

## ORIGINAL ARTICLE

# Ertapenem versus Cefotetan Prophylaxis in Elective Colorectal Surgery

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## ABSTRACT

**BACKGROUND**

Ertapenem, a long-acting carbapenem, may be an alternative to the recommended prophylactic antibiotic cefotetan.

**METHODS**

In this randomized, double-blind trial, we assessed the efficacy and safety of antibiotic prophylaxis with ertapenem, as compared with cefotetan, in patients undergoing elective colorectal surgery. A successful outcome was defined as the absence of surgical-site infection, anastomotic leakage, or antibiotic use 4 weeks postoperatively. All adverse events were collected until 14 days after the administration of antibiotic prophylaxis.

**RESULTS**

Of the 1002 patients randomly assigned to study groups, 901 (451 in the ertapenem group and 450 in the cefotetan group) qualified for the modified intention-to-treat analysis, and 672 (338 in the ertapenem group and 334 in the cefotetan group) were included in the per-protocol analysis. After adjustment for strata, in the modified intention-to-treat analysis, the rate of overall prophylactic failure was 40.2% in the ertapenem group and 50.9% in the cefotetan group (absolute difference, -10.7%; 95% confidence interval [CI], -17.1 to -4.2); in the per-protocol analysis, the failure rate was 28.0% in the ertapenem group and 42.8% in the cefotetan group (absolute difference, -14.8%; 95% CI, -21.9 to -7.5). Both analyses fulfilled statistical criteria for the superiority of ertapenem. In the modified intention-to-treat analysis, the most common reason for failure of prophylaxis in both groups was surgical-site infection: 17.1% in the ertapenem group and 26.2% in the cefotetan group (absolute difference, -9.1; 95% CI, -14.4 to -3.7). In the treated population, the overall incidence of *Clostridium difficile* infection was 1.7% in the ertapenem group and 0.6% in the cefotetan group ( $P=0.22$ ).

**CONCLUSIONS**

Ertapenem is more effective than cefotetan in the prevention of surgical-site infection in patients undergoing elective colorectal surgery but may be associated with an increase in *C. difficile* infection. (ClinicalTrials.gov number, NCT00090272.)

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**E**RTAPENEM IS A ONCE-DAILY PARENTERAL group 1 carbapenem antibiotic used in the treatment of complicated intraabdominal infection.<sup>1-3</sup> Several characteristics of ertapenem make its use attractive as a potential preoperative antimicrobial agent in elective colorectal surgery, since it is characterized by rapid intravenous administration, appropriate coverage against potential pathogens, a long half-life (so it does not require a second administration during most surgeries), and a safety profile similar to that of other commonly used antibiotics.<sup>4-7</sup> To assess the efficacy and safety of ertapenem in the prevention of surgical-site infection among patients undergoing colorectal surgery, we compared it with cefotetan, a cephalosporin indicated for prophylaxis in colorectal surgery whose availability has become somewhat limited.<sup>8-11</sup> Since there have been few previous prospective studies that examined possible preoperative and intraoperative risk factors for postoperative surgical-site infection,<sup>12</sup> we designed this large, prospective study to accommodate an analysis of risk factors.

## METHODS

### STUDY DESIGN

We conducted this prospective, double-blind, randomized study between May 2002 and March 2005 at 51 centers in the United States. The institutional review board at each center approved the protocol, and written informed consent was obtained from each patient before enrollment. The study was conducted in accordance with the guidelines of the International Conference on Harmonization.<sup>13</sup> Merck designed and sponsored the study with the participation of the academic authors, who were the lead investigators at each of their respective clinical sites. The sponsor collected and analyzed the data. An employee of the sponsor was the primary statistician for the study. All authors had full access to the data and contributed to the analysis and interpretation. All authors vouch for the accuracy and completeness of the data presented and the analyses.

### PATIENTS

Patients 18 years of age or older who were scheduled to undergo elective open surgery of the colon or rectum with sufficient time for bowel preparation were eligible for inclusion. Patients were ineligible if they required emergency colorectal sur-

gery, a second planned surgery requiring antibiotic prophylaxis, an elective colorectal procedure for revision of a previous surgery, laparoscopic-assisted surgery, or an isolated rectal procedure. Also excluded were patients who had a bacterial infection at the time of surgery or required antimicrobial therapy up to 1 week before surgery; those for whom the study drugs were contraindicated; those with active inflammatory bowel disease, neutropenia, or immunosuppression; those with aminotransferase levels or prothrombin times that were at least three times the upper limit of the normal range; and pregnant or nursing women.

### STUDY THERAPY

Patients were stratified according to whether the scheduled surgery was to include a resection of any portion of the rectum. To ensure that each group at each study center had an equivalent number of patients, randomization was performed in blocks through a central computerized system. At each center, the pharmacist prepared the intravenous study drugs to be administered by clinical personnel who were not aware of assignments to treatment groups. A single dose of 1 g of ertapenem (Invanz, Merck) or 2 g of cefotetan (Cefotan, AstraZeneca) was infused over a 30-minute period within 60 minutes before the initial surgical incision was made.

### STUDY END POINTS

The primary efficacy end point was the proportion of patients who could be evaluated and for whom prophylaxis was successful at the 4-week follow-up assessment after treatment. Success was defined as no signs or symptoms of infection at the surgical site and no further need for antimicrobial therapy or surgery. A determination of prophylactic failure was made by the site investigator on the basis of criteria for surgical-site infection developed by the Centers for Disease Control and Prevention.<sup>14</sup> Surgical-site infection was defined as incisional (either superficial or deep) infection or organ-space infection. Superficial incisional infection involved only skin and subcutaneous tissue and excluded stitch abscesses, and deep incisional infection involved deeper soft tissue of the incision. Organ-space infection involved any organ or space other than the incised layer of body wall that was opened or manipulated during the initial surgical procedure. Criteria for clinical failure, in addition to those listed above, included antibiot-

ics for any reason within 4 weeks after surgery and anastomotic leakage of the involved bowel requiring additional surgery or antibiotics.

A modified intention-to-treat analysis was also performed. In addition to the above-mentioned criteria, treatment was considered to have failed in this analysis if patients received antibiotics for a distant-site infection (even in the absence of signs or symptoms of infection at the surgical site) or missed a 4-week assessment.

#### CRITERIA FOR ANALYSES

To qualify for inclusion in the modified intention-to-treat analysis, patients were required to have undergone electively scheduled open colorectal surgery with completion of standard bowel preparation (sodium phosphate or polyethylene glycol) and to have received a complete dose of a study drug.

In addition to the above-mentioned criteria, in order to be included in the per-protocol analysis, patients were required to have received a study drug within 2 hours before surgical incision and 6 hours before surgical closure and to have undergone a 4-week follow-up assessment (defined as 21 to 60 days after surgery). Patients who received antibiotics — including oral antibiotics for bowel preparation, antibiotic lavage, or other non-study antibiotics at the time of surgery or in the week before surgery — could not be included in the analysis. Also excluded from the analysis were patients who underwent surgery with delayed primary closure or closure by secondary intent, who required a second surgery to correct or reverse the initial surgery, or who had a distant-site infection (i.e., infection at any site other than the primary surgical site).

#### CLINICAL ASSESSMENT

Investigators took a complete medical history, performed a physical examination, and obtained baseline information regarding preoperative risk factors for postoperative infection, vital signs, and laboratory tests. Vital signs were measured daily while the patient was hospitalized and at the 4-week follow-up assessment. Investigators performed detailed wound assessments at least every other day for up to 7 days during hospitalization, at discharge, and at the 4-week follow-up visit.

If postoperative infection developed, specimens from the surgical site were cultured for aerobic and anaerobic bacteria. Local laboratories performed all aerobic culture and susceptibility test-

ing, and a duplicate specimen was sent for anaerobic culture and susceptibility testing to a specialized laboratory (R.M. Alden Research Laboratory, Santa Monica, CA). The susceptibility of all isolates to antibiotics, including ertapenem and cefotetan, was determined in accordance with the guidelines of the Clinical and Laboratory Standards Institute.<sup>15-17</sup>

#### SAFETY ASSESSMENTS

The safety evaluation included all patients who received a complete dose of a study drug. Investigators monitored patients for clinical adverse events daily during hospitalization; after discharge, investigators monitored each patient by telephone until 14 days after the administration of a study drug. Investigators, masked to treatment, assessed the seriousness of all adverse events and rated the likelihood that any event was related to a study drug. Laboratory studies were performed at enrollment and at least once postoperatively.

To address the safety objective, a set of clinical safety end points was prespecified in the protocol and the associated statistical analysis plan before investigators were made aware of the data. These end points consisted of the incidence of any clinical adverse event, any clinical drug-related adverse event, any serious adverse event, any serious drug-related adverse event, and any clinical adverse event causing discontinuation of a study drug.

#### STATISTICAL ANALYSIS

This study was designed to test the noninferiority of ertapenem to cefotetan in the prophylaxis of surgical-site infection. Assuming an 80% response rate and a one-sided significance level of 0.025, we needed to enroll 340 patients per treatment group for the study to have a power of 90%. For the primary efficacy variable, the proportion of patients with a successful clinical outcome at 4 weeks after treatment who could be evaluated and the associated two-sided 95% confidence intervals (CIs) were calculated. The CI for the difference in response rates was calculated, accounting for the surgical procedure performed, including whether resection of the rectum had been performed.

An exploratory evaluation assessed whether preoperative and intraoperative risk factors contributed to the development of surgical-site infection. For the univariate analysis, the significance level of each factor was tested alone. For the mul-

tivariate analysis, a backward-elimination approach in a multiple logistic-regression model was performed. In this model, the significant factors from the univariate analysis were removed one at a time, starting with the factor that had the largest P value, until all remaining factors had a two-sided P value of less than 0.10. Odds ratios and P values were reported for each factor alone and for the factors found to be significant from the backward elimination.

## RESULTS

### PATIENTS

Of the 1002 patients who were randomly assigned to study groups, 901 qualified for the modified intention-to-treat analysis, and 672 were included in the per-protocol analysis (Fig. 1). Baseline demographic and surgical characteristics were generally balanced between the two treatment groups (Table 1). At baseline, the indication for surgery showed an imbalance between treatment groups ( $P=0.05$ ), with patients receiving ertapenem having a higher prevalence of rectal cancer (20.4% in the ertapenem group and 14.1% in the cefotetan group).

### MODIFIED INTENTION-TO-TREAT ANALYSIS

After adjustment for strata, the overall failure rates were 40.2% in the ertapenem group and 50.9% in the cefotetan group (absolute difference,  $-10.7\%$ ; 95% CI,  $-17.1$  to  $-4.2$ ). Rates for all the components of the modified intention-to-treat analysis are shown in Table 2.

### PER-PROTOCOL ANALYSIS

After adjustment for strata, the overall failure rates were 28.0% in the ertapenem group and 42.8% in the cefotetan group (absolute difference,  $-14.8\%$ ; 95% CI,  $-21.9$  to  $-7.5$ ), which fulfilled statistical criteria for the superiority of ertapenem.

In the group of patients who underwent surgical procedures that did not include resection of the rectum (253 patients receiving ertapenem and 265 patients receiving cefotetan), clinical failure occurred in 26.9% of patients in the ertapenem group and 43.4% of those in the cefotetan group (absolute difference,  $-16.5\%$ ; 95% CI,  $-24.5$  to  $-8.3$ ). In the group of patients who underwent surgical procedures that included resection of the rectum (85 patients receiving ertapenem and 69 patients receiving cefotetan), clinical failure

occurred in 31.8% of patients in the ertapenem group and 40.6% of those in the cefotetan group (absolute difference,  $-8.8\%$ ; 95% CI,  $-23.9$  to  $6.4$ ).

Rates for all components of the study end points are shown in Table 2. The most common reason for failure of prophylaxis in both groups was surgical-site infection, particularly that involving a superficial incisional infection.

### MICROBIOLOGIC ANALYSIS

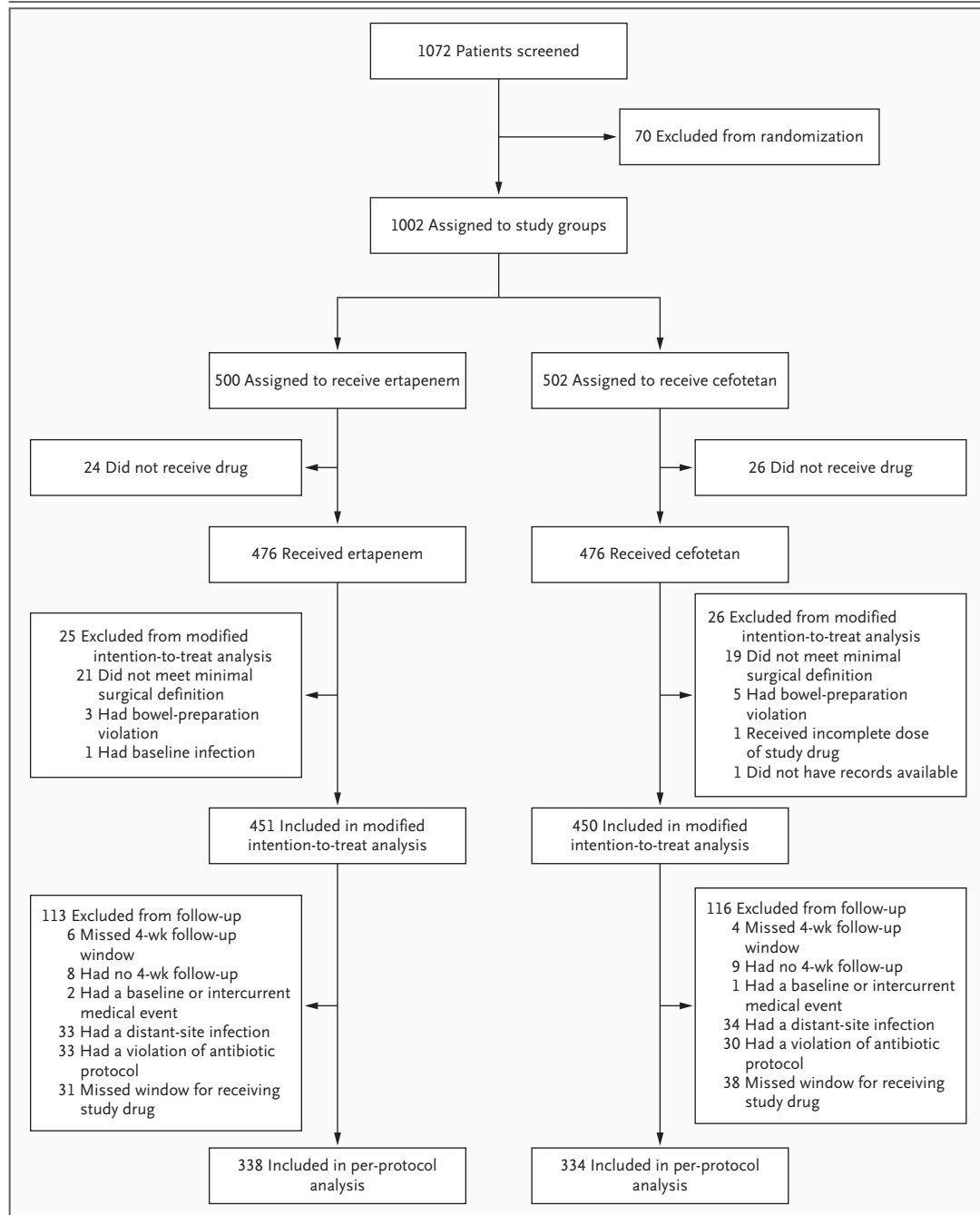
At least one organism was isolated in a total of 30 patients in the ertapenem group and 55 patients in the cefotetan group (124 organisms in the ertapenem group and 151 organisms in the cefotetan group). The distribution and prevalence of species isolated were generally similar in the two treatment groups (see the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)). Gram-positive aerobic cocci were the most common group isolated (42 isolates [33.9%] in the ertapenem group and 51 isolates [33.8%] in the cefotetan group); within that group, *Staphylococcus aureus* was the most common species isolated (9 isolates [7.3%] in the ertapenem group and 10 isolates [6.6%] in the cefotetan group).

Gram-negative anaerobic organisms were the next most common group of organisms isolated (36 isolates [29.0%] in the ertapenem group and 44 isolates [29.1%] in the cefotetan group); within that group, *Bacteroides fragilis* was the most common species isolated (9 isolates [7.3%] in the ertapenem group and 12 isolates [7.9%] in the cefotetan group). Although gram-negative aerobic bacilli were isolated less commonly (17 isolates [13.7%] in the ertapenem group and 23 isolates [15.2%] in the cefotetan group), *Escherichia coli* was the most frequently isolated pathogen in this group (7 isolates [5.6%] in the ertapenem group and 7 isolates [4.6%] in the cefotetan group).

Of the pathogens that were isolated and tested, 66.7% in the cefotetan group were resistant to cefotetan, whereas 16.3% percent in the ertapenem group were resistant to ertapenem (Table 3).

### ADVERSE EVENTS

None of the safety end points differed significantly between the two study groups (Table 4). In the majority of patients with drug-related clinical adverse events (14 patients in the ertapenem group and 17 in the cefotetan group), the events were associated with the primary study outcome (e.g., postoperative wound infection, cellulitis, and wound



**Figure 1. Enrollment and Outcomes.**

Patients may have been excluded from the per-protocol analysis for more than one reason but were counted in only one exclusion category. Patients who were excluded from this analysis because they had a distant-site infection had concomitant use of antibiotics and no evidence of surgical-site infection.

drainage). Other drug-related adverse events occurring in 1% or more of the 476 patients in either treatment group included skin-related events (including pruritus and rash) in 6 patients (1.3%) in the ertapenem group and 4 patients (0.8%) in the cefotetan group; gastrointestinal events (including diarrhea and nausea) in 5 patients (1.1%) in the ertapenem group and 3 patients (0.6%) in the

**Table 1. Baseline Preoperative and Intraoperative Characteristics of the Patients.\***

Variable	Patients in Per-Protocol Analysis			Patients in Modified Intention-to-Treat Analysis		
	Ertapenem (N=338)	Cefotetan (N=334)	P Value	Ertapenem (N=451)	Cefotetan (N=450)	P Value
Male sex — %	56.2	52.7	0.36	57.2	55.3	0.57
Age — yr			0.30			0.13
Mean	61.3±13.7	60.2±14.4		61.6±13.8	60.2±14.0	
Range	23 to 92	21 to 94		23 to 92	21 to 94	
White race — %†	78.7	75.4	0.32	79.4	76.7	0.33
Surgical procedure — %			0.17			0.20
With rectal resection	25.1	20.7		26.8	23.1	
Without rectal resection	74.9	79.3		73.2	76.9	
Indication for surgery — %			0.05			0.23
Colon cancer	47.9	45.8		47.5	44.2	
Rectal cancer	20.4	14.1		21.5	17.8	
Diverticulitis	11.2	11.1		10.9	12.2	
Benign colonic neoplasm	8.0	10.2		7.1	9.6	
Other condition‡	12.5	18.9		13.0	16.2	
Bowel preparation — %			0.31			0.40
Polyethylene glycol	47.1	43.1		45.4	42.6	
Sodium phosphate	52.9	56.9		54.6	57.4	
Nonuse of tobacco — %	48.5	45.5	0.73	47.9	44.2	0.59
Obesity (body-mass index >30) — %§	30.5	27.5	0.37	29.0	28.9	0.82
Creatinine clearance ≤30 ml/min/1.73 m <sup>2</sup> — %	1.2	1.5	0.73	1.1	1.8	0.41
History of diabetes — %	17.5	17.7	0.97	18.0	18.4	0.85
Baseline albumin ≤3.5 g/dl — %	22.5	20.1	0.47	23.9	20.0	0.17
History of chronic obstructive pulmonary disease — %	4.4	7.5	0.10	5.8	7.3	0.34
Baseline hematocrit — %			0.07			0.30
Mean	39.4±5.1	38.7±5.5		39.2±5.3	38.8±5.6	
Range	22.0 to 50.8	12.8 to 53.5		22.0 to 50.8	12.8 to 53.5	
Corticosteroid use at the time of surgery (<40 mg) — %	5.3	5.4	0.97	6.2	5.6	0.67
Time from administration of prophylaxis until skin incision — min			0.22			0.93
Mean	59.0±22.6	56.7±25.0		62.1±32.2	63.2±34.0	
Range	13 to 120	0 to 119		-242 to 215	-32 to 265	
Ileostomy or colostomy performed — %	17.2	15.6	0.58	19.1	18.0	0.68
No surgical drain used — %	72.2	74.0	0.61	70.7	70.9	0.96
Duration of surgery — min			0.93			0.94
Mean	133.3±60.1	132.8±60.4		143.5±71.1	143.8±71.7	
Range	15 to 314	9 to 313		15 to 432	9 to 518	
Occurrence of inadvertent perforation or spillage — %	3.6	1.8	0.16	4.2	3.3	0.49
Hair at operative site not removed — %	18.0	18.0	0.93	18.8	19.1	0.50

\* Plus-minus values are means ±SD.

† Race was assigned by the investigators.

‡ Other conditions include bowel motility disorder, inflammatory bowel disease, colonic stricture, familial adenomatous polyposis, fistula, and rectal prolapse.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

**Table 2. Adjusted Proportion of Patients with Failed Prophylaxis of Infection 4 Weeks after Surgery, According to Reason for Failure.\***

Reason for Failure	Patients in Per-Protocol Analysis			Patients in Modified Intention-to-Treat Analysis		
	Ertapenem (N=338)	Cefotetan (N=334)	Absolute Difference	Ertapenem (N=451)	Cefotetan (N=450)	Absolute Difference
	no. (%)	no. (%)	% (95% CI)	no. (%)	no. (%)	% (95% CI)
Any failure	95 (28.0)	143 (42.8)	-14.8 (-21.9 to -7.5)	182 (40.2)	229 (50.9)	-10.7 (-17.1 to -4.2)
Surgical-site infection	62 (18.1)	104 (31.1)	-13.0 (-19.5 to -6.5)	78 (17.1)	118 (26.2)	-9.1 (-14.4 to -3.7)
Superficial incisional infection	45 (13.1)	75 (22.4)	-9.3 (-15.0 to -3.5)	56 (12.3)	81 (17.9)	-5.6 (-10.3 to -0.9)
Deep incisional infection	13 (3.7)	17 (5.1)	-1.4 (-4.7 to 1.9)	15 (3.3)	23 (5.1)	-1.8 (-4.6 to 0.8)
Organ-space infection	4 (1.2)	12 (3.7)	-2.5 (-5.2 to -0.2)	7 (1.5)	14 (3.2)	-1.7 (-3.9 to 0.4)
Unexplained use of antibiotics	23 (6.9)	25 (7.5)	-0.6 (-4.6 to 3.4)	45 (10.0)	42 (9.4)	0.6 (-3.3 to 4.6)
Anastomotic leakage	10 (3.0)	14 (4.2)	-1.2 (-4.2 to 1.8)	13 (2.9)	18 (4.0)	-1.1 (-3.6 to 1.4)
Missed follow-up assessment†	—	—	—	19 (4.2)	24 (5.4)	-1.2 (-4.2 to 1.6)
Concomitant use of antibiotics for distant-site infection‡	—	—	—	27 (6.0)	27 (6.0)	0 (-3.2 to 3.2)

\* The absolute difference is for the ertapenem group as compared with the cefotetan group. All percentages and 95% CIs were computed from a statistical model adjusting for surgical procedure; therefore, the percentages may not equal the number of patients whose treatment failed divided by the total number of patients in each treatment group. Dashes denote not applicable.

† Patients in the per-protocol analysis who missed a follow-up assessment or had concomitant use of antibiotics for a distant-site infection were excluded from the analysis.

‡ In the modified intention-to-treat analysis, the protocol deemed that prophylaxis had failed in patients who had concomitant use of antibiotics for a distant-site infection, even though these patients had no signs or symptoms of infection at the operative site. Distant-site infections included pneumonia (in 13 patients in the ertapenem group and 23 in the cefotetan group), urinary tract infection (20 in the ertapenem group and 29 in the cefotetan group), and other infections (19 in the ertapenem group and 12 in the cefotetan group). Examples of other distant-site infections included *Clostridium difficile* infection, respiratory tract infection, and bloodstream infection. Patients with multiple distant-site infections were counted only once in this category.

cefotetan group; and *Clostridium difficile* infection in 5 patients (1.1%) in the ertapenem group and 1 patient (0.2%) in the cefotetan group ( $P=0.22$ ). *C. difficile* infection, regardless of whether it was drug-related, occurred in 8 of 476 patients in the ertapenem group (1.7%) and in 3 of 476 patients (0.6%) in the cefotetan group ( $P=0.22$ ).

The only drug-related laboratory adverse event that occurred in 1% or more of tested patients was a prolonged prothrombin time, which was reported in 1 of 386 patients (0.3%) in the ertapenem group and 4 of 385 (1.0%) in the cefotetan group.

Ten deaths were reported during the study (which included the study therapy period and the 14-day follow-up): three in the ertapenem group (0.6%) and seven in the cefotetan group (1.5%).

None of these deaths were considered to be drug-related.

#### ANALYSES OF RISK FACTORS

##### Univariate Analysis

The univariate model (Table 5) that was used to evaluate the association between postoperative infection and each of the potential preoperative and intraoperative risk factors for infection showed that the following factors were significant: prophylaxis with cefotetan, obesity (a body-mass index [the weight in kilograms divided by the square of the height in meters] of more than 30), an increased duration of surgery, a history of chronic obstructive pulmonary disease, a baseline albumin level of no more than 3.5 g per deciliter, bowel preparation

**Table 3. In Vitro Susceptibility of Documented Pathogens in the Two Treatment Groups.\***

Pathogen	Total No. of Isolates	Ertapenem		Cefotetan	
		Isolates Tested for Resistance	Resistant Isolates	Isolates Tested for Resistance	Resistant Isolates
		no.	no. (%)	no.	no. (%)
<b>Patients receiving ertapenem</b>					
Gram-positive aerobic cocci	42	24	14 (58.3)	24	18 (75.0)
Gram-positive aerobic bacilli	3	0	0	0	0
Gram-negative aerobic bacilli	17	11	1 (9.1)	11	2 (18.2)
Gram-positive anaerobic bacteria	25	24	0	24	5 (20.8)
Gram-negative anaerobic bacteria	36	33	0	33	17 (51.5)
Other unspecified bacteria	1	0	0	0	0
Total	124	92	15 (16.3)	92	42 (45.7)
<b>Patients receiving cefotetan</b>					
Gram-positive aerobic cocci	51	24	14 (58.3)	24	19 (79.2)
Gram-positive aerobic bacilli	0	0	0	0	0
Gram-negative aerobic bacilli	23	10	1 (10.0)	15	8 (53.3)
Gram-positive anaerobic bacteria	30	29	0	29	19 (65.5)
Gram-negative anaerobic bacteria	44	37	1 (2.7)	37	24 (64.9)
Other unspecified bacteria	3	0	0	0	0
Total	151	100	16 (16.0)	105	70 (66.7)

\* Patients with infections caused by these pathogens had superficial and deep surgical-site infections, organ-space infections, and anastomotic leakage. Pathogens that occurred in more than 1% of patients in either treatment group included the following: gram-positive aerobic cocci — enterococcus species, *Staphylococcus aureus*, staphylococcus species (coagulase negative), and streptococcus species; gram-positive aerobic bacilli — bacillus species; gram-negative aerobic bacilli — *Enterobacter aerogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Morganella morganii*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*; gram-positive anaerobic bacteria — peptostreptococcus species, clostridium species, eubacterium species, *Lactobacillus plantarum*, and *Propionibacterium acnes*; gram-negative anaerobic bacteria — porphyromonas species, bacteroides species, and fusobacterium species; and other unspecified bacteria — gram-negative bacillus (not otherwise specified).

with polyethylene glycol, current or former use of tobacco, an increased time from the initiation of prophylaxis to the start of surgery, the occurrence of inadvertent perforation or spillage of luminal contents, a history of diabetes, no removal of hair from the surgical site, and male sex.

#### Multivariate Analysis

In a multivariate logistic-regression model (Table 5), prophylaxis with cefotetan, obesity, an increased duration of surgery, current use of tobacco, no removal of hair from the surgical site, a history of chronic obstructive pulmonary disease, and the occurrence of inadvertent perforation or spillage of luminal contents remained significantly associated with the incidence of postoperative surgical-site infections.

#### DISCUSSION

This large, multicenter, randomized, double-blind clinical trial involving patients undergoing elective colorectal surgery showed that prophylaxis with ertapenem was superior to prophylaxis with cefotetan. Although the intention was to demonstrate the noninferiority of ertapenem, as compared with conventional prophylaxis for elective colorectal surgery, ertapenem was superior in terms of the proportion of favorable clinical responses and the reduction of postoperative surgical-site infections (including superficial infection and organ-space infection) 4 weeks after surgery. Cefotetan and cefoxitin are currently recommended as prophylactic antibiotic therapy in patients undergoing colorectal surgery.<sup>6-10</sup> Since the manufactur-

**Table 4. Clinical Adverse Events during Study Therapy and the 14-Day Follow-up Period.\***

Adverse Event	Ertapenem (N=476)	Cefotetan (N=476)	Absolute Difference % (95% CI)	P Value†
	no. (%)			
<b>Clinical adverse events (≥5% of patients in either treatment group)</b>				
Patients with one or more adverse events	357 (75.0)	381 (80.0)	-5.0 (-10.3 to 0.3)	0.07
Type of event				
Anemia	27 (5.7)	33 (6.9)	-1.2 (-4.4 to 1.9)	0.51
Diarrhea	27 (5.7)	15 (3.2)	2.5 (-0.1 to 5.3)	0.08
Hypertension	20 (4.2)	27 (5.7)	-1.5 (-4.3 to 1.3)	0.37
Ileus	55 (11.6)	45 (9.5)	2.1 (-1.8 to 6.0)	0.34
Localized numbness	17 (3.6)	25 (5.3)	-1.7 (-4.4, 1.0)	0.27
Nausea	95 (20.0)	121 (25.4)	-5.4 (-10.8 to -0.1)	0.053
Oliguria	25 (5.3)	26 (5.5)	-0.2 (-3.2 to 2.7)	>0.99
Pruritus	31 (6.5)	27 (5.7)	0.8 (-2.3 to 4.0)	0.69
Pyrexia	72 (15.1)	64 (13.4)	1.7 (-2.8 to 6.1)	0.52
Tachycardia	26 (5.5)	38 (8.0)	-2.5 (-5.8 to 0.7)	0.15
Urinary tract infection‡	18 (3.8)	26 (5.5)	-1.7 (-4.5 to 1.0)	0.28
Vomiting	54 (11.3)	52 (10.9)	0.4 (-3.6 to 4.4)	0.92
Wound infection‡	31 (6.5)	59 (12.4)	-5.9 (-9.7 to -2.2)	0.003
Patients with drug-related adverse event	31 (6.5)	33 (6.9)	-0.4 (-3.7 to 2.8)	0.90
<b>Serious adverse events (≥1% of patients in either treatment group)</b>				
Patients with serious adverse event	98 (20.6)	121 (25.4)	-4.8 (-10.2 to 0.5)	0.09
Type of event				
Abdominal abscess	4 (0.8)	6 (1.3)	-0.5 (-2.0 to 1.0)	0.75
Abdominal pain	5 (1.0)	7 (1.5)	-0.4 (-2.1 to 1.2)	0.77
Anastomotic leakage	7 (1.5)	4 (0.8)	0.7 (-0.9 to 2.2)	0.55
Ileus	19 (4.0)	10 (2.1)	1.9 (-0.3 to 4.3)	0.13
Pneumonia	2 (0.4)	7 (1.5)	-1.1 (-2.6 to 0.3)	0.18
Small-bowel obstruction	7 (1.5)	8 (1.7)	-0.2 (-2.0 to 1.5)	>0.99
Urinary tract infection	5 (1.1)	5 (1.1)	0.0 (-1.5 to 1.5)	>0.99
Wound infection	10 (2.1)	20 (4.2)	-2.1 (-4.5 to 0.2)	0.09
Patients with serious drug-related adverse event§	3 (0.6)	3 (0.6)	0 (-1.3 to 1.3)	>0.99
Patients who discontinued treatment because of adverse event¶	0	1 (0.2)	-0.2 (-1.2 to 0.6)	>0.99
Death	3 (0.6)	7 (1.5)	-0.9 (-2.4 to 0.6)	0.34

\* The absolute difference is for the ertapenem group as compared with the cefotetan group. All 95% CIs were calculated with the use of Wilson's score method.

† P values were calculated with the use of Fisher's exact test.

‡ Investigators were instructed that wound infection and distant-site infections (e.g., urinary tract infection) were an outcome of the study and were not required to be reported as adverse events unless they met the criteria for a serious adverse event. Some centers reported these items as adverse events. However, not all wound infections and distant-site infections were reported as adverse events. Therefore, the number of wound infections and distant-site infections does not correspond to the number of treatment failures.

§ Reported serious drug-related adverse events consisted of sinus bradycardia (in one patient in the ertapenem group), *Clostridium difficile* colitis (in two patients in the ertapenem group), and wound infection (in three patients in the cefotetan group).

¶ These events are reported even though the rate did not exceed 1% in either group.

|| One patient in the cefotetan group discontinued treatment because of hypersensitivity.

**Table 5. Univariate and Multivariate Analyses for the Association between Prespecified Risk Factors and Postoperative Surgical-Site Infection.\***

Risk Factor	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	P Value	Adjusted Odds Ratio (95% CI)	P Value
Prophylaxis with ertapenem (vs. cefotetan)	0.50 (0.35–0.70)	<0.001	0.41 (0.28–0.61)	<0.001
Obesity (body-mass index >30)	2.06 (1.44–2.97)	<0.001	2.19 (1.45–3.29)	<0.001
Increased duration of surgery (SD, 60.2 min) †	1.46 (1.24–1.73)	<0.001	1.34 (1.11–1.62)	0.003
History of chronic obstructive pulmonary disease	4.19 (2.17–8.09)	<0.001	2.95 (1.38–6.31)	0.005
Baseline albumin ≤3.5 g/dl	1.50 (1.01–2.23)	<0.001	NS	NS
Bowel preparation with sodium phosphate (vs. polyethylene glycol)	0.60 (0.43–0.85)	0.003	0.69 (0.46–1.02)	0.07
Current use of tobacco (vs. nonuse)	1.91 (1.24–2.96)	0.004	1.78 (1.08–2.95)	0.02
Former use of tobacco (vs. nonuse)	1.49 (1.01–2.19)	0.05	1.18 (0.76–1.84)	0.46
Removal of hair immediately before surgery (vs. no hair removal)	0.55 (0.36–0.82)	0.004	0.47 (0.29–0.76)	0.002
Removal of hair but not immediately before surgery (vs. no hair removal)	1.18 (0.25–5.51)	0.83	1.37 (0.28–6.76)	0.70
Time from prophylaxis to skin incision (SD, 23.8 min) †	0.80 (0.67–0.95)	0.01	0.83 (0.68–1.00)	0.06
Occurrence of inadvertent perforation or spillage	3.29 (1.28–8.47)	0.01	3.89 (1.40–10.86)	0.009
History of diabetes	1.58 (1.04–2.40)	0.03	NS	NS
Female sex (vs. male sex)	0.71 (0.50–1.00)	0.05	NS	NS
Decreased baseline hematocrit (SD, 5.3%) ‡	1.17 (0.99–1.39)	0.06	NS	NS
Nonwhite race (vs. white race)	1.40 (0.95–2.07)	0.09	NS	NS
Age (SD, 14.0 yr) †	0.90 (0.76–1.34)	0.21	NS	NS
Procedure required ileostomy or colostomy	1.29 (0.83–2.00)	0.26	NS	NS
Corticosteroid use at the time of surgery (<40 mg)	1.47 (0.73–2.96)	0.29	NS	NS
Creatinine clearance ≤30 (vs. >30)	0.33 (0.04–2.65)	0.30	NS	NS
Surgical procedure without rectal resection (vs. with rectal resection)	0.90 (0.61–1.34)	0.62	NS	NS
No surgical drains used	0.93 (0.64–1.36)	0.73	NS	NS

\* Postoperative infection included surgical-site infection and anastomotic leakage. The adjusted odds ratios, 95% CIs, and P values were estimated from a multiple logistic-regression model with the use of backward elimination. All factors displayed in the multivariate analysis section of the table remained in the final model (i.e.,  $P < 0.10$  for all comparisons). NS denotes not significant ( $P \geq 0.10$ ).

† Odds ratios represent the increased odds of a postoperative infection on the basis of an increase of 1 SD in the risk factor.

‡ Odds ratios represent the decreased odds of a postoperative infection on the basis of a decrease of 1 SD in the risk factor.

ers are planning to discontinue the production of both cefotetan and cefoxitin, ertapenem emerges as a potential option for prophylaxis in elective colorectal surgery.

In nine clinical trials in which cefotetan was used for surgical prophylaxis in a total of 1521 patients, the reported rates of surgical-site infection ranged from 9.4 to 28.0%, with a mean of 17.1%.<sup>18-26</sup> This rate is much lower than the 42.8% failure rate in the cefotetan group in our trial (Ta-

ble 2). The discrepancy can be explained in part by the precise definition of failure of prophylaxis adopted in this trial, which included not only surgical-site infection but also unexplained antibiotic use and anastomotic leakage. When the data are limited to surgical-site infection, the proportion of patients with an unfavorable response rate was similar to that in previous reports in the literature (18.1% in the ertapenem group and 31.1% in the cefotetan group). The most recently reported

rate of surgical-site infection in colorectal surgery, from a study by Smith et al.,<sup>27</sup> was 25.6%.

We also observed a higher-than-expected rate of superficial surgical-site infection (13.1% in the ertapenem group and 22.4% in the cefotetan group); the mean rate was 17.1% in the reported cefotetan trials and 25.6% in the study by Smith et al. One explanation is the variation in the prevalence of obesity in the studies. In our study, 28.9% of the patients met the criterion for obesity (a body-mass index of over 30), as compared with values ranging from 5.2 to 9.3% in three other studies.<sup>22,23,26</sup> In our trial, there was also a higher risk of surgical-site infection among obese patients in multivariate analysis (Table 5), as was the case in other studies.<sup>27,28</sup>

The distribution and prevalence of bacterial species that were isolated from each treatment group were generally similar. A higher percentage of pathogens that were isolated and tested in the cefotetan group were resistant to cefotetan, as compared with the percentage of pathogens in the ertapenem treatment group that were resistant to ertapenem. However, we could not measure the development of resistance (either hospital-acquired or community-acquired), since no colonizing organisms were obtained at baseline.

Furthermore, we cannot assess the potential effect of the prophylaxis on the emergence of patient-specific and community-wide resistant organisms because of the single-dose nature of the prophylaxis, the absence of surveillance cultures obtained after administration, and the 4-week duration of follow-up.

The frequency and nature of adverse events were similar in the ertapenem group and the cefotetan group. The two treatment groups did not differ in regard to any of the prespecified measures of adverse events. Even though the difference in the incidence of *C. difficile* infection (higher in the ertapenem group than in the cefotetan group) was not statistically significant, it is a concern, given the emergence of a highly virulent form of the bacterium.

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#### APPENDIX

In addition to the authors, the following investigators participated in the study by enrolling at least one patient: Akron General Medical Center, Akron, OH — M.C. Horattas; Albany Medical College, Albany, NY — E. Lee; University of New Mexico Health Sciences Center, Albuquerque — D. Fry; General Surgical Associates, Allentown, PA — R.C. Boorse; Medical College of Georgia, Augusta — R.G. Martindale; Northwest Gastroenterology Associates, Bellevue, WA — R.A. Wohlman; Mercy Health Center, Bentonville, AR — G.B. Waldon; Alabama Research Center, Birmingham — J. Isobe, D. Mirelman; New England Medical Center, Boston — S.D. Schwaartzberg; University of North Carolina, Chapel Hill — M. Koruda; University of Virginia Health System, Charlottesville — R. Sawyer; Northwestern University, Chicago — A.L. Halverson; University of Cincinnati, Cincinnati — J. Rafferty; Cleveland Clinic Foundation, Cleveland — F. Remzi; University of Missouri Healthcare, Columbia — M.H. Metzler; Bassett Healthcare, Cooperstown, NY — A.N. Nafziger; Veterans Affairs North Texas Health Care Service, Dallas — T. Anthony; Detroit Receiving Hospital and Henry Ford Hospital Medical Center, Detroit — S.A. Dulchavsky; Penn State Milton S. Hershey Medical Center, Hershey — W. Koltun; Memorial Regional Hospital, Hollywood, FL — E. Carrillo; Heritage Physicians Group, Hot Springs, AR — J.W. Webb; St. Luke's Episcopal Hospital, Houston — H.B. Bailey; University of Kansas Medical Center, Kansas City — M. Moncure; Wilford Hall Medical Center, Lackland Air Force Base, TX — W. Perry; University of Kentucky Medical Center, Lexington — P. Kearney; University of Louisville, Louisville, KY — S. Galandiuk; Los Angeles County and University of Southern California Medical Center, Los Angeles — A.E. Yellin; University of Miami School of Medicine, Miami — L.R. Sands; Manhattan Surgical Association, New York — S.R. Gorfine; University of Oklahoma Health Sciences Center, Oklahoma City — R.G. Postier; Opelousas General Hospital, Opelousas, LA — K. Thibodeaux; Hahnemann University Hospital, Philadelphia — A.D. Brooks; Phoenix, AZ — J.E. Bauwen; McGuire Veterans Affairs Medical Center, Richmond, VA — M.L. Schubert; Southern Regional Medical Center, Riverdale, GA — S.M. Cohen; Royal Oak, MI — J. Bodzin; University of California Davis Medical Center, Sacramento — H. Ho; LDS Hospital, Salt Lake City — M.J. Ott; University of Utah, Salt Lake City — E. Nelson; Colon and Rectal Surgical Association of San Antonio, San Antonio, TX — J.L. Mayoral; Virginia Mason Medical Center, Seattle — R.C. Thirlby; Pennridge Surgical Associates, Sellersville, PA — G.S. Finkelstein; Inland Surgical Association, Spokane, WA — R. Sinha; Tampa General Hospital, Tampa, FL — J.E. Marcelet; University of California at Los Angeles Medical Center, Torrance — S.R. Klein; and Wesley Medical Center, Wichita, KS — M.G. Porter.

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