

Ertapenem for the Prevention of Surgical Site Infection Following Colorectal Surgery

Gregory B. Tallman, PharmD¹; David T. Bearden, PharmD^{1,2}; James S. Lewis II, PharmD²; Miriam R. Elman, MPH¹; Yoojin Kim, PhD²; Kevin Langstaff, BA²; Jessina C. McGregor, PhD¹

1. Oregon State University/Oregon Health & Science University College of Pharmacy 2. Oregon Health & Science University



ABSTRACT (Updated)

Introduction: Recent data from randomized control trials suggest ertapenem prophylaxis may be superior to cefotetan for prevention of surgical site infections (SSIs) in colorectal surgeries, however, these trials may have limited generalizability. The primary objective of this study was to compare the frequency of SSI in patients receiving ertapenem and other prophylactic regimens prior to colorectal surgery.

Methods: We conducted a retrospective cohort study of adult patients (age ≥ 18 years) undergoing colorectal procedures between Jul. 2012 and Sept. 2015. Patients with history of surgery in the prior 30 days, surgery due to trauma, or systemic antibiotics at the time of surgery were excluded. The primary outcome was surgical site infection within 30 days of surgery; outcome frequencies were compared between patients receiving ertapenem and other antibiotics for surgical prophylaxis using multivariable logistic regression to adjust for potential confounders.

Results: A total of 1,129 encounters were considered for inclusion; 767 were excluded. In the 362 encounters included in the study, 296 received ertapenem and 66 received alternative prophylaxis agent(s). Patients receiving ertapenem were younger (54.9 vs. 58.7 years), more likely to be male (50.7% vs. 36.4%), and have inflammatory bowel disease (26.4% vs. 6.1%). Cancer was significantly more common in patients not receiving ertapenem (83.3% vs. 69.3%). The median duration of surgery was significantly shorter among patients receiving ertapenem (178 minutes) compared to those receiving other antibiotics (198 minutes). SSI occurred in 16 (5.4%) of patients receiving ertapenem and 11 (16.7%) of patients receiving other agents (OR 0.29, 95% CI: 0.13 to 0.65). After adjusting for surgical group and surgery duration, the adjusted OR for developing SSI after ertapenem use was 0.43 (95% CI: 0.12 to 1.60).

Conclusion: After adjusting for confounding, ertapenem did not significantly reduce the risk of SSI following colorectal surgery compared to alternative agents, and routine use as prophylaxis may not be warranted. Further study is needed to determine the generalizability of these findings and compare ertapenem prophylaxis to individual regimens.

INTRODUCTION

- Risk of SSI is high after colorectal surgery
- Antibiotic prophylaxis significantly reduces risk of SSI
- Ertapenem has shown superiority to cefotetan prophylaxis in colorectal procedures; data indicate ertapenem is not superior to other regimens
- National guidelines recommend against ertapenem use, except in institutions with high rates of third-generation cephalosporin resistance
- Increased carbapenem use associated with increased prevalence of carbapenem-resistant *Enterobacteriaceae*
- Despite low rates of cephalosporin resistance, our institutional policy includes ertapenem as an acceptable prophylaxis agent
- Public health risks of increased antibiotic resistance and CRE must be evaluated against individual benefits of ertapenem prophylaxis

OBJECTIVE

To evaluate the efficacy of ertapenem compared to other guideline-concordant antibiotic prophylaxis regimens at preventing SSI after colorectal surgery

METHODS

Design
Retrospective cohort at Oregon Health & Science University hospital

Inclusion/Exclusion Criteria

- Encounters for colorectal surgery between Jul. 2012 and Sep. 2015 identified using CPT codes and ICD-9 procedure codes provided by National Healthcare Safety Network (NHSN)
- Excluded patients < 18 years, admitted due to trauma, receiving systemic antibiotics at time of index procedure, received non-guideline prophylaxis agents, or had previous surgery in 30 days prior to index procedure

Data

- Demographics and covariates electronically extracted
- Chart review performed for variables not captured electronically (e.g., surgeon, ASA classification, wound class)
- Outcome data obtained from infection control surveillance and chart review

METHODS (Cont.)

Outcomes

- Primary outcome was SSI defined using NHSN surveillance definitions
 - SSI classified as superficial incisional, deep incisional, or organ space based on depth of infection using these definitions
- Secondary outcomes include SSI by classification and pathogen

Analysis

- Patients receiving ertapenem vs. other prophylaxis compared using descriptive statistics
- Multivariable logistic regression performed to adjust for confounders of the relationship between ertapenem prophylaxis and SSIs
 - Forward selection with entry threshold of 20% change in odds ratio
 - Tests for interaction between all covariates in the model to assess for homogeneity between treatment groups
- Post-hoc sensitivity analysis comparing ertapenem to cefoxitin only

RESULTS

Patient Population

- 1,129 patient encounters reviewed; 362 included in the study (Figure 1)
- Heterogeneous selection of prophylactic antibiotic regimens (Table 1)
- Many demographic and operative differences between groups (Table 2)
 - ASA classification, wound class not significantly different

Figure 1. Patient Selection

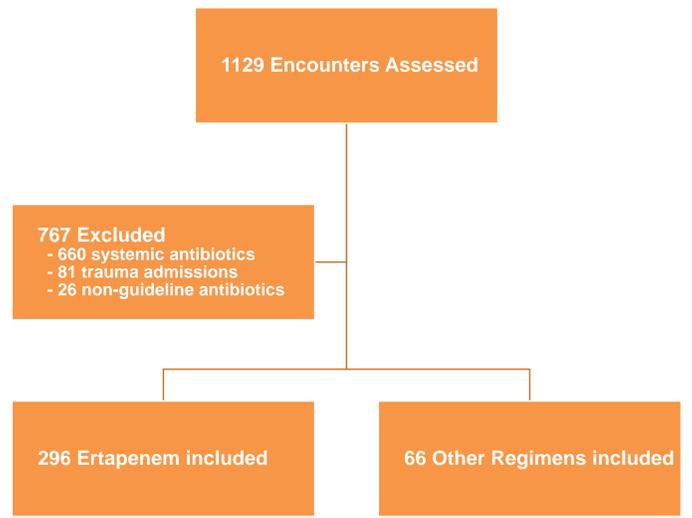


Table 1. Antibiotic Prophylaxis Regimens Used

Antibiotic Regimens Used	Frequency (n= 388)
Ertapenem	296 (76.3)
Other Antibiotics	
Cefoxitin	53 (13.7)
Ciprofloxacin + metronidazole	11 (2.8)
Cefazolin + metronidazole	1 (0.3)
Cefoxitin + metronidazole	1 (0.3)
Non-guideline antibiotics	26 (6.7)

Non-guideline antibiotics included: cefazolin (12), metronidazole (3), piperacillin/tazobactam (3), ciprofloxacin (2), clindamycin (2), vancomycin (2), ampicillin (1), and gentamicin with vancomycin (1). All data are reported as n (%) unless otherwise indicated.

RESULTS (Cont.)

Table 2. Demographics and Operative Characteristics

Characteristic	Ertapenem (n = 296)	Other Antibiotics (n = 66)
Mean Age, yr. (SD)	54.9 (16.6)	58.7 (14.4)
Male Sex [†]	150 (50.7)	24 (36.4)
Comorbidities		
Diabetes Mellitus	41 (13.6)	9 (13.6)
COPD	38 (12.8)	7 (10.6)
IBD [‡]	78 (26.4)	4 (6.1)
Malignancy [†]	205 (69.3)	55 (83.3)
BMI > 30	76 (25.7)	19 (28.8)
Elixhauser Score [†]	0 (0 to 8)	11 (0 to 13)
Antibiotic within SCIP timeframe	264 (89.2)	62 (93.9)
Surgeon Specialty [†]		
GI/General Surgery	288 (97.3)	19 (28.8)
Other	8 (2.7)	47 (71.2)
ASA Classification		
I or II	154 (52.0)	30 (45.6)
III, IV, or V	142 (48.0)	36 (54.6)
Wound Class		
Clean-contaminated	211 (71.3)	54 (81.8)
Contaminated	55 (18.6)	7 (10.6)
Dirty/Infected	30 (10.1)	5 (7.6)
Median Surgery Duration, min. (IQR) [†]	178 (121 to 240)	198 (140 to 295)
Laparoscopic Approach [†]	108 (36.5)	3 (4.6)

ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; IBD, inflammatory bowel disease; IQR, interquartile range; SCIP, Surgical Care Improvement Plan; SD, standard deviation. All data are reported as n (%) unless otherwise indicated. † p < 0.05; ‡ p < 0.01.

Table 3. Surgical Site Infections

Infection Classification	Ertapenem (n = 296)	Other Antibiotics (n = 66)
Any SSI	16 (5.4)	11 (16.7)
Superficial Incisional SSI	11 (3.7)	7 (10.9)
Deep Incisional SSI	0 (0.0)	0 (0.0)
Organ Space SSI	5 (1.7)	4 (6.1)

All data are reported as n (%) unless otherwise indicated.

Table 4. Microbiology

Organism	Ertapenem (n = 16)	Other Antibiotics (n = 11)
<i>S. aureus</i>	4	-
<i>S. lugdunensis</i>	1	-
<i>S. anginosus</i>	-	1
<i>Enterococcus</i> spp.	2	1
<i>E. coli</i>	2	-
<i>P. aeruginosa</i>	2	-
<i>Clostridium</i> spp.	1	-
<i>B. fragilis</i>	1	-
<i>Peptostreptococcus</i>	-	1
<i>C. albicans</i>	1	1
No culture data	7	9

All data are reported as counts.

RESULTS (Cont.)

Surgical Site Infections

- SSIs were less common in the ertapenem group (Table 3)
- Superficial SSIs were the most common type of SSI
- 14 of 33 SSIs cultured, microbiology results in Table 4

Multivariable Regression Analysis

- Ertapenem no longer significantly protective (Table 5)
- Duration of surgery and surgeon specialty were strongest confounders
- Similar results on sensitivity analysis of ertapenem vs. cefoxitin, adjusting for the same confounders (ertapenem aOR: 0.61, 95% CI: 0.18 to 2.05)

Interaction Testing

- No interactions observed between ertapenem and surgery duration or surgery duration and surgeon specialty
- Sample size insufficient to fully assess possible interaction between ertapenem and surgeon specialty (Table 6)

Table 5. Regression Analysis of Factors Associated With SSI

Covariate	OR	95% CI	aOR	95% CI
Ertapenem	0.29	0.13 - 0.65	0.43	0.12 - 1.60
Laparoscopic approach	0.49	0.18 - 1.33		
Sex	1.00	0.46 - 2.20		
Age (per year)	1.02	0.99 - 1.04		
Elixhauser score	1.05	1.00 - 1.09		
Wound class	1.16	0.49 - 2.75		
Duration of surgery (per hr.)	1.37	1.17 - 1.61	1.34	1.14 - 1.57
Obesity	1.44	0.63 - 3.34		
Diabetes	2.38	0.95 - 5.96		
Surgeon specialty	3.14	1.33 - 7.41	1.38	0.36 - 5.39
ASA Class	5.05	1.87 - 13.65		

aOR, adjusted odds ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; OR, odds ratio

Table 6. Interaction of Surgeon Specialty and Ertapenem

Subgroup	Total in Subgroup	Outcome (%), Ertapenem	Outcome (%), Other Antibiotics
GI/General Surgery	307	16 (5.6)	2 (10.5)
Other	55	0 (0.0)	9 (19.2)

All data are reported as n (%) unless otherwise indicated.

DISCUSSION

- Overall SSI frequency of 7.5% higher than national surveillance rate, but lower than those in trial of ertapenem vs. cefotetan
- Study limited by several major differences in treatment groups, suggesting underlying difference in populations
- Non-GI surgeons more likely to perform more complicated procedures (e.g. total abdominal hysterectomy with partial colectomy)
 - These patients likely have higher SSI risk at baseline
 - In analysis restricted to only GI surgeons, protective effect of ertapenem remained non-significant

CONCLUSION

- Ertapenem use was associated with non-significant protective effect against SSI after adjusting for measured confounders
- In certain settings with low antibiotic resistance, routine ertapenem for colorectal prophylaxis may not be justified given risk of collateral damage
- Further study needed to better explore the risks and benefits of ertapenem prophylaxis in colorectal surgery in settings of low resistance

