was assessed as a single course. In 49% of the procedures, the antibiotic choice was completely according to the guideline. Prophylaxis with an antibiotic of a broader spectrum was not associated with fewer SSIs than prophylaxis with an antibiotic with a more narrow spectrum (OR, 0.7; 95% CI, 0.5–1.4; $P = .43$). Prophylaxis with an antibiotic with a longer half-life (erythromycin [half-life, 1.75 h] and cefazolin [half-life, 2 h]) was not associated with fewer SSIs than prophylaxis with an antibiotic with a shorter half-life (flucloxacillin and cefamandole [half-lives, 0.75 h] and cefuroxime [half-life, 1 h]; OR, 1.1; 95% CI, 0.5–2.3; $P = .75$). For 34% of the procedures, no postoperative doses were administered, and for 59%, the first dose was administered within 30 min before incision, according to the guidelines. Antibiotic-impregnated bone cement was used in 757 case patients (39%). SSI occurred in 50 patients (2.6%). Of these infections, 40 were superficial (2.1%), and 10 (0.5%) were deep (including prosthesis-related). The average duration of stay (±SD) for patients without SSI was 9.9 ± 6.0 days, compared with 14.1 ± 12.0 days for patients with SSI.

Univariate analysis. The crude association of the selected prophylaxis-, patient-, and procedure-related variables with SSI is presented in table 1. Administration of the first dose of prophylactic antibiotics after incision was associated with an increased (although statistically nonsignificant) incidence of SSI. Dividing the timing of prophylaxis into 3 categories—within 60 min before incision, >60 min before incision, and during or after incision—did not change the results (OR for timing during or after incision, 2.9; $P = .06$). Postoperative antibiotic doses and the use of antibiotic-impregnated bone cement were not inversely associated with SSI risk. Older age, comorbidity expressed by ASA score of >2, and prolonged surgery were associated with a higher rate of SSI. Undergoing surgery in a teaching hospital did not affect the risk of SSI ($P = .30$, by χ^2 for risk). The incidence of SSI per hospital was not correlated with the annual volume of total hip procedures (Pearson R, −0.19; $P = .58$). Rates of SSI according to the time of administration of the first dose are shown in figure 1.

Multivariate logistic regression analysis. The multivariable analysis confirmed that multiple-dose postoperative prophylaxis and the use of antibiotic-impregnated bone cement were not inversely associated with the rate of SSI. Of the 4 potential patient- and procedure-related risk factors that reached the threshold of statistical significance and therefore were included in the model, only duration of surgery of >75th percentile was independently and significantly associated with SSI (OR, 2.5; 95% CI, 1.1–5.8) (table 2). Relatively high ORs could be calculated for the independent associations of rate of SSI with ASA score of >2 (OR, 2.8; 95% CI, 0.8–9.2) and with timing of administration of prophylaxis after incision (OR, 2.8; 95% CI, 0.9–8.6).

The mean predicted probability of the model was .076 for patients with an SSI and .024 for patients without an SSI. The ratio of the means was 3.2, which indicated that according to the model, the likelihood of developing an SSI was 3.2 times higher for patients with the selected risk factors than for patients without the risk factors.

DISCUSSION

In this multivariable analysis of prophylaxis-, patient-, and procedure-related risk factors for SSI following THA, prolonged duration of surgery (>75th percentile) was the only independent and statistically significant confounding risk factor. Al-

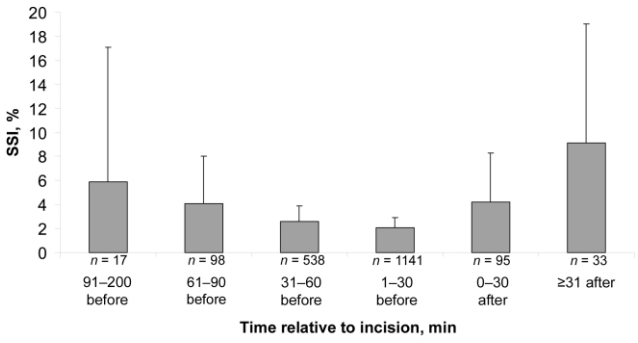

Figure 1. The association between the timing of administration of prophylaxis and the incidence of surgical site infection (SSI) following total hip arthroplasty.

Table 2. Multivariate analysis of risk factors for surgical site infection following total hip arthroplasty corrected for clustering of effects within hospitals.

Variable	OR (95% CI)	P^a
Antibiotic prophylaxis		
Duration of prophylaxis		
Single dose[b]	Reference	
Multiple postoperative doses for ⩽24 h	2.0 (0.6–7.0)	.26
Multiple postoperative doses for >24 h	1.4 (0.2–9.2)	.69
Timing of administration of prophylaxis		
>60 min before incision	1.3 (0.4–4.4)	.68
31–60 min before incision	0.9 (0.4–2.1)	.82
1–30 min before incision	Reference	
During or after incision	2.8 (0.9–8.6)	.07
Use of antibiotic-impregnated bone cement	0.8 (0.3–1.9)	.57
Patient- and procedure-related variables		
Age, years[c]	1.4 (1.0–2.1)	.08
Female sex	1.7 (0.7–3.9)	.19
ASA score [23][d]		
1	Reference	
2	1.5 (0.6–3.8)	.39
3+	2.8 (0.8–9.2)	.09
Duration of surgery of >75th percentile	2.5 (1.1–5.8)	.04

NOTE. ASA, American Society of Anesthesiology.

[a] Random coefficient model procedure NLMIXED in SAS Software (SAS Institute).

[b] Zero postoperative doses.

[c] Per 10-year increase.

[d] One, healthy; 2, mild systemic disorder; ⩾3, severe systemic disorder.

though it did not reach statistical significance, failure to administer the first dose of antibiotic before incision seemed the most important prophylaxis-related factor for increasing the risk of SSI. These findings are important for clinical practice. Although several other studies have made risk assessments for SSI in orthopedic surgery [4, 14, 15, 26], this is, to our knowledge, the first study to have evaluated the association of SSI with duration of surgery, timing of administration of prophylaxis, and use of antibiotic cement. In addition, by excluding emergencies and revisions, the findings indicate the net effect of antibiotic prophylaxis on incidence of SSI in patients undergoing primary elective THA; previous studies included both emergency and elective surgery [14, 15, 26]. In our surveillance, postdischarge surveillance was performed until 1 year after surgery, and therefore, the incidence of SSI might be higher than in other studies that did not perform postdischarge surveillance. Yet, the SSI incidence rate of 2.6% is comparable with incidence rates found in other surveillance studies of THA [4, 27].

Although not significant, the OR for timing of administration of prophylaxis after incision suggests that the relative risk of SSI increases in the presence of this factor. The number of patients in some timing categories was too small to draw firm conclusions about the optimal preincisional timing period. Previous studies of general and colorectal surgery also found that administering prophylaxis after incision had a detrimental effect on the incidence of SSI [28, 29].

Previous experimental studies have shown the importance of the presence of antibiotics in the tissue at the moment of potential contamination [30, 31]. In another study [32], injection of antibiotics as an intravenous bolus immediately prior to incision resulted in adequate antibiotic levels in the tissue at the start of surgery. During orthopedic surgery, administration of cephalosporins during incision resulted in sufficiently high concentrations of antibiotics in bone at the moment of removal of the femoral head [33, 34]. An advantage of the administration of antibiotics shortly before the incision is that, in most procedures, the concentration of the antibiotic will still be high enough to prevent infection at the end of the procedure, and repeated dosing during prolonged surgery is less often required. The importance of a sufficient concentration of an antibiotic at the time of closure of the wound on the SSI rate was recently established for gentamicin in colorectal surgery [35].

In the present analysis, duration of prophylaxis was not correlated with the rate of SSI. In a report that included data from 22,000 THA procedures in the Norwegian Arthroplasty Register (during 1987–2001), the incidence of SSI in the group who received single-dose prophylaxis was equal to that in the group who received 4 doses. However, the incidence of aseptic loosening of the joint was higher in the single-dose group [36]. Unfortunately, the authors did not provide data on dosing intervals and timing of administration of the first and subsequent doses, which may have confounded the effect on outcome in this long-term cohort. This is especially important because, in the majority of the cases, cephalothin was used—which has a very short half-life—and consequently, tissue concentrations quickly decrease [37]. It is likely that the use of cephalothin has confounded the results. Cefazolin, which has a much longer half-life and is recommended by many guidelines [11, 13], is likely to negate the use of repeated dosing, as was convincingly demonstrated in our study.

The duration of surgery—identified in our study as the most important risk factor for SSI—could be potentially confounded by other unmeasured factors. Detailed data about complications that could affect duration of surgery (e.g., bleeding, resulting in low antibiotic concentrations) were not collected in our study. Furthermore, duration of surgery seems not readily amenable to change by an intervention. The unchangeable patient risk factors of older age and higher ASA score also resulted in higher ORs for SSI. These risk factors are also described in other studies [4, 26, 29]. In contrast to findings by others, the duration of preoperative hospital stay could not be identified as a risk factor in our study. This discrepancy was probably

because of the fact that almost 95% of the patients in our study had a preoperative hospital stay of ⩽1 day.

Apart from patient- or procedure-related risk factors, hospital-related factors (e.g., surgical technique) can influence the incidence of SSI. By using the procedure NLMIXED in SAS with hospital as a level, we took the hierarchical structure of the data into account and thereby corrected for possible random variation among hospitals.

Our study does have some limitations. First, the number of risk factors included in our study was limited to those reported within the PREZIES network. Although diabetes mellitus, malignancy, and corticosteroid use are reflected in the ASA score, separate reporting of these known risk factors might have rendered risk assessment more precise. Other risk factors that are not reflected in the ASA score (e.g., obesity, perioperative body temperature, and oxygenation) were shown to be relevant in other studies [38–40]. Another limitation of our analysis was the relatively low number of SSIs ($n = 50$), which was the dependent outcome variable of our analysis. Of the 77 patients from the CHIPS database to whom prophylaxis was administered but who were excluded from this analysis because information on timing was not known, 8 patients (10.3%) developed an SSI, compared with 50 (2.6%) of 1922 patients who were included in our analysis ($P < .0003$). This difference could be because of the characteristics of these patients or could imply that reporting the time of administration of prophylaxis is in itself a marker of correct performance. Finally, the fact that the postdischarge surveillance depended on reporting by the surgeon could have resulted in the underreporting of SSI.

In conclusion, prolonged duration of surgery was the only significant risk factor for SSI following THA. Although it did not reach statistical significance, the timing of the administration of the first dose of an antibiotic after incision seems to be the most important prophylaxis parameter. Multiple postoperative dosing did not contribute to reduction of the incidence of SSI. We strongly recommend that intervention programs on surgical prophylaxis focus on timely administration of the prophylactic antibiotic.

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