Choice of Intravenous Antibiotic Prophylaxis for Colorectal Surgery Does Matter

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BACKGROUND: The Surgical Care Improvement Program endorses mandatory compliance with approved intravenous prophylactic antibiotics; however, oral antibiotics are optional. We hypothesized that surgical site infection (SSI) rates may vary depending on the choice of antibiotic prophylaxis.

STUDY DESIGN: A retrospective cohort study of elective colorectal procedures using Veterans Affairs Surgical Quality Improvement Program (VASQIP) and SSI outcomes data was linked to the Office of Informatics and Analytics (OIA) and Pharmacy Benefits Management (PBM) antibiotic data from 2005 to 2009. Surgical site infection rates by type of IV antibiotic agent alone (IV) or in combination with oral antibiotic (IV + OA) were determined. Generalized estimating equations were used to examine the association between type of antibiotic prophylaxis and SSI for the entire cohort and stratified by use of oral antibiotics.

RESULTS: After 5,750 elective colorectal procedures, 709 SSIs (12.3%) developed within 30 days. Oral antibiotic + IV (n = 2,426) had a lower SSI rate than IV alone (n = 3,324) (6.3% vs 16.7%, $p < 0.0001$). There was a significant difference in the SSI rate based on type of preoperative IV antibiotic given ($p \leq 0.0001$). Generalized estimating equations adjusting for significant covariates of age, body mass index, procedure work relative value units, and operation duration demonstrated an independent protective effect of oral antibiotics (odds ratio [OR] 0.37, 95% CI 0.29 to 0.46), as well as increased rates of SSI associated with ampicillin/sulbactam (OR 2.21, 95% CI 1.37 to 3.56) and second generation cephalosporins (cefoxitin, OR 2.50, 95% CI 1.83 to 3.42; cefotetan, OR 2.70, 95% CI 1.72 to 4.22) when compared with first generation cephalosporin/metronidazole.

CONCLUSIONS: The choice of IV antibiotic was related to the SSI rate; however, oral antibiotics were associated with reduced SSI rate for every antibiotic class (J Am Coll Surg 2013;217: 763–769. © 2013 by the American College of Surgeons)

Surgical site infections (SSI) are one of the most common hospital acquired infections, and reduction of SSI is a national priority.[1] Infections after surgery are presumed to be preventable, and SSI process and outcomes measures are used as metrics of surgical quality.[2,3] Colorectal operations are frequently complicated by SSI, with reported rates ranging from 6% to 30%.[4,5] Furthermore, SSI after colorectal surgery leads to increased hospital readmissions, costs, and mortality.[6]

In 2002, through a joint effort of the Centers for Disease Control and the Centers for Medicare and Medicaid Services (CMS), the Surgical Improvement Project was developed to reduce preventable SSIs. This program created 3 measures to improve antibiotic prophylaxis: appropriate timing for administration, appropriate choice of antibiotic agent, and discontinuation within 24 hours after surgery. These measures were included in the Surgical Care Improvement Project (SCIP), which was implemented in 2006 with the objective of reducing surgical complications by 25% by 2010.[7]

Few studies have shown that adoption of SCIP prophylactic antibiotic measures have reduced SSI; however,

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Abbreviations and Acronyms

OR = odds ratio
SCIP = Surgical Care Improvement Project
SSI = surgical site infection
VASQIP = Veterans' Affairs Surgical Quality Improvement Project

these reports do not specifically link SCIP measure compliance and SSI at the patient level.[8-10] In contrast, 3 large cohort studies with patient level data on SCIP adherence and SSI have failed to link SCIP adherence with SSI reduction.[11-13] Each of these studies identified trends approaching significance for appropriate antibiotic selection and SSI, suggesting that the agent selected may be more important than timing of administration and discontinuation. Furthermore, 2 recent large cohort studies have identified a significant reduction in colorectal SSI with the use of oral antibiotics as part of a bowel preparation regimen.[14,15] Within the guidelines provided by the SCIP, several intravenous antibiotic agents are acceptable and oral antibiotics are discretionary. The purpose of this study was to examine the comparative effectiveness of approved intravenous antibiotics and the use of oral antibiotics on SSI risk for colorectal surgery.

METHODS

This is a retrospective cohort study linking the Veterans Affairs Surgical Quality Improvement Program (VASQIP) preoperative risk and SSI outcomes and the VA Decision Support Systems pharmacy data from 112 hospitals on patients undergoing elective colorectal resections from 2005 to 2009. The study protocol was reviewed and approved by the local VA Research and Development Committee and the Institutional Review Board at the institution of each coauthor, as well as by the Surgical Quality Data Use Group (SQDUG) and the Office of Informatics and Analytics in the VA Central Office, Washington, DC.

Data sources

The VHA Office of Information and Analytics External Peer Review Program contracts with the West Virginia Medical Institute to collect VA hospital SCIP measures. The process began in 2005 according to guidelines set forth by the Joint Commission on Accreditation of Healthcare Organizations and the Centers for Medicaid and Medicare Services. Frequent assessment of the abstracted information to assure reliability is performed.[16] The Veterans' Affairs Surgical Quality Improvement Program (VASQIP) was started in 1991 to analyze risk-adjusted 30-day postoperative morbidity and mortality data within the VA health care system.[17,18] The VASQIP collects demographics, preoperative risk and laboratory data, operative data, and 30-day postoperative morbidity and mortality outcomes on a majority of patients undergoing major surgery in the VA health care system. Clinical nurse reviewers, trained in clinical medicine and quality assurance, complete in-depth training on the data collection procedures and detailed definitions of each of the variables. A report of the quality of the data at a sample of VA medical centers showed that the VASQIP data are highly reliable.[16] The VA Decision Support System was queried for prescriptions for oral antibiotic agents of erythromycin, neomycin, and metronidazole within 60 days of surgery.

Study cohort

The study cohort included all elective colorectal operations based on Current Procedural Terminology (CPT) codes with SCIP measure on appropriate antibiotic with matched VASQIP records. We excluded operations for which prophylactic antibiotic agent information was missing (n = 2,562) and cases in which an SCIP-approved antibiotic was not used (n = 1,635), resulting in a final cohort of 5,750 operations.

Study variables

The independent variable of interest was the specific SCIP-approved prophylactic antibiotic agent. We summarized the choice of intravenous antibiotic or combination as cefoxitin; cefotetan; ertapenem; ampicillin/sulbactam; cefazolin plus metronidazole; and floroquinolone plus clindamycin or metronidazole. We also classified whether the patient was prescribed an oral antibiotic in preparation for surgery based on query of the pharmacy data, as previously published.[13] The dependent variable of interest was the occurrence of a superficial or deep incisional SSI within 30 postoperative days as reported by VASQIP, following the Centers for Disease Control definition. Superficial and deep incisional SSI were combined to create a composite SSI outcomes variable. The VASQIP did not consistently collect organ space SSI during our study period, so we did not include it in our outcomes.

Patient level covariates known to predict the occurrence of SSI, including demographics, lifestyle variables (eg, tobacco and alcohol use), cardiovascular, pulmonary, renal, hepatobiliary, nutritional, and immune comorbidities, were obtained from VASQIP. Surgery characteristics considered in our analyses include type of colectomy (partial, total, rectal, and ileocecetomy), approach (laparoscopic or open), American Society of Anesthesiologist (ASA) status, wound classification, and duration of the operation (incision to surgery end time).

Table 1. Distribution of Surgical Care Improvement Project-Approved Antibiotics Given for Colorectal Surgery Prophylaxis

		Oral plus intravenous antibiotics preoperatively		Intravenous antibiotics preoperatively	
Variable	**Overall, n**	**n**	**%**	**n**	**%**
Total receiving antibiotics		2,426	42.2	3,324	57.8
Cefazolin/metronidazole	363	359	39.9	540	60.1
Ampicillin/sulbactam	899	183	50.4	180	49.6
Cefotetan	775	299	38.6	476	61.4
Cefoxitin	3,051	1,376	45.1	1,675	54.9
Ertapenem	317	68	21.5	249	78.5
Fluoroquinolone/clindamycin or metronidazole	345	141	40.9	204	59.1

$p \leq 0.0001$.

Statistical analyses

Unadjusted testing for association between patient characteristics, prophylactic antibiotic choice, and SSI was done using chi-square and Wilcoxon rank sum tests. Patients were stratified by whether or not they were prescribed an oral antibiotic agent. Multivariable backward stepwise generalized estimating equations analyses were performed to determine predictors of SSI with alpha set at 0.05. All analyses were completed using SAS v 9.2.

RESULTS

We identified 5,750 colorectal operations performed at 112 VA hospitals during the study period of 2005 to 2009 with matched VASQIP and prophylactic antibiotic data. Table 1 shows the distribution of IV antibiotic agents overall and stratified by the use of oral antibiotics. The second generation cephalosporin agents were most commonly used. Of the 5,750 cases, 2,426 (42%) had a prescription for oral antibiotics in addition to the intravenous antibiotics (Table 1). There were significant differences in the use of oral antibiotics by intravenous antibiotic category ($p < 0.0001$). The breakdown by oral antibiotic type was erythromycin and neomycin ($n = 1,792$); neomycin and metronidazole ($n = 379$); erythromycin, neomycin, and metronidazole ($n = 32$); erythromycin and metronidazole ($n = 18$); neomycin ($n = 94$); metronidazole ($n = 69$); and erythromycin ($n = 39$). The SSI rate was not significantly associated with oral antibiotic choice ($p = 0.92$).

We observed 709 (12.3%) 30-day SSIs in our study cohort. Factors significantly associated with SSI were age, body mass index, work relative value units, operation time, dyspnea, COPD, the intravenous prophylactic antibiotic agent, and the use of oral antibiotics (Table 2). In unadjusted analyses, the use of cefazolin/metronidazole was associated with the lowest rate of SSI. Oral antibiotics were associated with lower rates of SSI across all IV antibiotic types.

The rate of SSI by IV antibiotic type stratified by use of an oral antibiotic is shown in Table 3. When stratified by use of oral antibiotics, the choice of IV antibiotic agent was not significantly associated with SSI when given with oral antibiotics. In the absence of oral antibiotics, the IV antibiotic agent was strongly associated with SSI in unadjusted analyses (Table 3). To examine the comparative effectiveness of the various intravenous antibiotics, we used generalized estimating equations adjusting for age, body mass index, COPD, American Society of Anesthesiologists class, functional status, type of colectomy, procedure work relative value units, wound class, operation duration, use of an oral antibiotic, and timing of antibiotic administration to estimate odds of infection by antibiotic agent. The adjusted odds of SSI by antibiotic agent for the overall cohort are shown in Table 4. With cefazolin/metronidazole as the referent group, all other approved antibiotics were associated with higher SSI rates, with the exception of ertapenem. Oral antibiotics were strongly associated with reduced SSI risk. We did not observe any correlation between hospital rates of intravenous antibiotic agent and hospital rates of SSI after colorectal surgery (data not shown).

DISCUSSION

We report that within the approved agents for SSI prophylaxis in colorectal surgery, significant variation in effectiveness was observed. Second generation cephalosporins are the most commonly used, but least effective among the approved agents. Furthermore, the use of oral antibiotics appeared to be the most important factor in reducing SSI occurrence in this cohort of patients. These findings are important to help guide surgeons and hospitals in choosing the most effective processes in reducing SSI.

There are likely a number of factors that determine the effectiveness of an intravenous antibiotic agent in reducing SSI including unmeasured confounders of surgical technique, patient factors, and disease presentation.

Table 2. Demographics of the Study Cohort Stratified by Surgical Site Infection

Characteristic	Overall	Surgical site infection		p Value
		No (n = 5,041)	Yes (n = 709)	
Age, median (IQR), y	65.0 (59-75)	66.0 (60.0-75.0)	64.0 (59.0-73.0)	<0.0001
BMI, median (IQR), kg/m^2	27.2 (24.0-30.9)	27.0 (23.8-30.7)	28.5 (25.1-32.3)	<0.0001
Work RVU median, (IQR)	22.5 (21.0-26.3)	22.5 (21.0-26.3)	22.5 (22.5-28.5)	<0.0001
Operative time, median (IQR), h	2.8 (2.1-3.9)	2.8 (2.0-3.8)	3.3 (2.3-4.5)	<0.0001
Dyspnea, n (%)				
Yes	793	660 (83.2)	133 (16.8)	<0.0001
No	4,948	4,374 (88.4)	574 (11.6)	
Diabetes, n (%)				
None	4,347	3,833 (88.2)	514 (11.8)	0.10
Oral medication	916	792 (86.5)	124 (13.5)	
Insulin dependent	487	416 (85.4)	71 (14.6)	
COPD, n (%)				
Yes	786	663 (84.4)	123 (15.7)	0.002
No	4,964	4,378 (88.2)	586 (11.8)	
ASA class, n (%)				
1-2	1,173	1,042 (88.8)	131 (11.2)	0.38
3	4,069	3,557 (87.4)	512 (12.6)	
4-5	508	442 (87.0)	66 (13.0)	
Functional status, n (%)				
Independent	5,417	4,743 (87.6)	674 (12.4)	0.3
Dependent	333	298 (89.5)	35 (10.5)	
Type of colectomy, n (%)				
Ileocectomy	651	588 (90.3)	63 (9.7)	<0.0001
Partial	3,808	3,381 (88.8)	427 (11.2)	
Total	174	143 (82.2)	31 (17.8)	
Rectal resection	1,117	929 (83.2)	188 (16.8)	
Surgical approach, n (%)				
Laparoscopic	665	598 (89.6)	69 (10.4)	0.1
Open	5,085	4,445 (87.4)	640 (12.6)	
Use of oral antibiotic				
Yes	2,426	2,273 (93.7)	153 (6.3)	<0.0001
No	3,324	2,768 (83.3)	556 (16.7)	
Antibiotic timing, n (%)				
Early (>60 min)	345	303 (87.8)	42 (12.2)	0.66
On time (0−60 min)	5,143	4,513 (87.8)	630 (12.3)	
Late (after incision)	262	225 (85.9)	37 (14.1)	
Antibiotic choice, n (%)				
Ampicillin/sulbactam	363	322 (88.7)	41 (11.3)	<0.0001
Cefazolin/metronidazole	899	843 (93.8)	56 (6.2)	
Cefotetan	775	663 (85.6)	112 (14.4)	
Cefoxitin	3,051	2,628 (86.1)	423 (13.9)	
Ertapenem	317	278 (87.7)	39 (12.3)	
Fluoroquinolone/anaerobic	345	307 (89.0)	38 (11.0)	

ASA, American Society of Anesthesiologists; BMI, body mass index; IQR, interquartile range; RVU, relative value unit.

Furthermore, the optimal antibiotic for prophylaxis may vary based on local antibiotic resistance patterns. When the SCIP guidelines were established with a hope of reducing SSI, an expert panel named a number of antibiotics/antibiotic combinations that were considered acceptable options. For colorectal surgery, these included a first

Table 3. Unadjusted Incidence of Surgical Site Infection Based on Type of Antibiotic Prophylaxis

Variable	n	SSI				
		Overall	OA+IV	p Value*	IV	p Value†
Overall, n	5,750	709	2,426		3,324	
IV antibiotic agent						
Cefazolin/metronidazole	899	6.2	2.8	0.09	8.5	<0.0001
Ampicillin/sulbactam	363	11.3	7.1		15.6	
Cefotetan	775	14.5	6.7		19.3	
Cefoxitin	3,051	13.9	7.1		19.5	
Ertapenem	317	12.3	4.4		14.5	
Fluoroquinolone/plus anaerobic	345	11.0	7.0		13.7	

Unless stated otherwise, data are expressed as %.
*p Value refers to rate of SSI across agents among those also receiving OABP.
†p Value refers to rate of SSI across agents among those not receiving OABP.
IV, intravenous antibiotic alone; OA+ IV, oral antibiotic and intravenous antibiotic; OABP, oral antibiotic bowel preparation; SSI, surgical site infection.

generation cephalosporin or quinolone or aminoglycoside, each with added anaerobic coverage or one of several second generation cephalosporins. Ertapenem was added to the list, and at least 1 study showed it to be superior to a second generation cephalosporin.[19]

One assessment of the SCIP-2 appropriate antibiotic measure found a correlation between hospital adherence rates and hospital infection rates, using American College of Surgeons (ACS) NSQIP data from 200 hospitals and Centers for Medicare and Medicaid hospital comparison data. However, the procedures included in ACS NSQIP and hospital comparison data had little overlap.[20] Other studies with patient-specific data for antibiotic selection and SSI have not duplicated this result.[11,12] In a recent report from the Michigan Surgical Quality Collaborative using non-SCIP approved antibiotics as the reference group, patients receiving cephazolin/metronidazole, quinolone/metronidazole, and ertapenem had lower odds for SSI; patients receiving cefoxitin, cefotetan, ampicillin/sulbactam, and clindamycin/gentamycin had higher odds.[14] Our study also found that within the accepted choice of antibiotics for compliance with the SCIP measure, there was significant variation in the adjusted odds of SSI. This may, in part, explain why the SCIP has not been effective in reducing SSI, because the principal recommended antibiotics (second generation cephalosporins) are the least effective in both of these large cohort studies.

Table 4. Generalized Estimating Equations of Surgical Site Infection

IV antibiotic agent	Overall cohort	
	Odds ratio^{adj}*	95% CI
Cefazolin/metronidazole	ref	ref
Ampicillin/sulbactam	2.16	1.35–3.58
Cefotetan	2.53	1.51–4.22
Cefoxitin	2.56	1.73–3.81
Ertapenem	1.48	0.79–2.78
Fluoroquinolone/plus anaerobic	1.89	1.01–3.51
Oral antibiotic	0.37	0.29–0.46

*Adjusted odds ratio for oral antibiotic, age, body mass index, procedure work relative value units, operation duration, and dyspnea.

The high rate of SSI after colorectal surgery is thought to be at least in part due to the high bacteria count of colonic contents.[21] This fits with a lower infection rate seen with oral antibiotics that are given to decrease bacterial counts in the lumen of the colon. The protective effect of oral antibiotics has been observed in other studies.[15] Both organisms found in the bowel and those from the skin have been cultured from infected wounds after colorectal surgery.[19] The lack of culture data in most reports limits the ability to understand to what extent antibiotic resistance may explain the variation in effectiveness of prophylactic antibiotics. In one study comparing ertapenem to cefotetan, there was a higher percentage of resistant organisms to cefotetan (60%) than to ertapenem (16%) in cultured SSI.[19] A significant proportion of infections after colon surgery have an anerobic isolate, the most common being *Bacteroides fragilis*. There is an emerging resistance of Bacteroides species to the antibiotics we use to target anaerobic infections. Reports of Bacteroides resistance to clindamycin range from 20% to 60% resistance.[22,23] Likewise, high resistance rates for Bacteroides species have been reported with cefoxitin, cefotetan, and ampicillin/sulbactam.[23] This implies that targeting prophylactic antibiotics that have a broader spectrum and lower rate of resistance to common bowel organisms may help reduce SSI.

Increasing emphasis has been placed on public reporting of SSI rates for specific procedures. Although most see this as a move in the right direction for directly measuring

quality and informing patients and other stakeholders, it may disincentivize behaviors that could lead to further improvement. In order to further reduce SSI, we need to generate better data on when and why prophylaxis fails. Our current practice of not culturing surgical wounds needs to be addressed in a thoughtful manner. Systematic culture of wounds would help guide institution-specific antibiotic prophylaxis; however, surgeons will be concerned that this will increase their currently reported SSI rates.

Other factors related to antibiotic administration known to be important for reducing SSI include operative time and antibiotic redosing.[24] We did observe an association between operative time and SSI in both univariate analysis and in our adjusted model. Furthermore, we saw minimal evidence of redosing in this cohort. Given that cefoxitin is associated with the shortest half-life, this could contribute to the lack of effectiveness for this agent. However, we did test, in a sensitivity analysis, whether substituting the antibiotic half-life in place of the agent and did not find a correlation with SSI for this cohort.

Our study has several limitations. Because it was a veteran cohort, the majority of the patients were male. We could not determine factors associated with antibiotic choice or use of an oral antibiotic. Furthermore, we did not have culture data to assess whether lack of effectiveness was due to pathogen resistance or other factors. There are several strengths of these data including a multicenter cohort with detailed information on both antibiotic practices and infection outcomes that are assessed by 2 independent programs.

CONCLUSIONS

We observed varying effectiveness for SCIP-approved intravenous prophylactic antibiotics in reducing SSI for a national cohort of colorectal procedures; oral antibiotics were associated with a substantially lower SSI rate. Furthermore, the most commonly used antibiotic for prophylaxis was associated with the highest risk-adjusted odds of SSI. The SCIP needs to be revamped to become a program that measures and disseminates effective practices rather than continuing to measure the same variables year after year. To further reduce preventable SSI after colorectal surgery, we need to tailor the choice of intravenous antibiotics, routinely use preoperative oral antibiotics, and culture wounds when infection occurs.

Author Contributions

Study conception and design: Dawes, Vick, Itani, Hawn
Acquisition of data: Deierhoi, Vick
Analysis and interpretation of data: Deierhoi, Dawes, Vick, Itani, Hawn
Drafting of manuscript: Deierhoi, Dawes, Hawn
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