SURGICAL INFECTIONS
Volume 18, Number 4, 2017

DOI: 10.1089/sur.2016.164

Failure to Redose Antibiotic Prophylaxis in Long Surgery Increases Risk of Surgical Site Infection

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Abstract

Background: Antibiotic prophylaxis is a key component of the prevention of surgical site infection (SSI). Failure to manage antibiotic prophylaxis effectively may increase the risk of SSI. This study aimed to examine the effects of antibiotic prophylaxis on SSI risk.

Methods: A retrospective cohort study was conducted among patients having general surgery between May 2012 and June 2015 at the University of Washington Medical Center. Peri-operative data extracted from hospital databases included patient and operation characteristics, intra-operative medication and fluid administration, and survival outcome. The effects of antibiotic prophylaxis and potential factors on SSI risk were estimated using multiple logistic regression and were expressed as risk ratios (RRs).

Results: A total of 4,078 patients were eligible for analysis. Of these, 180 had an SSI. Mortality rates within and after 30 days were 0.8% and 0.3%, respectively. Improper antibiotic redosing increased the risk of SSI (RR 4.61; 95% confidence interval [CI] 1.33–15.91). Other risk factors were in-patient status (RR 4.05; 95% CI 1.69–9.66), smoking (RR 1.63; 95% CI 1.03–2.55), emergency surgery (RR 1.97; 95% CI 1.26–3.08), colectomy (RR 3.31; 95% CI 1.19–9.23), pancreatectomy (RR 4.52; 95% CI 1.53–13.39), proctectomy (RR 5.02; 95% CI 1.72–14.67), small bowel surgery (RR 6.16; 95% CI 2.13–17.79), intra-operative blood transfusion >500 mL (RR 2.76; 95% CI 1.45–5.26), and multiple procedures (RR 1.40; 95% CI 1.01–1.95).

Conclusions: These data demonstrate that failure to redose prophylactic antibiotic during long operations increases the risk of SSI. Strengthening a collaborative surgical quality improvement program may help to eradicate this risk.

Keywords: antibiotic prophylaxis; surgical site infection

Approximately 51.4 million operations are performed annually in the U.S. [1]. Surgical site infections (SSIs) are the most common complication. A multistate point-prevalence survey revealed that SSI is the most common healthcare–associated infection (HAI) (risk ratio [RR] 21.8%; 95% confidence interval [CI] 18.4–25.6%) [2]. The U.S. Centers for Disease Control and Prevention (CDC) estimated that 290,485 SSIs occur in a year [3]. Surgical site infections resulted in 3.7 million additional hospital days per year [4] or prolongation of 14 post-operative days per case [5]. Such infections are the most costly type of HAI. The average attributable cost of SSI per case was $11,874–$34,670. An aggregate attributable patient hospital costs by SSI was $3.45 billion–$10.07 billion [3].

Many U.S. hospitals use SSI prevention interventions that have been encouraged by the Surgical Care Improvement Project (SCIP) to improve the quality of surgical care and reduce impacts associated with SSI [6–8]. Appropriate choice and timing of antibiotic prophylaxis is one of the core interventions in this project [6–8]. Several studies confirm that use of these guidelines is associated with a reduction in SSI [9–12]. However, the compliance with surgical antibiotic

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prophylaxis guidelines [13] is not perfect in all settings or all operative procedures [14]. Current guidelines recommend that antibiotic selection be appropriate for the specific procedure [13]. Recommended timing of antibiotic administration is within one hour before the creation of the surgical incision, within two hours if vancomycin or a fluoroquinolone is used [13]. These recommendations are based on the pharmacokinetics and efficacy of antibiotics. It is important to maintain adequate antibiotic serum concentrations throughout the operation [13,15,16]. A study reported that redosing cefazolin in patients who underwent cardiac operations lasting more than four hours decreased the risk of SSI [17,18]. Another study showed that low concentrations of gentamicin in the serum at surgical closure among patients having colorectal procedures are strongly associated with SSI [19]. Currently, only a few studies have reported the association between redosing the prophylactic antibiotic during long surgery and SSI, that too in only a few types of surgical procedures [17,19].

The University of Washington Medical Center (UWMC) started participating in the National Surgical Infection Prevention Collaborative Project in 2002 [20] and joined the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) in 2006. The latter project is a data-driven, risk-adjusted, outcomes-based program to measure and improve the quality of surgical care. In both projects, appropriate antibiotic prophylaxis is a key means of reducing SSI. The UWMC also maintains an Anesthesia Information Management System (AIMS) database that contains high-fidelity intra-operative data, including surgical and anesthesia events, anesthesia techniques, laboratory results, fluid input and output, medications, and hemodynamic data. Combining data from these multiple sources, we conducted this study to examine the effects of antibiotic prophylaxis on SSI risk, including choice of antibiotics, timing of antibiotics before skin incision, and timing of antibiotic redosing in 15 operative procedures.

Patients and Methods

Ethical considerations

The study protocol was reviewed and approved by the Institutional Review Board, University of Washington (No. 50343).

Study design, setting, and sample

A retrospective cohort study was conducted between May 2012 and June 2015 at UWMC. Adult patients (18 years or older) who underwent general surgical operations were included. The procedures examined were appendectomy, bariatric surgery, breast surgery, cholecystectomy, colectomy, esophagectomy, exploratory laparotomy, gastric surgery, hepatectomy, pancreatectomy, proctectomy, small bowel surgery, spleen surgery, thyroidectomy, and ventral hernia repair. Patients who had an infection present at the time of surgery and those who followed for <30 days post-operatively were excluded.

Definition

We used the criteria of the CDC National Healthcare Safety Network (NHSN) [22] and ACS-NSQIP [23] to diagnose SSI and classify incisions. The NHSN cut-point of the duration of surgery for each procedure (75th percentile) was used [24]. Proper timing of the first antibiotic dose was defined as administration within one h before surgical incision or within two h if vancomycin or a fluoroquinolone was used. Proper timing of redose was defined according to surgical antibiotic guidelines [13] such as cefazolin redose within four h for long surgery. The other antibiotics used in substantial amounts have half-lives that do not require repeat doses for operations lasting for six h or less [13].

Data collection

Data on the antibiotic agent, prophylaxis timing before skin incision, redosing, and intra-operative medication, fluid administration, and vital signs were extracted from the AIMS database. Demographics, pre-operative clinical laboratory variables, surgical profile, SSI, and death within and after 30 days of discharge were obtained from the ACS NSQIP.

The main exposure variables of interest were the prophylactic agent, antibiotic timing before skin incision, and redosing. The primary outcome was SSI (superficial incisional, deep incision, and organ/space), and the secondary outcome was death (mortality rate within and after 30 days).

Patient characteristics comprised gender, age, body mass index, race, patient status, origin status/transfer, diabetes mellitus, smoker, dyspnea, functional status prior to surgery, chronic obstructive pulmonary disease, ascites, hypertension, renal failure, dialysis, steroid/immunosuppressant use, disseminated cancer, weight loss >10% in the six mos prior to surgery, bleeding disorders, pre-operative transfusion, sepsis/septic shock, creatinine concentration, albumin concentration, white blood cell count, hematocrit, and American Society of Anesthesiologists (ASA) classification (1 = healthy, 2 = mild systemic disease, 3 = severe systemic disease, 4 = life-threatening systemic disease, or 5 = moribund).

Operative characteristics included anesthesia technique, type of surgery, type of operative procedure, number of procedures, incision classification (clean, clean-contaminated, contaminated, or dirty/infected), and duration of surgery (time from skin incision to closure in minutes). Intra-operative medication, fluid administration, and vital signs, antibiotic prophylaxis use, opioid use, insulin administration, average blood glucose concentration, average crystalloid fluid administration, average colloid fluid administration, average blood transfusion volume, average estimated blood loss, average temperature, average systolic blood pressure, average diastolic blood pressure, average O_2 saturation, and average minimum alveolar concentration (MAC) were calculated.

Statistical analysis

Data of patient and operation characteristics, antibiotic prophylaxis, intra-operative medication, fluid administration, and vital signs were described using frequency, percentage, and mean (standard deviation). Categorical variables of SSI and non-SSI patients were compared using the χ^2 and Fisher exact tests.

Univariable analysis was used to examine the timing of antibiotic redose and other variables associated with SSI, including patient characteristics, operative characteristics, and intra-operative medication, fluid administration, and vital signs (see the details of these variables above). Potential confounding factors with p values <0.05 in the univariable analyses were included in the multivariable analyses. Adjusted risk ratios

(RRs) and 95% confidence intervals (CIs) were estimated using multivariable logistic regression models.

Subgroup analyses were performed to identify risk factors for SSI among in-patients and out-patients because most of the out-patients had short-duration of surgery, and antibiotic prophylaxis redosing might not be a key risk factor for SSI among this group.

All independent variables were checked for normality and multicollinearity. We did not find multicollinearity of predictor variables in our model. All analyses were conducted using STATA version 11.2 (StataCorp, College Station, TX).

Results

Patient and operation characteristics

A total of 4,078 patients were eligible for analysis. Of these, 180 (4.4%) were found to have an SSI. These infections were classified as superficial incisional in 2.4%, deep incisional SSI in 0.2%, and organ/space in 1.8%. Most patients were female (63.1%) and white (84.9%). One-third of the patients (33.7%) underwent laparoscopic surgery. The SSI rates after laparoscopic procedures were lower than after open surgery, 1.7% and 5.8%, respectively; appendectomy 1% (2/209) vs. 7.1% (1/14); bariatric surgery 1.9% (6/310) vs. 12.2 (10/82); cholecystectomy 1.7% (3/179) vs 14.3% (5/35); colectomy 4.8% (7/145) vs. 8.3% (35/424); exploratory laparotomy 1.8% (1/55) vs. 6.0% (7/117); gastric surgery 0 (0/275) vs. 6.1% (3/49); proctectomy 6.5% (2/31) vs. 11.3% (19/168); small bowel surgery 0.0% (0/12) vs. 12.1% (25/207); and ventral hernia repair 1.3% (2/159) vs. 5.1% (16/315). The mortality rates within and after 30 days were 0.8% and 0.3%, respectively. The mean age was 52.7 years (standard deviation [SD] 15.3 years). The mean body mass index was 25.8 kg/m^2 (SD 8.1 kg/m^2). The majority of patients had no underlying diseases and had normal creatinine and albumin concentrations, white blood cell counts, and hematocrits. Patients' physical health status indicated severe systemic disease (ASA 3) in 50.3% and mild systemic disease (ASA 2) in 36.6% (Table 1).

Most patients received general anesthesia (99.2%) and had elective surgery (87.7%). The three most common operative procedures were breast surgery (16.5%), colectomy (13.9%), and ventral hernia repair (11.6%). Some patients (38.8%) underwent multiple procedures. Surgical incisions were classified as clean-contaminated in 49.8% and clean in 42.5%. The mean duration of surgery was 198.1 min (SD 136.8 min) (Table 1).

Antibiotic prophylaxis administration

Most patients (98.1%) received antibiotic prophylaxis. Cefazolin was the most common agent (58.9%), followed by cefazolin plus metronidazole (24.3%). The timing of the first antibiotic dose was proper in nearly all cases (99.3%). Failure to redose antibiotic prophylaxis and delayed timing of the redose were observed in 0.5% and 1.8% of patients, respectively (Table 1).

Intraoperative medication, fluid administration, and vital signs

Opioid analgesia was used in most patients (99.7%), and insulin was given to some patients (21.9%). The blood glucose concentration was monitored in high-risk patients, the mean of

Table 1. Baseline Characteristics, Surgical Site Infection, and Deaths in 4,078 Patients

Characteristic	*No. (%)*
Patient	
Female	2,572 (63.1)
Age (years)	
<35	581 (14.2)
35–44	635 (15.6)
45–54	853 (20.9)
55–64	1,026 (25.2)
≥65	983 (24.1)
Mean ± SD	52.7 ± 15.3
Body mass index (kg/m^2)	
<18.5	599 (14.7)
18.5–24.9	1,715 (42.0)
25.0–29.9	822 (20.2)
30.0–39.9	697 (17.1)
≥40.0	245 (6.0)
Mean ± SD	25.8 ± 8.1
Caucasian	3,464 (84.9)
In-patient status	2,741 (67.2)
Origin status, not transferred	3,945 (96.7)
Co-morbidities	
Diabetes mellitus	
No	3,566 (87.4)
Non-insulin therapy	280 (6.9)
Insulin therapy	232 (5.7)
Smoker	335 (8.2)
Dyspnea	310 (7.6)
Dependent functional status prior to surgery	29 (1.7)
Chronic obstructive pulmonary disease	78 (2.0)
Ascites	85 (2.1)
Hypertension	1,406 (34.5)
Renal failure	51 (1.3)
Dialysis	81 (2.0)
Steroid/immunosuppressant use	582 (14.3)
Disseminated cancer	212 (5.2)
Weight loss >10% in 6 months prior tosurgery	44 (1.1)
Bleeding disorders	92 (2.3)
Pre-operative transfusion	36 (0.9)
Sepsis/septic shock	134 (3.3)
Creatinine (>1.02 F/>1.18 M mg/dL) (n = 2,341)	413 (17.6)
Mean ± SD	1.1 ± 1.4
Albumin (<35 g/dL) (n = 2,144)	587 (27.4)
Mean ± SD	3.7 ± 0.7
White blood cell count (>10×10^3 cells/μL) (n = 2,278)	474 (20.8)
Mean ± SD)	7.9 ± 4.3
Hematocrit (<36% F, <38% M) (n = 2,351)	941 (40.0)
Mean ± SD	37.0 (5.8)
ASA class	
1: Healthy	317 (7.8)
2: Systemic disease	1,493 (36.6)
3: Severe systemic disease	2,053 (50.3)
4: Life threatening systemic disease	205 (5.0)
5: Moribund	10 (0.3)

(*continued*)

TABLE 1. (CONTINUED)

Characteristic	*No. (%)*
Operation	
Laparoscopic surgery	1,375 (33.7)
General anesthesia	4,046 (99.2)
Emergency surgery	502 (12.3)
Operative procedure	
Appendectomy	223 (5.5)
Bariatric surgery	392 (9.6)
Breast surgery	671 (16.5)
Cholecystectomy	214 (5.3)
Colectomy	569 (13.9)
Esophagectomy	71 (1.7)
Exploratory laparotomy	172 (4.2)
Gastric surgery	324 (7.9)
Hepatectomy	203 (5.0)
Pancreatectomy	202 (5.0)
Proctectomy	199 (4.9)
Small bowel surgery	219 (5.4)
Spleen surgery	20 (0.5)
Thyroidectomy	125 (3.1)
Ventral hernia repair	474 (11.6)
Incision classification	
Clean	1,735 (42.5)
Clean-contaminated	2,030 (49.8)
Contaminated	251 (6.2)
Dirty/infected	62 (1.5)
Duration of surgery >75th percentile (min)	1,795 (44.0)
Mean ± SD)	198.1 ± 136.8
Multiple procedures	1,582 (38.8)
Antibiotic prophylaxis administration	
Total patients	4,001 (98.1)
Drug (n = 4,001)	
Cefazolin	2,356 (58.9)
Cefazolin + metronidazole	973 (24.3)
Levofloxacin + metronidazole	232 (5.8)
Ciprofloxacin + metronidazole	44 (1.1)
Clindamycin	179 (4.5)
Vancomycin	153 (3.8)
Piperacillin/tazobactam	26 (0.6)
Other	39 (1.0)
Proper time of first dose	3,971 (99.3)
Redose (n = 4,001)	
No: Proper	2,416 (60.4)
No: Improper	20 (0.5)
Yes	1,565 (39.1)
Proper time of redose (n = 1,565)	1,537 (98.2)
Intraoperative medication, fluid administration, and vital signs	
Opioid	4,067 (99.7)
Insulin	892 (21.9)
Average blood glucose (mg/dL) (n = 1,338)	
60–99	83 (6.2)
100–139	618 (46.2)
140–179	483 (36.1)
180–199	74 (5.5)
≥200	80 (6.0)
Mean ± SD	142.7 ± 33.5
Average crystalloid fluid administration (>2,000 mL)	2,021 (49.6)
Mean ± SD	2,528.7 ± 1,751.5
Average colloid fluid administration (mL)	
None	3,126 (76.7)
≤500	589 (14.4)
>500	363 (8.9)
Mean ± SD	714.7 ± 595.5
Average blood transfusion (mL)	
None	3,884 (95.3)
≤500	115 (2.8)
>500	79 (1.9)
Mean ± SD	838.1 ± 1,371.0
Average estimated blood loss (mL)	
≤100	2,974 (72.9)
101–500	791 (19.4)
>500	313 (7.7)
Mean ± SD	194.3 (604.2)
Average temperature (°C) (n = 3,934)	
<36.0	719 (18.3)
36.0–37.0	2,612 (66.4)
37.1–38.0	573 (14.6)
>38.0	30 (0.7)
Mean ± SD	36.5 ± 0.6
Average systolic blood pressure (mmHg)	
<100	676 (16.6)
100–140	3,322 (81.4)
>140	80 (2.0)
Mean ± SD	111.2 ± 12.0
Average diastolic blood pressure (mmHg)	
<60	1,660 (40.7)
60–90	2,394 (58.7)
>90	24 (0.6)
Mean ± SD	63.0 ± 8.8
Average O_2 saturation ≥95%	4,057 (99.5)
Mean ± SD	98.9 ± 1.2
Average minimum alveolar concentration ≥1	3,640 (89.3)
Mean (SD)	0.8 (0.2)
Surgical site infection	
Any type	180 (4.4)
Superficial incisional	98 (2.4)
Deep incisional	7 (0.2)
Organ/space	75 (1.8)
Survival outcome	
Death within 30 days	33 (0.8)
Death after 30 days	11 (0.3)

(*continued*)

blood glucose concentration in these patients being 142.7 mg/dL (SD 33.5 mg/dL). Patients received an average crystalloid fluid load of 2,528.7 mL. Colloid fluid and blood transfusion were administered in 23.3% and 4.7% of patients, respectively. When comparing patients undergoing laparoscopic or open procedures, there were no significant differences in the rates of intra-operative crystalloid fluid (mean 139.8 ± 58.0 mL/h vs. 139.0 ± 63.5 mL/h; p = 0.361) and colloid fluid administration (mean 139.3 ± 94.0 mL/h vs. 137.9 ± 93.2 mL/h; p = 0.332). The majority of patients had normal temperature, systolic and diastolic blood pressure, O_2 saturation, and MAC (Table 1).

Table 2. Comparison of Baseline Characteristics and Survival of Patients Who Did (N=180) and Did Not (N=3,898) Have a Surgical Site Infection

Characteristic	*Non-SSI* n *(%)*	*SSI* n *(%)*	p
Patient			
Female	2,476 (63.5)	96 (53.3)	0.006
Age (y)			
<35	563 (14.4)	18 (10.0)	0.110
35–44	603 (15.5)	32 (17.8)	
45–54	812 (20.8)	41 (22.8)	
55–64	990 (25.4)	36 (20.0)	
≥65	930 (23.9)	53 (29.4)	
Mean ± SD	52.7 ± 15.4	54.1 ± 14.2	
Body mass index (kg/m^2)			
<18.5	568 (14.6)	31 (17.2)	0.296
18.5–24.9	1,642 (42.1)	73 (40.6)	
25.0–29.9	782 (20.1)	40 (22.2)	
30.0–39.9	675 (17.3)	22 (12.2)	
≥40.0	231 (5.9)	14 (7.8)	
Mean ± SD	25.8 ± 8.1	25.9 ± 9.1	
Caucasian	3,299 (84.6)	165 (91.7)	0.010
In-patient status	2,569 (65.9)	172 (95.6)	0.000
Origin status, not transferred	3,780 (97.0)	165 (91.7)	0.000
Co-morbidities			
Diabetes mellitus			
No	3,412 (87.5)	154 (85.5)	0.465
Non-insulin therapy	268 (6.9)	12 (6.7)	
Insulin therapy	218 (5.6)	14 (7.8)	
Smoker	308 (7.9)	27 (15.0)	0.001
Dyspnea	300 (7.7)	10 (5.6)	0.289
Dependent functional status prior to surgery	26 (0.7)	3 (1.7)	0.119
Chronic obstructive pulmonary disease	78 (2.0)	7 (3.9)	0.083
Ascites	25 (0.6)	2 (1.1)	0.336
Hypertension	1,338 (34.3)	68 (37.8)	0.341
Renal failure	50 (1.3)	1 (0.6)	0.727
Dialysis	76 (1.9)	5 (2.8)	0.436
Steroid/immunosuppressant use	550 (14.1)	32 (17.8)	0.169
Disseminated cancer	198 (5.1)	14 (7.8)	0.111
Weight loss >10% in 6 mos prior to surgery	42 (1.1)	2 (1.1)	0.585
Bleeding disorder	86 (2.2)	6 (3.3)	0.319
Pre-operative transfusion	33 (0.9)	3 (1.7)	0.211
Sepsis/septic shock	125 (3.2)	9 (5.0)	0.187
Creatinine (>1.02 F; 1.18 mg/dL) (n = 2,341)	388 (17.6)	25 (18.8)	0.719
Mean ± SD	1.1 ± 1.4	1.1 ± 1.3	
Albumin (<3.5 g/dL) (n = 2,144)	541 (26.7)	46 (39.0)	0.004
Mean ± SD	3.7 ± 0.7	3.5 ± 0.7	
White blood cell count (>10 × 10^3 cells/μL) (n = 2,278)	447 (20.8)	27 (20.8)	0.991
Mean ± SD	7.9 ± 4.3	8.2 ± 5.0	
Hematocrit (< 36% F/<38% M) (n = 2,351)	884 (39.8)	57 (43.5)	0.402
Mean ± SD	37.1 ± 5.8	36.0 ± 5.7	
ASA class			
1: Healthy	310 (7.9)	7 (3.9)	0.000
2: Systemic disease	1,447 (37.1)	46 (25.6)	
3: Severe systemic disease	1,944 (49.9)	109 (60.6)	
4: Life-threatening systemic disease	189 (4.9)	16 (8.9)	
5: Moribund	8 (0.2)	2 (1.1)	
Operation			
General anesthesia	3,866 (99.2)	180 (100.0)	0.222
Emergency surgery	465 (11.9)	37 (20.6)	0.001
Operative procedures			
Appendectomy	220 (5.6)	3 (1.7)	0.000
Bariatric surgery	376 (9.7)	16 (8.9)	
Breast surgery	666 (17.1)	5 (2.8)	
Cholecystectomy	206 (5.3)	8 (4.4)	
Colectomy	527 (13.5)	42 (23.3)	

(*continued*)

TABLE 2. (CONTINUED)

Characteristic	*Non-SSI* n *(%)*	*SSI* n *(%)*	p
Esophagectomy	70 (1.8)	1 (0.6)	
Exploratory laparotomy	164 (4.2)	8 (4.4)	
Gastric surgery	321 (8.2)	3 (1.7)	
Hepatectomy	192 (4.9)	11 (6.1)	
Pancreatectomy	183 (4.7)	19 (10.6)	
Proctectomy	178 (4.6)	21 (11.7)	
Small bowel surgery	194 (5.0)	25 (13.9)	
Spleen surgery	20 (0.5)	0	
Thyroidectomy	125 (3.2)	0	
Ventral hernia repair	456 (11.7)	18 (10.0)	
Incision classification			
Clean	1,705 (43.7)	30 (16.7)	0.000
Clean-contaminated	1,896 (48.6)	134 (74.4)	
Contaminated	239 (6.1)	12 (6.7)	
Dirty/infected	58 (1.5)	4 (2.2)	
Duration of surgery >75th percentile (min)	1,685 (43.2)	110 (61.1)	0.000
Mean ± SD	194.5 ± 135.5	276.8 ± 141.1	
Multiple procedures	1,496 (38.4)	86 (47.8)	0.011
Prophylactic antibiotic administration			
Use	3,824 (98.1)	177 (98.3)	1.000
Drug (n = 4,001)			
Cefazolin	2,274 (59.5)	82 (46.3)	0.000
Cefazolin + metronidazole	901 (23.6)	72 (40.7)	
Levofloxacin + metronidazole	221 (5.8)	11 (6.2)	
Ciprofloxacin + metronidazole	43 (1.1)	1 (0.6)	
Clindamycin	173 (4.5)	6 (3.4)	
Vancomycin	150 (3.9)	3 (1.7)	
Piperacillin/tazobactam	25 (0.7)	1 (0.6)	
Other	37 (1.0)	1 (0.6)	
Proper time of 1st dose (n = 4,001)	3,797 (99.3)	174 (98.3)	0.145
Antibiotic redose (n = 4,001)			
No: proper	2,320 (60.7)	76 (42.9)	0.000
No: improper	35 (0.9)	5 (2.8)	
Yes	1,469 (38.4)	96 (54.2)	
Proper redose time (n = 1,565)	1,443 (98.2)	94 (97.9)	0.688
Intraoperative medication, fluid administration, and vital signs			
Opioid	3,887 (99.7)	180 (100.0)	0.608
Insulin	828 (21.2)	64 (35.6)	0.000
Average blood glucose (mg/dL) (n = 1,338)			
60–99	79 (6.2)	4 (5.6)	0.280
100–139	588 (46.5)	30 (41.7)	
140–179	450 (35.6)	33 (45.8)	
180–199	70 (5.5)	4 (5.6)	
≥200	79 (6.2)	1 (1.4)	
Mean ± SD	142.8 ± 33.8	140.1 ± 27.1	
Average crystalloid fluid administration (mL)			
≤2,000	2,015 (51.7)	42 (23.3)	0.000
>2,000	1,883 (48.3)	138 (76.7)	
Mean ± SD	2,481.7 ± 1,727.3	3,542.4 ± 1,956.4	
Average colloid fluid administration (mL)			
No	3,035 (77.9)	91 (50.6)	0.000
≤500	535 (13.7)	54 (30.0)	
>500	328 (8.4)	35 (19.4)	
Mean ± SD	720.4 ± 611.2	659.4 ± 411.3	
Average blood transfusion (mL)			
No	3,732 (95.7)	152 (84.4)	0.000
≤500	101 (2.3)	14 (7.8)	
>500	65 (1.7)	14 (7.8)	
Mean ± SD	868.6 ± 1,473.3	657.1 ± 364.1)	
Average estimated blood loss (mL)			
≤100	2,894 (74.2)	80 (44.4)	0.000
101–500	720 (18.5)	71 (39.4)	

(*continued*)

TABLE 2. (CONTINUED)

Characteristic	*Non-SSI* n *(%)*	*SSI* n *(%)*	p
>500	284 (7.3)	29 (16.1)	
Mean ± SD	186.5 ± 603.4	356.6 ± 600.0	
Average temperature (°C) (n = 3,934)			
<36.0	687 (18.3)	32 (18.3)	0.135
36.0–37.0	2,506 (66.7)	106 (60.6)	
37.1–38.0	537 (14.3)	36 (20.6)	
>38.0	29 (0.7)	1 (0.6)	
Mean ± SD	36.5 ± 0.6	36.5 ± 0.6	
Average systolic blood pressure (mm Hg)			
<100	654 (16.8)	22 (12.3)	0.239
100–140	3,168 (81.4)	154 (86.0)	
>140	72 (1.8)	3 (1.7)	
Mean ± SD	111.2 ± 12.1	111.6 ± 10.5	
Average diastolic blood pressure (mm Hg)			
<60	1,584 (40.6)	76 (42.2)	0.743
60–90	2,290 (58.8)	104 (57.8)	
>90	24 (0.6)	0	
Mean ± SD	63.0 ± 8.9	62.5 ± 8.1	
Average O_2 saturation (%)			
≥95	3,879 (99.5)	178 (98.9)	0.237
<95	19 (0.5)	2 (1.1)	
Mean ± SD	98.9 ± 1.2	99.1 ± 1.1	
Average minimum alveolar concentration ≤ 1	3,473 (89.1)	167 (92.8)	0.119
Mean ± SD	0.8 ± 0.2	0.8 ± 0.2	
Survival outcome			
Death within 30 d	32 (0.8)	1 (0.6)	0.568
Death after 30 d	8 (0.2)	3 (1.7)	0.011

Comparison of variables associated with SSI between non-SSI and SSI cases

The non-SSI and SSI cases were different in gender, race, patient status, origin status, smoker, serum albumin, ASA class, type of surgery, type of operative procedure, number of procedures, incision classification, duration of surgery, type of antibiotic prophylaxis, antibiotic redose, timing of antibiotic redose, insulin administration, average crystalloid fluid administration, average colloid fluid administration, average blood transfusion, average estimated blood loss, and mortality rate 30 days post-operatively (Table 2).

Effects of antibiotic prophylaxis on SSI risk and other risk factors for SSIs

In a univariable analysis before adjusting for confounding factors, we found that patients who received cefazolin plus metronidazole had a greater risk of SSI and observed that all of these were colorectal cases. Similarly, patients who had redoses of antibiotic had a greater risk, and these all are cases that lasted longer than four hours. We also found improper antibiotic prophylaxis redosing the increased the risk of SSI. Other risk factors were male patients, age >65 y, white race, in-patient status, transferred from other settings, smoker, serum albumin <3.5 g/dL, ASA class >2, emergency procedure, type of operative procedure, multiple procedures, incision class, duration of surgery >75th percentile, intra-operative insulin administration, intra-operative average crystalloid fluid administration >2,000 mL, intra-operative colloid fluid administration, intra-operative blood transfusion, and average estimated blood loss >100 mL (Table 3).

After adjusting for confounding factors, improper antibiotic redosing increased the risk of SSI (RR 4.61; 95% CI, 1.33–15.91). Other risk factors were in-patient status, smoking, emergency surgery, colectomy, pancreatectomy, proctectomy, small bowel surgery, multiple procedures, and intra-operative blood transfusion >500 mL (Table 4).

Subgroup analysis of risk factors for SSIs among in-patients and out-patients

Subgroup analysis among in-patients had similar results, as shown in Table 4, but in-patient status, smoker, and multiple procedures were excluded from the model (Table 5). For out-patients, only smoking was identified as a risk factor for SSI (RR 10.49; 95% CI 1.73–63.78).

Discussion

This study has shown that failure to redose prophylactic antibiotics during long operations substantially increases the risk of SSI.

The choice of antibiotics in our study was appropriate in most cases. This may be because this practice has been continuously and comprehensively implemented, closely monitored, and improved in our setting from 2002 to the present [20]. This success may be because all multidisciplinary teams who are involved in this practice were included in the Surgical Quality Improvement Program. The selection of antibiotic in our setting is based on normal flora at the surgical site, common pathogens in each procedure, hospital epidemiology and susceptibilities, expert opinion, cost, adverse effects, and drug allergy profile of each patient. Proper

Table 3. Risk Factors for Surgical Site Infection among All Cases Retrieved by Univariable Analysis (N=4,078)

Factor	*RR*	95% *CI*	p
Patient characteristic			
Male	1.52	1.13– 2.06	0.006
Age >65	1.78	1.03– 3.07	0.038
Caucasian	2.00	1.17– 3.41	0.011
In-patient	11.12	5.48–22.67	0.000
Transferred from other setting	2.91	1.66– 5.10	0.000
Smoker	2.06	1.34– 3.15	0.001
Albumin <3.5 g/dL	2.13	1.51– 3.01	0.000
ASA class			
1: Healthy	Reference		
3: Severe systemic disease	2.48	1.15– 5.38	0.021
4: Life threatening systemic disease	3.75	1.51– 9.28	0.004
5: Moribund	11.07	1.98–61.89	0.006
Operation			
Emergency	1.91	1.31–2.78	0.001
Procedure			
Breast surgery	Reference		
Bariatric surgery	5.67	2.06–15.60	0.001
Cholecystectomy	5.17	1.67–15.98	0.004
Colectomy	10.62	1.67–27.02	0.000
Exploratory laparotomy	6.50	2.10–20.12	0.001
Hepatectomy	7.63	2.62–22.23	0.000
Pancreatectomy	13.83	5.09–37.54	0.000
Proctectomy	15.71	5.84–42.26	0.000
Small bowel surgery	17.16	6.48–45.43	0.000
Ventral hernia repair	5.26	1.94–14.26	0.001
Incision class			
Clean	Reference		
Clean-contaminated	4.02	2.69– 5.60	0.000
Contaminated	3.01	1.44– 5.65	0.003
Dirty/infected	3.92	1.34–11.49	0.013
Duration of surgery >75th percentile	2.06	1.52– 2.80	0.000
Multiple procedures	1.47	1.09– 1.98	0.012
Antibiotic prophylaxis			
Cefazolin + metronidazole prophylaxis	2.22	1.60– 3.07	0.000
Antibiotic redose			
No: Proper	Reference		
No: Improper	7.59	2.48–23.25	0.000
Yes	1.99	1.46– 2.70	0.000
Intraoperative medication and fluid administration			
Insulin administration	2.05	1.49– 2.80	0.000
Average crystalloid fluid administration >2,000 mL	3.52	2.48– 4.99	0.000
Average colloid fluid administration (mL)			
No	Reference		
≤500	3.37	2.37– 4.77	0.000
>500	3.56	2.37– 5.34	0.000
Average blood transfusion (mL)			
No	Reference		
≤500	3.40	1.90– 6.09	0.000
>500	5.29	2.90– 9.63	0.000
Average estimated blood loss (mL)			
≤100	Reference		
101–500	3.58	2.57– 4.96	0.000
>500	3.69	2.37– 5.75	0.000

CI = confidence interval; RR = relative risk.

choice of antibiotic in our setting may help to optimize the use of antibiotic prophylaxis to prevent SSI and to avoid antibiotic-resistant organisms [20]. Proper choice of prophylactic antibiotic in surgical patients has been demonstrated to prevent SSI in several studies [9–12].

Another important factor influencing the efficacy of prophylaxis is the timing of antibiotic administration. In our study, the likelihood of administration of the first antibiotic dose during the 60 min before the incision was nearly 100%. We therefore cannot show that inappropriate timing of the

Table 4. Risk Factors for Surgical Site Infection among All Cases with Data Retrieved from Multivariable Analysis (N=4,078)

Factor	*RR*	*95% CI*	p
In-patient	4.05	1.69– 9.66	0.002
Smoker	1.63	1.03– 2.55	0.035
Emergency	1.97	1.26– 3.08	0.003
Operative procedure			
Breast surgery	Reference		
Colectomy	3.31	1.19– 9.23	0.022
Pancreatectomy	4.52	1.53–13.39	0.006
Proctectomy	5.02	1.72–14.67	0.003
Small bowel surgery	6.16	2.13–17.79	0.001
Multiple procedures	1.40	1.01– 1.95	0.047
Improper: No antibiotic prophylaxis redose	4.61	1.33–15.91	0.016
Intra-operative blood transfusion >500 mL	2.76	1.45– 5.26	0.002

CI = confidence interval; RR = relative risk.

first antibiotic dose is a risk factor for SSI. Recently, administration of antibiotic 60 min before incision has been recommended. However, the optimal timing of antibiotic prophylaxis before the incision is unclear because of different findings among studies [11,12,25,26]. A recent study suggests that the lowest infection rate might be seen with administration only four min before creation of the incision [25]. Another study demonstrated that cardiac patients who received cefuroxime 15 min prior to incision had a lower SSI rate (1.8%) than those in whom the drug was received longer than 45 min before the incision (2.2%). It also has been shown that giving vancomycin 32 min before the incision resulted in the lowest SSI rate (1.8%) compared with administration 45 min (2.2%) and 60 min (3.2%) before skin incision [26]. A randomized controlled trial is needed to determine the optimal timing of each antibiotic. These data will support evidence-based clinical decisions on appropriate timing of antibiotic prophylaxis.

Most patients in our study received proper antibiotic redosing as a result of the use of an intra-operative decision-support system called the Smart Anesthesia Manager (SAM) [27,28]. This system acquires nearly real-time information from AIMS and provides guidance alerts for clinical issues via ''pop-up'' messages on the AIMS computer in the operating room. Smart Anesthesia Manager improves timely antibiotic initial dosing and subsequent redosing [27,29]. In spite of high compliance with antibiotic redosing as a result of SAM, we still demonstrated that failure to redose prophylactic antibiotic during long operations significantly increases the risk of SSI. Failure to repeat the dose of cefazolin during long operations results in decreased efficacy of antibiotic prophylaxis [13,18]. The drug concentrations in the serum and tissues may be inadequate to inhibit or kill normal flora or pathogens, resulting in a greater risk of SSI [15–17,19]. This finding should be emphasized because poor adherence to antibiotic redosing guidelines can occur in any setting. A study in Australia reported that only 23.5% of the procedures complied with a redosing guideline [14].

The risk factors for SSI in our study are not only improper antibiotic redosing, but also smoking, emergency surgery, abdominal and colorectal operations, multiple procedures, and intra-operative blood transfusion. These findings reflect the fact that SSI occurrence depends on multiple risk factors [30]. Smoking is a risk for SSI because smoking even a single cigarette results in a substantial decrease in tissue oxygen tension for almost an hour [31]. This is because carbon monoxide in cigarette smoke competes with the oxygen in the blood. In addition, the nicotine in cigarettes has vasoconstrictive effects, resulting in less blood flow to the tissues. Investigators have shown that cigarette smoking is associated with delayed wound healing and SSI [32,33], whereas smoking cessation reduced SSI rates [34,35]. It is therefore recommended that patients who undergo elective surgery stop smoking for 30 days prior to surgery [36].

Emergency surgery is a risk factor for SSI [30,37]. This may be attributable to inadequate pre-operative preparation. Also, some emergency patients have predisposing factors for

Table 5. Risk Factors for Surgical Site Infection among In-Patients with Data Retrieved from Multivariable Analysis (N=2,741)

Factor	*RR*	*95% CI*	p
Emergency surgery	1.86	1.18– 2.93	0.007
Operative procedure			
Breast surgery	Reference		
Colectomy	4.35	1.03–18.41	0.046
Pancreatectomy	5.76	1.31–25.35	0.020
Proctectomy	6.74	1.54–29.49	0.011
Small bowel surgery	8.09	1.86–35.24	0.011
Improper: No antibiotic prophylaxis redose	4.61	1.32–16.08	0.016
Intra-operative blood transfusion >500 mL	2.93	1.54– 5.59	0.001

CI = confidence interval; RR = relative risk.

SSI, such as uncontrolled underlying diseases or remote infections. A study documented that emergency colorectal operations are more likely to be associated with contaminated or dirty incisions and suggested that delayed primary closure should be considered in emergency colorectal surgery in which there is colon perforation and generalized contamination [37]. For emergency cases, in the rush to start the procedure, antibiotic prophylaxis may be given after the skin incision is created, resulting in no antibiotic in the tissues or serum at the time of the incision.

Abdominal and colorectal operations increase the risk of SSI because there are numerous microorganisms in the gastrointestinal tract, especially the colon, which is the main site for bacteria in the human body. Incision of the gastrointestinal tract therefore increases the risk of bacterial contamination of the surgical site and is associated with SSI [38]. In our study, patients who underwent small bowel surgery had the highest incidence of SSI because most of them were elderly, having severe systemic disease, anemia, and obesity. Additionally, most operations were open and complicated, the incisions were classified as contaminated or dirty, and the operations were long.

Another risk factor for SSI in this study was multiple operations. Performing several surgical procedures may prolong surgery and increase the risk of contamination. It has been documented in the past that prolonged surgery increases the risk of SSI [38].

Receipt of intra-operative blood transfusion was another risk factor for SSI in our study. This may be because these patients have pre-operative anemia and intra-operative severe bleeding, resulting in deficits of intravascular volume, hemoglobin, and oxygen tension and hypothermia. Reduction in oxygen impacts the bactericidal activity of neutrophils because this process is mediated by oxidative killing. It also reduces the formation of collagen, which requires hydroxylation of proline and lysine residues. Hypothermia impairs platelet function by decreasing thromboxane A_2 and inhibits clotting factor enzyme function, prolongs prothrombin time and partial thromboplastin time, and causes vasoconstriction. Vasoconstriction results in decreased blood supply to the incision, oxygen tension, and oxidative killing by neutrophils [39,40].

Beyond risk factor identification, we found that surgical patients in our setting received proper clinical management and good-quality care during surgery. The study has shown that most patients have intra-operative normothermia. They also have systolic and diastolic blood pressure, O_2 saturation, and MAC within normal limits. Good management and control of intra-operative clinical risk factors may help to reduce the risk of SSI in these patients. This success may be secondary to continuous surgical improvement in our institution [20].

Our study has several strengths. This is a large sample observed over a four-y period, therefore increasing the validity of the findings. In addition, key confounding factors, including intra-operative factors, are adjusted for SSI in our study because we can combine both the NSQIP and AIMS databases. These databases are managed by highly trained personnel. Lastly, all patients included in this study had complete follow-up for 30 days.

This study has some limitations also. It was conducted at a single teaching medical hospital, and therefore, the results may not be generalizable to other settings. However, the effect of failure to redose the prophylactic antibiotic and risk factors for SSI identified in this study can transfer to both everyday practice and the process of quality improvement. Another limitation is the retrospective nature of the study such that some potential confounding factors are not accounted for. However, the databases used in this study have been prepared for quality improvement programs and research. Therefore, potential confounding factors for SSI are available for adjustment.

In conclusion, failure to redose prophylactic antibiotic during long operations increases the risk of SSI. Smoking, emergency surgery, abdominal operations, multiple procedures, and intra-operative blood transfusion also were risk factors in our study. Strengthening a collaborative surgical quality-improvement program and using a clinical decision support system may help to improve timely redosing of antibiotics and reduce the risk of SSI.

Acknowledgments

We thank Mrs. Shu-Fang Newman, MS, Department of Anesthesiology and Pain Medicine, University of Washington; and Mrs. Rosemary Mitchell Grant, BSN, CPHQ, the Sepsis Coordinator, Harborview Medical Center, previously employed at the Surgical Outcomes Research Center, University of Washington, who played key roles in data extraction, as well as those involved in the completion of this study.

An abstract of this manuscript was accepted as a poster presentation at IDWeek 2016. These abstracts will be published as an online supplement to Open Forum Infectious Diseases (OFID), the new open access journal from the Infectious Diseases Society of America.

Author Disclosure Statement

No conflicting financial interests exist. No funding was received for this study.

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