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Antibiotic Regimen and the Timing of Prophylaxis Are Important for Reducing Surgical Site Infection after Elective Abdominal Colorectal Surgery

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Abstract

Background: Surgical site infections (SSIs) cause morbidity after elective colorectal surgery, and antibiotic prophylaxis can decrease SSIs. The aim of this study was to determine compliance with an antibiotic administration protocol, including regimen, initial dose timing, and re-dosing, and determine the risk of SSI associated with each. We hypothesized that appropriate antibiotic administration reduces the risk of SSI.

Methods: Retrospective review from a prospective database of a random sample of patients undergoing elective abdominal colorectal procedures with anastomosis. Antibiotic regimens, initial dose timing (IDT), and re-dosing were evaluated. Appropriate regimens covered gram-positive cocci, gram-negative bacilli, and anaerobes. The IDT was considered proper if completed within 30 min prior to incision; re-dosing parameters were determined pharmacokinetically for each agent. The main outcome was SSI. Sequential logistic models were generated: Model 1 assessed antibiotic administration factors, whereas Model 2 controlled for patient and clinical factors, including disease process, patient characteristics, intra-operative factors, and post-operative factors.

Results: Six hundred five patients (mean age 59.7 [standard deviation 17.8] years, 42.8% male) were included. The most common diagnoses were cancer (38.8%) and inflammatory bowel disease (22.0%). Seventy-six patients (12.6%) had superficial or deep incisional SSI, and 54 (8.9%) had organ/space SSI. Regimens included cefazolin + metronidazole for 219 patients (36.2%), cefoxitin for 214 (35.4%), and levofloxacin + metronidazole for 48 (7.9%). One hundred fourteen patients (18.8%) received other/nonstandard regimens, and ten had no documented antibiotic prophylaxis. Fifty-five patients (9.1%) received insufficient coverage, whereas 361 patients (59.7%) had proper IDT, and 401 regimens (66.3%) were re-dosed properly. In Model 1, the use of other/nonstandard regimens (odds ratio [OR] 2.069; 95% confidence interval [CI] 1.078–1.868) and early administration of the initial prophylaxis dose (OR 1.725; 95% CI 1.147–2.596) were associated with greater odds of SSI. After adding clinical factors in Model 2, both of these factors remained significant (OR 2.505; 95% CI 1.066–5.886 and OR 1.733; 95% CI 1.017–2.954, respectively).

Conclusions: Appropriate antibiotic selection and timing of administration for prophylaxis are crucial to reduce the likelihood of SSI after elective colorectal surgery with intestinal anastomosis.

Surgical site infection (SSI) is the third most common hospital-acquired infection, following pneumonia and urinary tract infection. Among elective operations, colorectal surgery has the highest incidence of SSI, likely attributable to the diverse microbial flora present at high densities in the colon [1]. Published infection rates differ widely, from 3%–43%, largely as a result of variation in SSI definition and the method of follow-up [2-11]. Surgical site infection leads to substantial patient morbidity and cost; a recent study noted that SSI was associated with an additional cost of $30,000 per hospital discharge [12]. Appropriate administration of antimicrobial prophylaxis is one of the ways clinicians can

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decrease the risk of SSI. Milestone studies by Miles et al. in 1957 [13] and Burke in 1961 [14] showed the value of pre-operative antibiotic prophylaxis in preventing SSI.

Antimicrobial prophylaxis regimens in colorectal surgery should be effective against gram-positive cocci, enteric gram-negative bacilli, and anaerobic pathogens [15]. Prophylaxis should be administered within 1 h of surgical incision to ensure adequate tissue coverage for the duration of the operation [16], and regimens with short half-lives should be re-dosed on a schedule determined pharmacokinetically for each agent [1]. Despite the existence of published guidelines, compliance in the United States is imperfect [17]. Correct initial dose timing (IDT) of prophylaxis occurs between 5.9% and 68% of the time without targeted compliance improvement programs, but can improve with specific compliance measures [18-20]. In an effort to improve compliance, the Surgical Care Improvement Project (SCIP) was developed, initiated by the Centers for Medicare and Medicaid Services (CMS) and the U.S. Centers for Disease Control and Prevention (CDC) [16]. Despite recent attention to specific guidelines, studies evaluating the effect of compliance on the incidence of SSI in colorectal surgery have produced conflicting results [7, 18-20].

The aim of this study was to determine the effect of individual antibiotic administration factors, including regimen, coverage, initial dose timing, and re-dosing, on the incidence of SSI. We hypothesized that compliant antibiotic administration reduces the risk of SSI.

Patients and Methods

Patients undergoing colorectal surgery by the Section of Colon and Rectal Surgery at the New York-Presbyterian Hospital/Weill Cornell Medical Center over a seven-year period between June 2001 and July 2008 were identified via a prospectively managed database. A random sample of 605 patients who underwent abdominal surgery of the colon and rectum that required anastomosis was extracted from the database via a random number generation algorithm. Sample size was determined, assuming a significance of $\alpha = 0.05$ and a power of 0.8 to detect a difference of $\Delta = 0.06$ between subgroups. The exclusion criteria were age <18 years, procedures involving the perineum, simple ostomy closures, and designation of the operation as an emergency by the surgeon or anesthesiologist.

The study was approved by the Committee on Human Rights in Research of Weill Cornell Medical College. A retrospective chart review was performed using inpatient and outpatient records; records examined included at least 30-day follow-up for all patients. Physician's notes were cross-referenced with ancillary staff notes, pharmacy and antibiotic order records, and inpatient and outpatient ancillary staff notes (e.g., nursing, social work). Antibiotic regimen, time of administration, and re-dose parameters were collected and operationalized. Potential risk factor variables included patient characteristics, co-morbidities, pre-operative laboratory values, medications, pre-operative infection, operative details, and post-operative glucose concentration. Surgical site infection was defined by CDC criteria [21]; patients with both incisional and organ/space SSI were classified as having organ/space SSI. Retrospective discrimination between superficial and deep incisional infection was impossible; therefore, these diagnoses were considered collectively as incisional SSI. All data were analyzed using STATA/IC, Version 11.0 (Stata Corp, College Station, TX). Statistical significance was accepted at $\alpha = 0.05$.

Consistent with SCIP guidelines, approved antibiotic regimens given in this institution included cefazolin + metronidazole, cefoxitin monotherapy, or a fluoroquinolone (either levofloxacin or ciprofloxacin) + metronidazole. Ertapenem is not on the institutional formulary. The remaining regimens were grouped as other/non-standard. Coverage was operationalized as appropriate, under-coverage, or over-coverage. Under-coverage was classified as a regimen that did not cover one or more of the following pathogens: Gram-positive cocci, enteric gram-negative bacilli, or anaerobic bacteria. Over-coverage was classified as inclusion of an antibiotic that had no additional coverage benefit (e.g., metronidazole given in addition to cefoxitin). Standard practice at this institution for elective colorectal surgery utilizes mechanical bowel preparation without oral antibiotics, but this was documented rarely and therefore not included in the database.

In this retrospective review, the time of administration of antibiotics, if given prior to the patient's arrival to the operating room, was not recorded reliably. Because antibiotic administration time could not be determined for patients who had antibiotics administered prior to arrival to the operating room, appropriate timing was defined as antibiotic administration within 30 min prior to incision, as the timing was noted in the anesthesia and operating room nursing records. Initial dose timing was subsequently operationalized into the following groups: >30 min prior to incision, within 30 min before the incision, or after the incision. Each antibiotic given was evaluated for timing; a patient was deemed to have received an incorrectly timed regimen if one incorrectly timed antibiotic was recorded in a multi-drug regimen. Antibiotics were continued routinely for 24 h post-operatively.

Two logistic regression models were created to determine the association of antibiotic administration factors with SSI. Model 1 included antibiotic administration factors only. In order to test the stability of the effect of the antibiotic factors in the setting of other clinically important control and confounder variables, a second multivariable logistic model was created. Model 2 incorporated potential control or confounder variables from the database, including patient diagnosis, year of surgery, surgeon experience, transfusion, wound class, type of surgery, history of radiation, serum albumin concentration, co-morbidities, intra-operative hypotension, intra-operative hypothermia, post-operative glycemic control, and intensive care unit admission.

Results

Six hundred five patients were included (Table 1), with a mean age of 59.7 years (standard deviation 17.8). Two hundred ninety-two patients (48.3%) were male. Of the 605 patients, 428 (70.7%) had an American Society of Anesthesiologists (ASA) Score of ≤ 2 points. Seventy-six patients (12.6%) developed an incisional SSI, and 54 patients (8.9%) developed an organ/space SSI, for an overall SSI rate of 21.5%. The SSI rate for patients who had minimally invasive operations was 19.8% (superficial SSI rate 12.3%, organ/space SSI rate 7.5%), compared with 25.3% (superficial SSI rate 13.2%, organ/space SSI rate 12.1%) for open operations ($p = 0.13$).

Table 1. Patient Characteristics

Factor	N = *605*
Male (%)	292 (48.3)
Age, years (mean ± SD)	59.7 ± 17.8
Body mass index, kg/m^2 (mean ± SD)	26.2 ± 5.8
Preoperative albumin, g/dL (mean ± SD)	3.8 ± 0.7
Diagnosis (%)	
Colorectal cancer	235 (38.8)
Inflammatory bowel disease	133 (22.0)
Diverticular disease	112 (18.5)
Co-morbidities (%)	
Coronary artery disease	60 (9.9)
Hypertension	211 (34.9)
Diabetes	60 (9.9)
Chronic obstructive pulmonary disease	24 (4.0)
History of pelvic radiation	21 (3.5)
Operation type (%)	
Clean-contaminated	566 (93.6)
Contaminated	22 (3.6)
Dirty/infected	17 (2.8)
Operative time, h (mean ± SD)	3.67 ± 1.66
Procedure method (%)	
Open	99 (16.4)
Minimally invasive	415 (68.6)
Laparoscopic	193 (31.9)
Hand-assisted laparoscopy	222 (36.7)
Converted	91 (15.0)
American Society of Anesthesiologists Score (%)	
1	17 (2.8)
2	411 (67.9)
3	163 (26.9)
4	14 (2.3)
Procedure (%)	
Colectomy only	435 (71.9)
Rectal resection	170 (28.1)
Stoma	145 (24.0)

Table 2. Antibiotic Prophylaxis Used

Factor	*No. (%) of patients*
Antibiotic regimen	
Cefazolin + metronidazole	219 (36.2)
Cefoxitin	214 (35.4)
Levofloxacin + metronidazole	48 (7.9)
Other regimen	114 (18.8)
No recorded antibiotic	10 (1.7)
Regimen coverage	
Appropriate	518 (85.6)
Under-coverage	55 (9.1)
Over-coverage	24 (4.0)
Initial dose timing[a]	
Appropriate	361 (59.7)
Early	202 (33.4)
Late	33 (5.5)
Re-dosing	
Appropriate	401 (66.3)
Early	204 (22.7)

[a]Early administration = antibiotics given > 30 min prior to incision; late administration = antibiotics given after incision.

The most common prophylaxis regimens were cefazolin + metronidazole, given to 219 patients (36.2%), and cefoxitin monotherapy, given to 214 patients (35.4%) (Table 2). Ten patients (2.3%) had no record of antibiotic prophylaxis being given. One hundred fourteen patients received a nonstandard regimen, which included permutations of ampicillin, gentamicin, metronidazole, clindamycin, vancomycin, and piperacillin/tazobactam. Fifty-five patients (9.1%) received antibiotic regimens with inadequate coverage, including 32 who received cefazolin monotherapy. Twenty-four patients had redundancy (over-coverage) in the antibiotic regimen. The initial dose was given within 30 min before incision to 361 patients (59.7%), early to 202 patients (33.4%), and after the incision to 22 patients (5.5%).

Logistic regression models are presented in Table 3. Cefazolin + metronidazole was used as the reference antibiotic regimen. Model 1, which includes the antibiotic administration factors only, demonstrated that use of another/nonstandard regimen (odds ratio [OR] 2.069; 95% confidence interval [CI] 1.078–3.969) and early administration of the initial dose of antibiotics (OR 1.725; 95% CI 1.147–2.596) were associated with a higher risk of SSI. These two factors were both significant in the adjusted model also (other/nonstandard regimen OR 2.505; 95% CI 1.066–5.886; early initial dose administration OR 1.733; 95% CI 1.017–2.954).

Discussion

Antibiotic prophylaxis for colorectal surgery consistently has been beneficial in randomized clinical trials (RCTs) when the antibiotic is administered prior to the incision and the regimen demonstrates appropriate activity against colonic flora [1, 3, 11, 22, 23]. A Cochrane meta-analysis of prophylaxis in colorectal surgery reported results from 11 RCTs comparing any regimen with placebo, clearly showing a decrease in the risk of SSI with any prophylaxis regimen (relative risk 0.30; $p < 0.05$) [15]. Many antibiotic regimens have been studied for prevention of SSI after colorectal surgery, but there is no consensus as to which is best.

One comprehensive guideline, by the SCIP group, recommends a variety of regimens, including cefoxitin monotherapy, cefazolin + metronidazole, or metronidazole + a fluoroquinolone for patients with β-lactam allergy [24]. A 1990 randomized trial by Stellato et al. compared rates of SSI in 146 patients who received one of three antibiotic prophylaxis regimens: Oral neomycin + erythromycin, parenteral cefoxitin, and both oral and parenteral antibiotics [25]. No difference in SSI rates was noted among the groups. Cefazolin monotherapy has benefit over placebo [11], and cefazolin + oral neomycin and erythromycin has benefit over metronidazole monotherapy [26]. Modern guidelines add metronidazole to cefazolin, but this has not been studied in a RCT. The regimen of a fluoroquinolone + metronidazole likewise has been less studied. One study that compared ciprofloxacin + metronidazole with moxalactam, a third-generation cephalosporin, in a randomized trial of 150 patients noted one SSI in the moxalactam group and four in the ciprofloxacin group (p = NS) [27]. The data in the present study support the SCIP recommendations: Patients who received

Table 3. Model Parameters

Model	Odds ratio	95% confidence interval
1		
Antibiotic(s)		
Cefazolin + metronidazole	1	Reference
Cefoxitin	1.152	0.710–1.868
Levofloxaxin + metronidazole	0.753	0.312–1.814
Other regimen	2.069[a]	1.078–3.969
No antibiotic recorded	0.897	0.160–5.018
Coverage		
Correct	1	Reference
Under	0.62	0.250–1.535
Over	0.788	0.274–2.266
Re-dosing		
Appropriate	1	Reference
Inappropriate	0.839	0.543–1.297
Initial dose timing		
Appropriate	1	Reference
Early	1.725[a]	1.147–2.596
Late	0.898	0.349–2.306
Model characteristics		
R^2	0.023	
Area under ROC curve	0.602	
Hosmer-Lemeshow goodness of fit	2.63	
2[b]		
Antibiotic(s)		
Cefazolin + metronidazole	1	Reference
Cefoxitin	1.039	0.566–1.908
Fluoroquinolone + metronidazole	0.594	0.207–1.707
Other regimen	2.505[a]	1.066–5.886
No antibiotic recorded	0.796	0.0668–9.482
Coverage		
Correct	1	
Under	0.366	0.113–1.181
Over	0.436	0.112–1.704
Re-dosing		
Appropriate	1	
Inappropriate	0.782	0.447–1.367
Initial dose timing		
Appropriate	1	
Early	1.733[a]	1.017–2.954
Late	1.023	0.297–3.522
Model characteristics		
R^2	0.120	
Area under ROC curve	0.735	
Hosmer-Lemeshow goodness of fit	2.27	

[a]$P < 0.05$.

[b]Model 2 includes adjustment for disease, year, surgeon experience, transfusion, wound class, type of surgery, history of radiation, serum albumin concentration, co-morbidities, intraoperative hypotension, intraoperative hypothermia, postoperative glycemic control, and intensive care unit admission.

ROC = receiver operating characteristic curve.

non-standard regimens were at higher risk of SSI. All recommended regimens are likely to have comparable efficacy.

Proper timing of administration of the initial dose of antibiotics allows therapeutic tissue concentrations to be achieved at the time of the incision. Although guidelines generally state that the antibiotic should be administered within 1 h of the incision, this recommendation has not been tested rigorously [15, 16, 28]. In 1992, a study of antibiotic timing in 2,847 clean-contaminated surgical procedures showed a significantly lower incidence of SSI when prophylaxis was given within 2 h of incision [29]. However, a more recent study of 9,195 elective procedures performed at the Department of Veterans Affairs hospitals found no difference in SSI rates between timely and untimely administration of prophylactic antibiotics, where timely was considered administration between one and two hours of skin incision [30]. Another study of 3,836 consecutive colorectal surgery patients who underwent prophylaxis with cefuroxime + metronidazole looked more closely at intervals within the 2-h time frame. Prophylaxis administered within 30 min of incision or between 60–120 min prior to incision were both associated with higher rates of SSI than administration between 30–60 minutes prior to incision [31]. A recent study evaluating the effect of the components of the SCIP guidelines in 104 colorectal surgery patients concurred, noting a significantly higher incidence of SSI among patients who did not receive prophylaxis within one hour of incision. Another issue we encountered was that antibiotics were documented reliably only if patients were given prophylaxis while in the operating room; antibiotic dosing outside the operating room results in early IDT [32]. In our study, antibiotics administered more than 30 min prior to incision were associated with higher odds of SSI, which concurs with published data. Dosing the antibiotic in a timely manner to ensure therapeutic tissue concentrations at the time of incision likely is crucial in the prevention of SSI.

Re-dosing strategies are less studied. Many straightforward general surgical procedures shorter than 3 h do not require additional doses. Cefoxitin monotherapy boasts ease of administration (by a 5-min bolus if necessary for proper timing) with relatively low toxicity, but the drug has a notably short half-life of 40 min and should be re-dosed at between 2–3 h; cefazolin can be re-dosed at 4 h, whereas fluoroquinolones and metronidazole have much longer half-lifes and do not generally require intra-operative re-dosing [1]. Appropriate re-dosing of antibiotics may help reduce the risk of SSI in procedures longer than 4 h, but must be given correctly [33]. An RCT comparing parenteral cefoxitin with parenteral cefazolin + oral erythromycin and neomycin found that patients who received cefoxitin monotherapy had a higher incidence of SSI than the other group in procedures longer than 4 h, whereas there was no difference in the SSI rate in those lasting < 4 h [6]. It is unclear whether the protective effect was attributable to the oral antibiotics or the longer half-life of cefazolin. In our data, the procedures had a mean operative time of 3.67 h, with 66.3% of the antibiotic regimens being redosed appropriately. Proper re-dosing did not have a significant effect on SSI (OR 0.782; 95% CI 0.447, 1.367). The majority of operations studied were relatively short and may not have been as affected by re-dosing. Therefore, our data may be underpowered to identify a small effect of this parameter. Data collected on larger samples of longer operations may be required to see the true effect of re-dosing.

The limitations of this study are largely attributable to its retrospective nature. For example, antibiotics that were ordered but had no documentation of administration were recorded as not given. Thirty-two patients were identified as having received cefazolin monotherapy, and ten had no antibiotic prophylaxis, but it is possible that additional antibiotics were given but not recorded. Appropriate regimens thus

may have been counted as under-covered, or as an "other/non-standard" regimen. This would have biased the effect toward the null, so the effect of an "other" regimen may be larger than estimated by the model. Additionally, we could not capture in retrospect the method of bowel preparation for each patient, so this factor was not included in the analysis. However, the practice at this institution is to use mechanical bowel preparation without oral antibiotics, and there would likely not have been a large enough sample of any comparator group. Another limitation is that the sample size was not large enough to control for temporal changes in management. Systematic measures were implemented in this institution during the study period to decrease the incidence of SSIs, such as a shift in administration of the antibiotic from the preoperative nursing team to the anesthesiologist in order to improve the timing of the first dose. Selection by random number generation should have allowed a temporally unbiased picture of the overall effect of the risk factors on SSI over the eight-year period.

The goal of surgical antimicrobial prophylaxis is to maintain adequate and appropriate antibiotic exposure during the surgery. Appropriate antibiotic selection and proper timing of administration are crucial to limit SSIs in elective abdominal colorectal surgery with intestinal anastomosis. Future research should continue to elucidate optimal prophylaxis regimens and timing and follow changes in clinical outcomes with implementation of quality control measures.

Author Disclosure Statement

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