A Retrospective, Non-Inferiority, Cohort Study of Cefazolin Plus Metronidazole Versus Cefoxitin for Perioperative Colorectal Surgery Prophylaxis

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ABSTRACT

PURPOSE: Surgical site infections (SSIs) are a frequent complication of colorectal surgery (CRS), and are known to contribute to increased mortality and hospital readmissions. National susceptibilities indicate increased *Bacteroides fragilis* group resistance to many first-line antibiotics used for perioperative prophylaxis, particularly with cefoxitin. The objective of this study is to determine if there is a difference in outcomes in patients receiving prophylaxis with cefazolin plus metronidazole versus cefoxitin for elective CRS.

METHODS: This is a retrospective, non-inferiority, cohort study comparing outcomes of patients who received cefazolin plus metronidazole versus cefoxitin for perioperative elective CRS prophylaxis. The study was approved by the network Institutional Review Board at Seton Healthcare Family. Patients at least 18 years of age who received at least one dose of antimicrobial prophylaxis with cefazolin plus metronidazole or cefoxitin for elective colorectal surgery were included. Exclusion criteria are emergency colorectal surgery, revision of previous colorectal surgery, bacterial infection at the time of procedure, perforation during surgery, antimicrobial therapy within one week prior to procedure, patients greater than 89 years of age and pregnancy. The primary outcome is the incidence of surgical site infections within 30 days after surgery. A one-sided test for non-inferiority with a stepwise logistic regression analysis was used for the primary outcome. Secondary outcomes include incidence of *Clostridium difficile* infection and incidence of secondary bloodstream infection.

RESULTS: After 400 colorectal procedures, 36 patients (9%) developed SSIs. Twelve SSIs (6%) occurred in the cefazolin plus metronidazole group compared to 24 (12%) in the cefoxitin group. There were no cases of *C. difficile* or secondary bloodstream infections in the study cohort.

CONCLUSIONS: Fewer patients in the cefazolin plus metronidazole group developed SSIs within 30 days of CRS than in the cefoxitin group. These results support the use of cefazolin plus metronidazole for prevention of SSIs in CRS.

BACKGROUND

- Surgical site infections are one of the most common types of healthcare-associated infections
- Recent studies have shown that optimization of antimicrobial prophylaxis is an important modifiable risk factor for SSIs in colorectal surgery
- The Infectious Diseases Society of America (IDSA) Guidelines for antimicrobial prophylaxis in CRS recommend:
  - Monotherapy: cefoxitin, cefotetan, ertapenem, or ampicillin-sulbactam
  - Combination therapy: cefazolin plus metronidazole or ceftriaxone plus metronidazole
- Cefoxitin for CRS may be suboptimal due to significant resistance and poor target attainment

PHARMACODYNAMICS

Probability of Target Attainment (%) for Cefoxitin and Cefazolin at Susceptibility Breakpoints Recommended by CLSI

		E. coli				*B. fragilis*			
		Time after dose (h)				Time after dose (h)			
Antibiotic	Dose	1	2	3	4	1	2	3	4
Cefoxitin	1 g	54	0	0	0	14	0	0	0
	2 g	84	25	0	0	55	0	0	0
Cefazolin	1 g	**100**	**100**	**100**	**100**	---			

CLSI breakpoint for cefoxitin (at time of study) ≤ 8 mg/L for E.coli
CLSI breakpoint for cefazolin (at time of study) ≤ 1 mg/L for E.coli

Adapted with permission from Moine et al, 2012.

LOCAL SUSCEPTIBILITIES

Antimicrobial	*E. coli*	*B. fragilis* group
Cefoxitin	89-95% (FY12-13)	40% (FY12-13)
Cefazolin*	88-93% (FY12-15)	N/A
Metronidazole	N/A	100%

*CLSI breakpoint ≤8 used for antibiogram data

Seton Healthcare Family susceptibilities

STATISTICAL ANALYSIS

- 1262 patients needed to achieve 80% power with a 5% non-inferiority margin based on a 15% event rate
- One-sided test for non-inferiority
- Stepwise logistic regression

BASELINE DEMOGRAPHICS

Characteristic	Cefoxitin (n=200)	Cefazolin + Metronidazole (n=200)
Male (%)	90 (45.0)	94 (47.0)
Age, year (mean ± SD)	58.2 ± 16.2	57.6 ± 13.1
Weight, kg (mean ± SD)	81.3 ± 24.1	79.9 ± 20.5
BMI > 30 kg/m^2 (%)	65 (32.5)	71 (35.5)
COPD (%)	6 (3.0%)	19 (9.5)
Malignancy (%)	87 (43.5)	79 (39.5)
Diabetes mellitus (%)	42 (21.0)	31 (15.5)
Smoking (%)	21 (10.5)	21 (10.5)
Alcohol abuse (%)	37 (18.5)	51 (25.5)

RESULTS

Enrollment

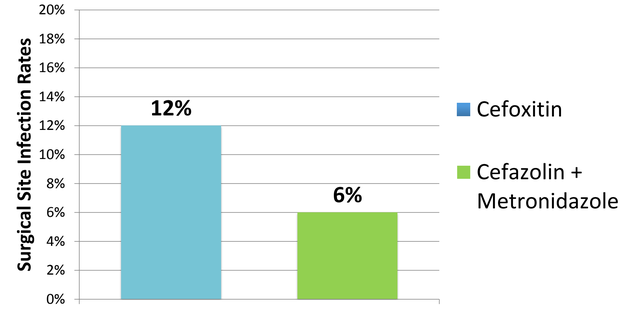
- 651 patients were reviewed
- 251 patients excluded (most common reasons for exclusion: perforation, non-elective surgery, existing infection/receiving antibiotics prior to surgery, revision, age, missing data)
- 400 patients included (200 per group)

Surgical Variables

	Cefoxitin (n=200)	Cefazolin + Metronidazole (n=200)
Wound class 3-4 (%)	52 (26.0)	40 (20.0)
Operation longer than 2 h (%)	96 (48.0)	131 (65.5)
Laparoscopic technique	96 (48.0)	76 (38.0)
Antibiotics within 60 minutes of incision (%)	197 (98.5)	186 (93.0)
Appropriate re-dosing (%)	193 (96.5)	191 (95.5)
Post-operative antibiotics (%)	154 (77.0)	130 (65.0)
Adequate weight-based dosing* (%)	175 (87.5)	170 (85.0)

*Weight-based dosing for cefazolin and cefoxitin: < 80 kg, 1 gram; 80-120 kg, 2 grams; > 120 kg, 3 grams

Primary Endpoint: Surgical Site Infections



- **Difference in SSI rate: 6%, 90% CI (1.3-10.9);**
- **p value for non-inferiority < 0.001**

- There were no cases of *C. difficile* infection or secondary BSI
- Hypothesis-driven stepwise logistic regression did not find lack of post-operative antibiotics to be a predictor of SSI

DISCUSSION

- Previous studies investigating antimicrobial prophylaxis in CRS have relied on extracting variables and outcomes data from claims databases
- This study is the first to directly compare SSI rates for cefoxitin and cefazolin plus metronidazole using individual chart review
- These results are clinically relevant, as many institutions use cefoxitin for this indication, which may be suboptimal based on this data
- Limitations to this study include the retrospective design, small sample size which did not meet statistical power, and the likelihood of under-reporting of SSIs in the hospital medical record

CONCLUSIONS

- Study results support use of cefazolin plus metronidazole for prevention of SSIs in colorectal surgery
- No conclusions can be made regarding the difference in *C. difficile* infection rates between the two groups
- An adequately-powered study is necessary to confirm these results

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