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ORIGINAL ARTICLE

Gentamicin–Collagen Sponge for Infection Prophylaxis in Colorectal Surgery

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ABSTRACT

BACKGROUND

Despite the routine use of prophylactic systemic antibiotics, surgical-site infection continues to be associated with significant morbidity and cost after colorectal surgery. The gentamicin–collagen sponge, an implantable topical antibiotic agent, is approved for surgical implantation in 54 countries. Since 1985, more than 1 million patients have been treated with the sponges.

METHODS

In a phase 3 trial, we randomly assigned 602 patients undergoing open or laparoscopically assisted colorectal surgery at 39 U.S. sites to undergo either the insertion of two gentamicin–collagen sponges above the fascia at the time of surgical closure (the sponge group) or no intervention (the control group). All patients received standard care, including prophylactic systemic antibiotics. The primary end point was surgical-site infection occurring within 60 days after surgery, as adjudicated by a clinical-events classification committee that was unaware of the study-group assignments.

RESULTS

The incidence of surgical-site infection was higher in the sponge group (90 of 300 patients [30.0%]) than in the control group (63 of 302 patients [20.9%], P=0.01). Superficial surgical-site infection occurred in 20.3% of patients in the sponge group and 13.6% of patients in the control group (P=0.03), and deep surgical-site infection in 8.3% and 6.0% (P=0.26), respectively. Patients in the sponge group were more likely to visit an emergency room or surgeon's office owing to a wound-related sign or symptom (19.7%, vs. 11.0% in the control group; P=0.004) and to be rehospitalized for surgical-site infection (7.0% vs. 4.3%, P=0.15). The frequency of adverse events did not differ significantly between the two groups.

CONCLUSIONS

Our large, multicenter trial shows that the gentamicin–collagen sponge is not effective at preventing surgical-site infection in patients who undergo colorectal surgery; paradoxically, it appears to result in significantly more surgical-site infections. (Funded by Innocoll Technologies; ClinicalTrials.gov number, NCT00600925.)

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Postoperative surgical-site infection continues to be a significant problem after general surgical procedures, especially colorectal surgery. Reported incidences of surgical-site infection among patients who undergo colorectal surgery range from 8.2%[1] to 26%,[2] with an incidence of approximately 18 to 20% in most series.[3-7] Postoperative surgical-site infection is associated with a significant rate of complications and cost.[8-10] Thus, prevention of these frequent infections has been the focus of numerous strategies.[2-7,11]

The gentamicin–collagen sponge was developed to prevent and treat wound infections by providing high gentamicin concentrations locally, avoiding the high systemic concentrations associated with nephrotoxicity. The sponge's collagen matrix biodegrades and disappears within days to weeks. Pharmacokinetic data show that implantation of one to five sponges (corresponding to a gentamicin dose of 130 to 650 mg) resulted in local-tissue gentamicin concentrations of 170 to 9000 μg per milliliter. These concentrations exceed the minimum inhibitory concentrations for many microorganisms. Systemic concentrations of gentamicin, however, remained below 2 μg per milliliter 24 hours after implantation.[12]

The sponge received marketing approval in Germany in 1985 and is currently approved for use in another 53 countries. Since 1985, more than 2 million sponges manufactured by Innocoll Technologies (Gallowston, Ireland) have been used to treat more than 1 million patients across a broad range of clinical indications. Several studies suggest that the sponge may be effective in the prevention and treatment of infections after general surgery.[6,13,14] In a single-center, randomized trial, patients who underwent colorectal surgery and received a sponge had a 70% decrease in surgical-site infection, as compared with those who did not receive a sponge.[6] The current phase 3 trial was designed to confirm these promising data and support regulatory approval in the United States.

METHODS

STUDY OVERSIGHT

Patients were enrolled at 39 sites in the United States. The study was coordinated by the Duke Clinical Research Institute (DCRI). The DCRI–Duke University coauthors wrote the study protocol, gathered and analyzed the data, vouch for the accuracy and integrity of the data and analysis, and wrote the manuscript. Institutional review boards at participating institutions approved the study protocol, and the study was performed in accordance with it.

PATIENTS

All patients provided written informed consent. A complete list of inclusion and exclusion criteria, along with a detailed list of the surgical procedures, is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. Inclusion criteria were an age of 18 years or older and having 1 of 13 types of colorectal surgery scheduled. Laparoscopically assisted procedures requiring an incision of at least 7 cm were allowed, a length that is consistent with the use of a laparotomy "hand port" in many so-called laparoscopic colorectal procedures. Exclusion criteria included the presence of a clinically significant concomitant surgical procedure, use of a laparoscopic or other minimally invasive surgical approach involving a laparotomy incision shorter than 7 cm, laparotomy within the 60-day period before the screening visit or a planned second laparotomy within the 60-day period after surgery, and a situation in which it was technically impossible to insert two sponges above the fascia.

STUDY PROCEDURE

Study Treatment and Randomization

Each sponge (10 by 10 cm) contained 280 mg of collagen and 130 mg of gentamicin. In patients who were randomly assigned to receive a sponge, two sponges were inserted anteriorly to the fascia, along the full length of the incision, immediately before closure of the surgical wound. To facilitate placement in the wound, the sponges could be cut into strips while dry. No sponges were placed in control patients. Patients in the sponge group in whom reexploration of the surgical site was necessary within 1 week after the first surgery had two new sponges inserted at the time of closure. All participating surgeons underwent a training and certification process that included the viewing of a video outlining proper use of the study sponge.

Randomization occurred after the surgical incision had been made, with the use of a cen-

tral randomization system. Control patients did not receive a placebo sponge (a sponge containing collagen but not gentamicin), since bacteria might have grown on a sponge that did not contain the antibiotic. Therefore, surgeons could not be unaware of the study-group assignments, but patients and members of the adjudication committee did remain unaware.

ADMINISTRATION OF ANTIBIOTICS AND BOWEL PREPARATION

In accordance with published guidelines,[15] the protocol called for initiation of one of the following antibiotic regimens within 60 minutes before incision: cefazolin plus metronidazole, cefoxitin, or ciprofloxacin plus clindamycin or metronidazole. Dosing was based on body weight, and the drugs were not to be continued for more than 24 hours after surgery. Preoperative oral antibiotics were not required but could be added to the systemic antibiotic prophylaxis: oral neomycin plus oral erythromycin or oral neomycin plus oral metronidazole.[15] The use of topical antibiotics, other than the gentamicin in the sponge, was prohibited in patients randomly assigned to receive the sponge. At least one of the following bowel-preparation regimens was required: use of a laxative (polyethylene glycol, sodium phosphate, or a magnesium citrate–based regimen) or a high-volume enema.

DATA COLLECTION

Standard preoperative demographic and intraoperative characteristics were recorded, and we also collected data on variables suspected to play a role in surgical-site infection. The risk of infection was assessed with the use of the National Nosocomial Infection Surveillance System.[4,16]

PRIMARY AND SECONDARY END POINTS

The primary study end point was surgical-site infection within the laparotomy wound during the period from surgery through postoperative day 60. Key secondary efficacy end points included the incidence of deep surgical-site infections, superficial surgical-site infections, surgically treated surgical-site infections (defined as infection treated with any type of surgical intervention, including opening of the wound), postoperative hospital length of stay, and ASEPSIS score through 60 days after colorectal surgery.[4,17,18] The validated ASEPSIS score assigns points for nine variables related to infection, including use of antibiotics, drainage of pus under local anesthesia, wound débridement under general anesthesia, isolation of bacteria, prolonged postoperative hospitalization, and findings on daily examination of the wound.[4,17,18] The minimum score is 0, and there is no theoretical maximum score; higher scores indicate a worse infection. We assessed the change in the serum creatinine level from baseline, reporting the peak level during the first 7-day postoperative period or the period until hospital discharge if discharge occurred before day 7. Patients assessed their pain and wound healing according to a structured questionnaire administered 30 and 60 days after surgery. Data were recorded for death from any cause at 60 days, visits to the emergency department or surgical office in association with wound-related signs or symptoms, rehospitalization for surgical-site infection, and serum gentamicin levels at several sites. Blood samples were obtained at baseline (after incision) and then at 2±0.5, 6±0.5, 12±1, 24±2, and 48±2 hours after surgical-wound closure for the determination of serum gentamicin levels.

CLINICAL EVENTS COMMITTEE

The independent clinical events committee consisted of three independent infectious disease experts who were unaware of the study-group assignments. All suspected wound-infection events were reviewed independently by two of the three experts. Cases for which the two experts disagreed were reviewed by the third expert. Possible wound infections were identified by events including signs of infection, administration of postoperative antibiotics, rehospitalization, and death. After review of blinded medical records,[4,17,18] the committee ascertained the presence or absence, extent, and severity of all infections according to standardized criteria, including those from the Centers for Disease Control and Prevention[4,16,17,19] and Itani and colleagues[2]: superficial infections that involved the skin and superficial fat but did not threaten the fascia, deep infections involving deeper soft tissue of the incision and potentially threatening the fascia, and organ-space infections below the fascia (which are usually manifested as abscess). Data for infections not considered to be related to laparotomy (e.g., perineal-incision infection, peristomal infection, infection at the intravenous catheter site, or pneumonia) were not included in the analysis.

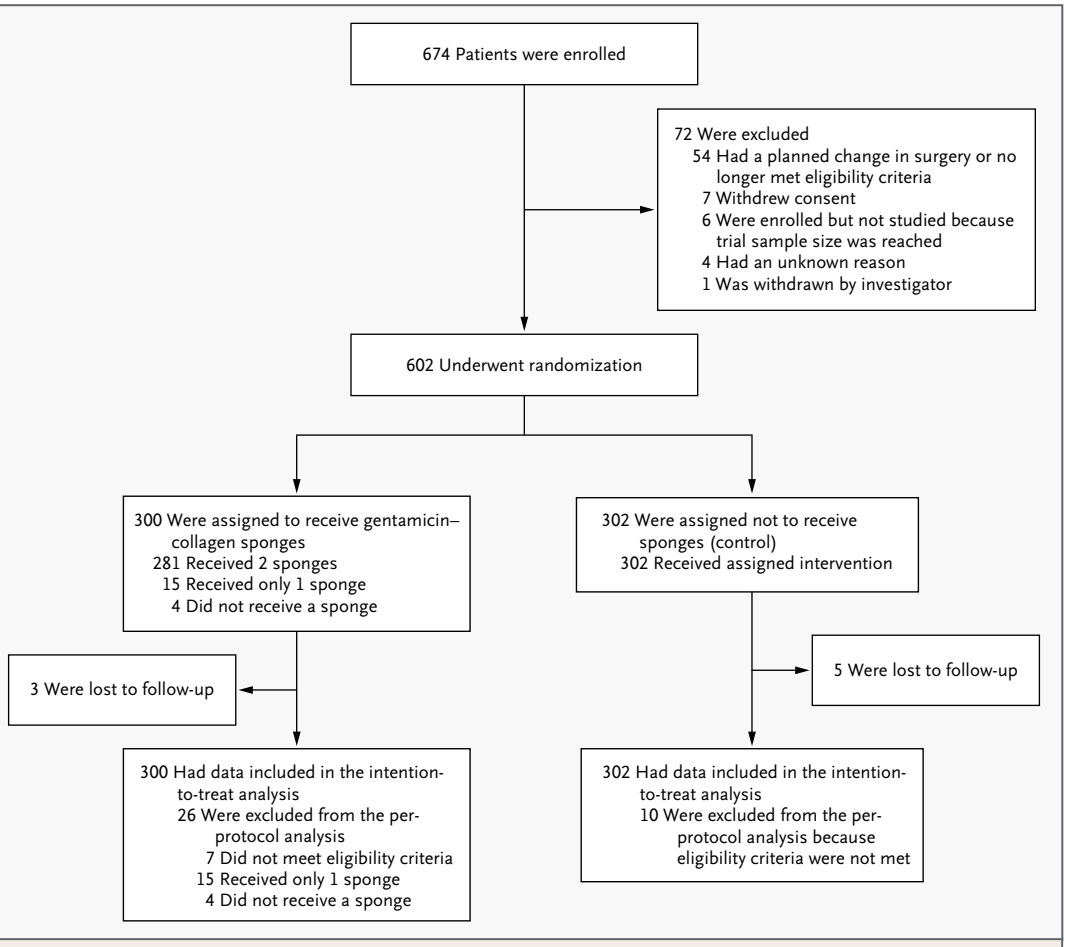

Figure 1. Enrollment, Randomization, and Follow-up of the Patients, According to Study Group.

STATISTICAL ANALYSIS

All analyses were performed by the statistical team at the DCRI. Calculations during the planning phase indicated that enrollment of 592 patients (296 per study group) would be required to detect a 50% relative reduction in the incidence of surgical-site infection in the sponge group as compared with the control group, with a power of at least 85% and a two-sided type I error rate of 0.05. On the basis of previous trials, we assumed a 16% incidence of surgical-site infection.

The primary analysis was based on intention-to-treat methods. We also performed a per-protocol analysis, as a prespecified secondary analysis, which included all patients who completed the study and had no major deviations from the prespecified protocol. We compared the primary end point between the two study groups by means of a two-sided chi-square test involving data across all sites, after checking the treatment-by-site interaction. In all secondary efficacy and subgroup analyses, a nominal two-sided P value of less than 0.05 was considered to indicate statistical significance, and the results were considered to be descriptive.

Descriptive statistical comparisons between the two study groups were performed with the use of chi-square tests or Fisher's exact test, as appropriate, for categorical secondary efficacy end points and with the use of analysis-of-variance techniques or Wilcoxon rank-sum tests, as appropriate, for continuous secondary efficacy end points. The log-rank tests were used to compare the time to first surgical-site infection between two study groups. Kaplan–Meier survival estimates of the time to first surgical-site infection were also calculated.

No formal interim analysis was planned. An independent data and safety monitoring committee monitored the trial on an ongoing basis.

All statistical analyses were performed with the use of SAS software (version 9.2).

RESULTS

Overall, 602 patients were enrolled at 39 U.S. sites between February 2008 and March 2009 (Fig. 1). Of the 300 patients randomly assigned to receive two sponges, 281 (93.7%), 15 (5.0%), and 4 (1.3%) received two, one, and no sponges, respectively. A total of 8 of the 602 patients (1.3%; 3 in the sponge group and 5 in the control group) were lost to follow-up at day 60.

Patients in both groups underwent bowel resection primarily for colon or rectal carcinoma (in 307 of 602 patients [51.0%]) or diverticulitis or inflammatory bowel disease (217 of 602 patients [36.0%]). The study groups were balanced with regard to baseline characteristics (Table 1) as well as surgical preparation and intraoperative characteristics (Table 2). Laparoscopically assisted surgery that was not converted to an open procedure was performed in 51 of the 300 patients (17.0%) in the sponge group and 58 of the 302 patients (19.2%) in the control group. Adjudicated surgical-site infection was more likely to occur in association with open surgery (139 of 493 patients [28.2%]) than with laparo-

Table 1. Baseline Characteristics of the Patients, According to Study Group.*

Characteristic	Gentamicin–Collagen Sponge (N=300)	Control (N=302)
Age — yr		
Median	57.8	58.0
IQR	45.5–67.7	47.4–67.0
White race — no. (%)†	272 (90.7)	273 (90.4)
American Society of Anesthesiologists score of 3 or 4 — no. (%)‡	132 (44.0)	126 (41.7)
Weight — kg		
Median	79.5	80.0
IQR	67.9–93.0	69.4–93.2
Body-mass index§		
Median	26.8	27.2
IQR	23.8–30.8	24.0–30.8
Waist circumference — cm		
Median	96.0	96.5
IQR	86.0–106.7	86.4–106.7
Male sex — no. (%)	181 (60.3)	158 (52.3)
Hypertension — no. (%)	140 (46.7)	122 (40.4)
Diabetes — no. (%)	37 (12.3)	47 (15.6)
Smoking status — no. (%)		
Current or previous	142 (47.3)	147 (48.7)
Current	47 (15.7)	46 (15.2)
Chronic obstructive pulmonary disease — no. (%)	17 (5.7)	12 (4.0)
Peripheral vascular disease — no. (%)	12 (4.0)	13 (4.3)
Previous laparotomy — no./total no. (%)	131/300 (43.7)	124/301 (41.2)
Previous radiation to abdomen — no. (%)	42 (14.0)	45 (14.9)
Chemotherapy within 6 wk before surgery — no. (%)	22 (7.3)	17 (5.6)
Corticosteroid use within 1 mo before surgery — no. (%)	25 (8.3)	17 (5.6)
History of abdominal fistula — no. (%)	10 (3.3)	10 (3.3)
Renal insufficiency — no. (%)¶	5 (1.7)	5 (1.7)

Table 1. (Continued.)

Characteristic	Gentamicin–Collagen Sponge (N=300)	Control (N=302)
Preoperative laboratory values		
Serum albumin — g/dl		
Median	4.0	4.0
IQR	3.6–4.3	3.7–4.4
Serum glucose — mg/dl		
Median	99	96
IQR	89–111	89–109
Serum glycated hemoglobin — %		
Median	5.5	5.6
IQR	5.2–6.0	5.3–6.0
Hematocrit — %		
Median	39.0	40.0
IQR	36.0–42.5	36.0–43.0
Serum creatinine — mg/dl		
Median	0.9	0.9
IQR	0.8–1.1	0.8–1.0
Preoperative core temperature — °C		
Median	97.7	97.7
IQR	97.0–98.2	97.0–98.2
Preoperative hospital stay — days		
Median	0.0	0.0
IQR	0.0–0.0	0.0–0.0
NNISS score — no. (%)‖		
0	32 (10.7)	38 (12.6)
1	166 (55.3)	159 (52.6)
2	102 (34.0)	105 (34.8)
3	0	0

* To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for creatinine to micromoles per liter, multiply by 88.4. IQR denotes interquartile range.
† Race was self-reported.
‡ The American Society of Anesthesiologists physical status classification score can range from 0 to 6, with higher scores representing a worse condition. A score of 3 or 4 represents severe systemic disease.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ Renal insufficiency was defined as a preoperative serum creatinine level of 2.5 mg per deciliter (221 μmol per liter) or more.
‖ The National Nosocomial Infection Surveillance System (NNISS) score can range from 0 to 3 points, with a higher score representing a higher risk of infection. One point is awarded for an American Society of Anesthesiologists physical status classification score of 3 or more, one point is awarded for a contaminated or nonsterile operation, and one point is awarded for a duration of surgery of more than 2 hours.

scopically assisted surgery (14 of 109 patients [12.8%]).

In the primary analysis, surgical-site infections occurred more frequently in the sponge group (90 of 300 patients [30.0%]) than in the control group (63 of 302 [20.9%]) (P=0.01) (Table 3). The incidence of superficial surgical-site infection was 20.3% in the sponge group, versus 13.6% in the control group, and the incidence of deep surgical-site infections was 8.3% versus 6.0%. Patients in the sponge group were more likely than those in the control group to visit an

Table 2. Characteristics of Surgical Preparation and Procedure, According to Study Group.*

Characteristic	Gentamicin–Collagen Sponge (N=300)	Control (N=302)
Oral antibiotics administered preoperatively — no. (%)	44 (14.7)	38 (12.6)
Preoperative bowel preparation — no. (%)		
Laxative use and complete bowel preparation	273 (91.0)	277 (91.7)
Enema	4 (1.3)	5 (1.7)
Other	9 (3.0)	12 (4.0)
None	17 (5.7)	16 (5.3)
Preoperative shower with chlorhexidine soap — no. (%)	39 (13.0)	44 (14.6)
Hair at operative site not removed — no./total no. (%)	61/299 (20.4)	82/302 (27.2)
Preincision skin preparation — no. (%)		
With povidone–iodine	220 (73.3)	220 (72.8)
With alcohol	42 (14.0)	42 (13.9)
With chlorhexidine-based agent	110 (36.7)	117 (38.7)
IV antibiotics administered within 60 min before incision	284 (94.7)	289 (95.7)
Antibiotic administered before incision — no. (%)		
Aztreonam	0	1 (0.3)
Cefotetan	4 (1.3)	2 (0.7)
Cefazolin	89 (29.7)	92 (30.5)
Cefoxitin	111 (37.0)	105 (34.8)
Clindamycin	6 (2.0)	6 (2.0)
Ciprofloxacin	83 (27.7)	88 (29.1)
Metronidazole	173 (57.7)	182 (60.3)
Other	6 (2.0)	8 (2.6)
Prophylactic IV antibiotics discontinued within 24 hr after incision — no./total no. (%)	262/296 (88.5)	267/301 (88.7)
Surgical procedure performed — no. (%)		
Left hemicolectomy	17 (5.7)	21 (7.0)
Transverse colectomy	12 (4.0)	11 (3.6)
Segmental (sleeve) left colon resection	1 (0.3)	6 (2.0)
Total abdominal colectomy with ileorectal anastomosis	12 (4.0)	14 (4.6)
Total abdominal colectomy with ileostomy	18 (6.0)	15 (5.0)
Total abdominal proctocolectomy	23 (7.7)	15 (5.0)
Low anterior resection	77 (25.7)	105 (34.8)
Sigmoid resection	65 (21.7)	60 (19.9)
Nonemergency Hartman's procedure	7 (2.3)	4 (1.3)
Colotomy with polypectomy distal to hepatic flexure	0	1 (0.3)
Colostomy takedown through laparotomy incision	21 (7.0)	15 (5.0)
Ileal pouch anal anastomosis with or without stoma	40 (13.3)	29 (9.6)
Abdominal–perineal resection of the rectum	22 (7.3)	16 (5.3)
Other	7 (2.3)	11 (3.6)
Laparoscopically assisted surgery†	51 (17.0)	58 (19.2)

Table 2. (Continued.)

Characteristic	Gentamicin–Collagen Sponge (N = 300)	Control (N = 302)
Laparotomy incision length — cm		
Median	16.0	14.0
IQR	9.3–23.0	9.0–20.0
Method to close laparotomy incision — no. (%)		
Staples	239 (79.7)	219 (72.5)
Sutures	68 (22.7)	88 (29.1)
Glue	3 (1.0)	5 (1.7)
Duration of surgery — hr		
Median	2.8	2.9
IQR	2.1–4.0	2.2–3.7
Abdominal surgical drain inserted — no. (%)	111 (37.0)	113 (37.4)
Crystalloid volume administered intraoperatively — liters		
Median	3.0	3.0
IQR	2.3–4.0	2.4–4.0
Colloid volume administered intraoperatively — liters		
Median	0.0	0.0
IQR	0.0–0.5	0.0–0.5
Nitrous oxide used — no. (%)	33 (11.0)	18 (6.0)
F_IO_2 during surgery — %		
Lowest value		
Median	53	52
IQR	46–70	47–65
Estimated average value		
Median	60	60
IQR	54–87	52–77
Administered any dexamethasone in perioperative period — no. (%)	31 (10.3)	41 (13.6)
Peak serum glucose in first 24 hr after surgery — mg/dl		
Median	140	142
IQR	119–167	116–173
Perioperative allogeneic red-cell transfusion — no. (%)	48 (16.0)	56 (18.5)
Core temperature at end of surgery — °C		
Median	36.5	36.4
IQR	36.2–36.8	36.2–36.8
Core temperature at end of surgery ≥36°C — no./total no. (%)	264/297 (88.9)	250/297 (84.2)

* To convert the values for glucose to millimoles per liter, multiply by 0.05551. F_IO_2 denotes fraction of inspired oxygen, IQR interquartile range, and IV intravenous.
† Laparoscopically assisted surgery did not include procedures in which the laparoscopic approach was abandoned (i.e., conversion to open laparotomy).

emergency department or surgical office with a wound-related sign or symptom (19.7 vs. 11.0%, P=0.004); rehospitalization for surgical-site infection occurred in 7.0% of patients in the sponge group and 4.3% of patients in the control group (P=0.15). Times to surgical-site infection are shown in Figure 2.

The frequency of adjudicated surgical-site infection was 44.7% (134 of 300 patients) in the sponge group, versus 34.4% (104 of 302 patients) in the control group, as assessed by the site investigators (which is similar to results on the basis of assessment by the clinical events committee). Analyses performed in the per-protocol population of 566 patients yielded results similar to those for the intention-to-treat population (Table 3).

Among patients in the per-protocol population with adjudicated surgical-site infection, potential pathogens were isolated in samples from 44 patients in the sponge group and 28 patients in the control group (Table 1 in the Supplementary Appendix). The organisms found to be most frequently resistant to gentamicin include *Enterococcus faecalis* (in 3 of 9 isolates), *Enterococcus faecium* (1 of 3 isolates), *Escherichia coli* (1 of 9 isolates), *Proteus mirabilis* (1 of 5 isolates), and *Staphylococcus epidermidis* (9 of 12 isolates) (Table 2 in the Supplementary Appendix). All but 2 of the 15 resistant isolates were cultured from patients in the sponge group.

Peak serum gentamicin levels ranged from 0.9 to 4.7 μg per milliliter (mean, 2.4) and decreased to a mean (±SD) of 0.4±0.4 μg per milliliter by 48 hours after sponge insertion (Fig. 1 in the Supplementary Appendix). The mean percent increase from baseline in the peak serum creatinine level was similar in the two groups (14.8±42.6% in the sponge group and 15.4±45.1% in the control group).

Eighteen patients required reexploration of the surgical wound: 11 patients in the sponge group and 7 patients in the control group. Exclusion of data from these patients from the primary analysis did not change the overall results (with a rate of adjudicated surgical-site infection of 29.4% in the sponge group vs. 21.4% in the control group, P=0.03). Six patients had died by day 60 (1 patient in the sponge group and 5 patients in the control group). No significant differences were found between the two groups regarding serious adverse events (Table 3 in the Supplementary Appendix).

Given the increase in surgical-site infection observed with the gentamicin–collagen sponge, a post hoc analysis was performed to investigate a possible mechanism for this effect. We speculated that the presence of sponge mass (assuming two sponges were placed) may have been a mechanical barrier to early wound healing that promoted infection. However, no clear association was seen between surgical-site infection and incision length, waist circumference, or body-mass index according to study group (results not shown). In addition, there was no overt difference in the degree of wound healing between the two groups at 30 or 60 days, on the basis of data from a structured patient questionnaire (Table 4 in the Supplementary Appendix).

DISCUSSION

The gentamicin–collagen sponge, developed to deliver a high local and wound concentration of gentamicin, has undergone testing throughout northern Europe. For example, a single-center, nonblinded study involving 221 patients undergoing colorectal surgery showed a 70% relative reduction of the incidence of surgical-site infection with the use of the sponge (18.4%, vs. 5.6% with no sponge; P<0.01).[6] These results served as strong preliminary data for our trial. However, the results of our large, randomized clinical trial showed that use of the sponge, as compared with no sponge, did not reduce the incidence of surgical-site infection in patients undergoing colorectal surgery. Contrary to initial expectations, patients randomly assigned to undergo sponge placement, as compared with those who did not undergo sponge placement, had a higher incidence of surgical-site infection, were more likely to visit an emergency room or surgical office for a wound-related sign or symptom, and more frequently underwent rehospitalization for surgical-site infection. These results raise important new questions about the best method for reducing the risk of this important complication, which still affects about one in five patients undergoing colorectal surgery, despite skin decontamination and administration of systemic antibiotics.[3-7]

Our data do not allow us to identify with certainty the cause of the lack of efficacy we observed. However, we can speculate that several factors may have been operational. First, though the microorganisms cultured from in-

Table 3. Surgical-Site Infection (SSI) and Other Postoperative End Points through Postoperative Day 60, According to Study Group.*

Characteristic	Gentamicin–Collagen Sponge (N=300)	Control (N=302)	P Value
Intention-to-treat analysis			
SSI — no. of patients (%)			
Any (primary end point)	90 (30.0)	63 (20.9)	0.01
Surgically treated	71 (23.7)	49 (16.2)	0.02
Superficial	61 (20.3)	41 (13.6)	0.03
Deep	25 (8.3)	18 (6.0)	0.26
Organ space	4 (1.3)	4 (1.3)	1.00
ASEPSIS score†			0.17
Median	0.0	0.0	
IQR	0.0–10.0	0.0–4.0	
Rehospitalization for SSI — no. of patients (%)	21 (7.0)	13 (4.3)	0.15
Visit to ER or physician for wound-related sign or symptom — no. of patients/total no. (%)	57 (19.7)	31 (11.0)	0.004
Postoperative hospital length of stay — days	6.0 (5.0–8.0)	6.0 (4.0–8.0)	0.44
Median			
IQR			
	Gentamicin–Collagen Sponge (N=274)	**Control (N=292)**	
Per-protocol analysis			
SSI — no. of patients (%)			
Any (primary end point)	83 (30.3)	62 (21.2)	0.01
Surgically treated	68 (24.8)	48 (16.4)	0.01
Superficial	56 (20.4)	41 (14.0)	0.04
Deep	23 (8.4)	18 (6.2)	0.31
Organ space	4 (1.5)	3 (1.0)	0.72
ASEPSIS score†			0.19
Median	0.0	0.0	
IQR	0.0–10.0	0.0–5.0	
Rehospitalization for SSI — no. of patients (%)	20 (7.3)	12 (4.1)	0.10
Visit to ER or physician for wound-related sign or symptom — no. of patients/total no. (%)	53/265 (20.0)	30/272 (11.0)	0.004
Postoperative hospital length of stay — days			0.48
Median	6.0	6.0	
IQR	5.0–8.0	4.0–8.0	

* ER denotes emergency room, and IQR interquartile range.
† The ASEPSIS score reflects nine variables related to the infection, including use of antibiotics, drainage of pus under local anesthesia, wound débridement under general anesthesia, isolation of bacteria, prolonged postoperative hospitalization, and findings on daily examination of the wound. The minimum score is 0, and there is no theoretical maximum score; higher scores indicate a worse infection. The mean (±SD) score was 6.1±10.4 in the sponge group and 5.2±11.0 in the control group in the intention-to-treat population and 6.0±10.2 and 5.3±11.1, respectively, in the per-protocol population.

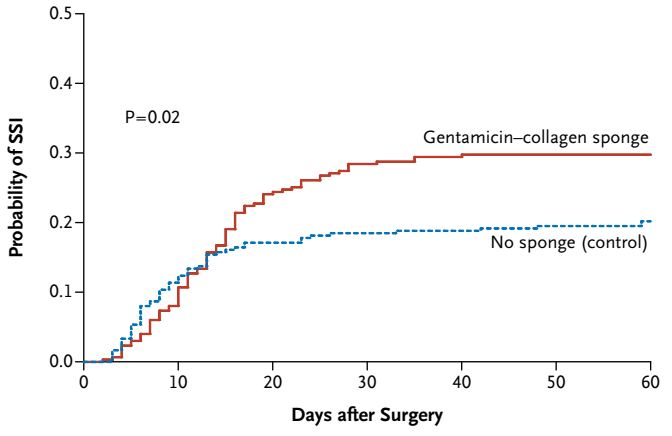

Figure 2. Kaplan–Meier Estimates of the Number of Days from Surgery to Surgical-Site Infection (SSI) within the 60-Day Postoperative Period, According to Study Group.

fected surgical wounds were similar in distribution between the two study groups (Table 1 in the Supplementary Appendix), cultures from the sponge group contained significantly more resistant bacteria than cultures from the control group. These findings may be partly explained by the results of the time-kill testing (which measures the antimicrobial activity of a drug) independently performed by the sponsor with doses of 100 μg and 300 μg of gentamicin sulfate per milliliter (Prior D: personal communication). Regrowth of *S. aureus*, coagulase-negative staphylococci, and enterococcus was found at 24 hours. These results are consistent with the conclusion by Tam and colleagues[20] that gentamicin should be administered every 8 hours to eliminate staphylococci and enterococci, in contrast to administration every 24 hours, which is effective against gram-negative bacilli. Second, gentamicin may elute too rapidly to increase the efficacy of systemic preoperative antibiotics. In support of this hypothesis are data showing low wound and local levels of gentamicin 12 hours after sponge insertion.[21] We found what appeared to be a transient early benefit of the sponge (Fig. 2), with a subsequent reversal in that effect, which may be consistent with the failure of the sponge to provide a sustained local level of gentamicin. A sponge with depleted antibiotic levels could harbor bacteria and thereby increase the risk of infection. Third, the collagen used to construct the sponges we used could have stimulated a deleterious local effect. An additional possibility is that the collagen may have been a mechanical barrier to rapid and effective closure of the wound, thus providing additional time for bacterial penetration to occur. Arguing against this hypothesis is the fact that our post hoc analyses showed no clear association between treatment effect and wound length or surrogates for wound depth (waist circumference and body-mass index).

If the sponge is not effective, why did results of an earlier study by Rutten and Nijhuis[6] suggest such a strong treatment benefit? In the previous study, the duration of follow-up was not reported; duration could be a factor, since evidence of harm became apparent in our study only 3 weeks after surgery. In addition, the previous study used a lower dose of gentamicin (one sponge containing 130 mg of gentamicin) than was used in our study (two sponges, each containing 130 mg of gentamicin). However, it is unclear why our use of a higher dose of gentamicin would yield such different results, unless harm was mediated by a mechanical effect of the sponge. An important difference between the study by Rutten and Nijhuis and ours is that they did not use several quality-control measures (e.g., verification of data from on-site monitoring and source documents, central adjudication of end points by an independent committee that was unaware of the group assignments, and the inclusion of a large number of surgical sites [1, vs. 39 in our study] and patients). The discrepancy in results may be related to the fact that findings from positive single-center trials are often not confirmed in larger multicenter trials.[22] Furthermore, differences among races and ethnic groups and among regions may have resulted in the different results between our U.S.-based trial and previous studies.[23]

A limitation of our trial is that it was designed to study the prevention of infection, so its results cannot be used to address whether the sponge is effective for the treatment of infection.[13] Another limitation of our trial is that it did not address the efficacy of sponge placement below the fascia.

In conclusion, our large, multicenter trial shows that the gentamicin–collagen sponge is not effective at preventing surgical-site infection

in patients undergoing colorectal surgery and, as compared with the placement of no sponges, appears to result in significantly more surgical-site infections.

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APPENDIX

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