ONLINE FIRST

Evaluating an Evidence-Based Bundle for Preventing Surgical Site Infection

A Randomized Trial

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Objective: To determine if an evidence-based practice bundle would result in a significantly lower rate of surgical site infections (SSIs) when compared with standard practice.

Design: Single-institution, randomized controlled trial with blinded assessment of main outcome. The trial opened in April 2007 and was closed in January 2010.

Setting: Veterans Administration teaching hospital.

Patients: Patients who required elective transabdominal colorectal surgery were eligible. A total of 241 subjects were approached, 211 subjects were randomly allocated to 1 of 2 interventions, and 197 were included in an intention-to-treat analysis.

Interventions: Subjects received either a combination of 5 evidenced-based practices (extended arm) or were treated according to our current practice (standard arm). The interventions in the extended arm included (1) omission of mechanical bowel preparation; (2) preoperative and intraoperative warming; (3) supplemental oxygen during and immediately after surgery; (4) intraoperative intravenous fluid restriction; and (5) use of a surgical wound protector.

Main Outcome Measure: Overall SSI rate at 30 days assessed by blinded infection control coordinators using standardized definitions.

Results: The overall rate of SSI was 45% in the extended arm of the study and 24% in the standard arm ($P=.003$). Most of the increased number of infections in the extended arm were superficial incisional SSIs (36% extended arm vs 19% standard arm; $P=.004$). Multivariate analysis suggested that allocation to the extended arm of the trial conferred a 2.49-fold risk (95% confidence interval, 1.36-4.56; $P=.003$) independent of other factors traditionally associated with SSI.

Conclusions: An evidence-based intervention bundle did not reduce SSIs. The bundling of interventions, even when the constituent interventions have been individually tested, does not have a predictable effect on outcome. Formal testing of bundled approaches should occur prior to implementation.

Trial Registration: clinicaltrials.gov Identifier: NCT00953784

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SURGICAL SITE INFECTIONS (SSIs) are among the most common postoperative complications in patients who have colorectal operations. The occurrence of an SSI results in reduced quality of life, increased hospital length of stay, increased likelihood of mortality, and markedly increased cost.[1-4] Therefore, identifying and implementing evidence-based strategies designed to minimize SSI is an important clinical goal. Prior research has focused mainly on antibiotic choice and timing[5,6] and improving these processes[7]; however, a number of adjunctive measures have also been individually evaluated in high-risk populations (including patients who have colorectal surgery) and have shown promise in reducing SSI. These adjunctive measures include (1) omission of mechanical bowel preparation[8]; (2) preoperative and intraoperative patient warming[9,10]; (3) the use of an increased concentration of inspired oxygen during and immediately after the procedures' conclusion[11]; (4) limiting intraoperative intravenous fluid volumes[12]; and (5) the use of wound barriers to protect the surgical wound from contamination during the procedure[13] (**Table 1**). De-

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Table 1. Evidence-Based Interventions That Reduce Surgical Site Infections

Intervention	Trial Type; Subjects	Study Arms	Outcome
Omission of mechanical bowel preparation			
Guenaga et al, 2009[14]	Updated from 2006 meta-analysis, now including 14 RCTs; >4000 subjects	Mechanical preparation vs no preparation	Nonsignificant trend toward fewer anastomotic leaks and a lower number of wound infections among subjects who did not have mechanical preparation
Guenaga et al, 2006[8]	Meta-analysis including 9 randomized trials; 1592 subjects had elective colorectal surgery	Mechanical preparation vs no preparation	Significantly fewer anastomotic leaks (3.2% vs 6.2%; OR, 2.03; 95% CI, 1.27-3.26; *P*=.003) and trend toward decreased number of wound infections (5.4% vs 7.4% Peto OR, 1.46; 95% CI, 0.97-2.18; *P*=.09)
Perioperative supplemental oxygen			
Qadan et al, 2009[11]	Meta-analysis of 5 RCTs; 3001 subjects: 3 trials included subjects who had elective colorectal surgeries, 1 major elective abdominal surgery, and 1 noncardiothoracic surgery lasting more than 2 h.	80% FIO_2 vs 30%-35% FIO_2 during operation and for variable periods postoperatively	Infection rate was 9% in those treated with 80% FIO_2 and 12% in those maintained with lower FIO_2 (RR, 0.742; 95% CI, 0.6-0.92; *P*=.006)
Preoperative and intraoperative warming			
Kurz et al, 1996[9]	RCT; 200 subjects had colorectal surgery	Intraoperative fluid warming and forced air heating of torso vs standard thermal care	Infection rate was lower in subjects who received intraoperative warming (6% vs 19%; *P*=.009)
Melling et al, 2001[10]	RCT; 421 subjects had clean surgeries (breast, varicose veins, or hernia)	3-arm study: standard care vs systemic preoperative and intraoperative warming vs local preoperative and systemic intraoperative warming	Two groups where preoperative, and intraoperative warming used when combined had significantly fewer infections than standard care (5% vs 14%; *P*=.001)
Reduction of intraoperative intravenous fluids			
Brandstrup et al, 2003[12]	RCT; 172 subjects had elective colorectal resections	Restricted intraoperative fluid regimen vs standard fluid regimen	Superficial wound infection, hematoma, or dehiscence was reduced in subjects receiving restricted fluid regimen (13% vs 25%; *P*=.03)
Use of wound barriers			
Sookhai et al, 1999[13]	RCT; 352 subjects had transabdominal surgery for gastrointestinal disease	Impervious wound edge protector vs no wound edge protector	Fewer infections occurred in the group in which wound edge protector was used (13% vs 29%; OR, 0.31; 95% CI, 0.16-0.60)

Abbreviations: CI, confidence interval; FIO_2, fraction of inspired oxygen; OR, odds ratio; RCTs, randomized controlled trials; RR, relative risk.

spite the evidence supporting these measures, most have not been widely adopted to clinical practice. Furthermore, the effect on SSI rate that these interventions may have when used as a bundled intervention has not been defined.

The purpose of this study was to test the hypothesis that a series of evidence-based interventions not currently in widespread use, incorporated as a single bundle, would significantly decrease overall SSI rate for patients who have elective colorectal surgery.

METHODS

This institutional review board–approved, nationally registered (NCT00953784), prospective, randomized clinical trial was designed to enroll patients who were having elective transabdominal colorectal procedures at a Veterans Administration teaching hospital. Both subjects undergoing laparoscopic and open procedures were eligible, as well as patients undergoing diverting or bypass procedures during which the colon or rectum required division or resection. This included the surgical creation or reversal of a colostomy. Patients undergoing emergency operations, transrectal procedures, or procedures involving only the small bowel or appendix were excluded from the study. Potential subjects were approached concerning the trial by the study coordinator. Subjects meeting eligibility criteria signed written consent and then were randomized. Randomization was by a block method (computer generated, 50 subjects per block; generated by principal investigator, T.A.). The randomization sequence was concealed prior to subject assignment by the study coordinator. Subjects were allocated 1 to 1 between the intervention (extended) and control (standard) arms of this study.

EXTENDED ARM INTERVENTION

A review of the literature was conducted that focused on evidence-based measures that could be expected to reduce SSI and could be instituted in our practice setting. We identified evidence-based support (1 or more randomized controlled trial) for (1) omission of mechanical bowel preparation[8]; (2) use of preoperative and intraoperative warming designed to maintain normothermia[9,10]; (3) maintenance of increased concentration of inspired oxygen during and immediately after surgery[11]; (4) reduction of intravenous fluids during the operation[12]; and (5) the use of wound edge protection.[13] We theorized that incorporation of these interventions as a bundle would reduce

SSIs for subjects undergoing elective colorectal surgery. These measures taken together were designated as the extended arm of the study.

Subjects assigned to the extended arm of the trial did not receive either mechanical bowel preparation or oral antibiotics. (Subjects in both arms of the trial received a clear liquid diet for the calendar day prior to their operation and phosphosoda enemas if they were having operations involving the colon distal to the splenic flexure.) Preoperative warming was accomplished by placement of a forced-air heating blanket on the torso of the subject while in the surgical holding area. Once in the operating room, a conductive heating blanket was used beneath the subject in addition to the forced air unit. Warmed fluids were not used. Subjects received an increased concentration of inspired oxygen (80%) from the point of intubation until 2 hours after surgery. After extubation, subjects were given 80% face-mask oxygen. Restriction of intraoperative, intravenous fluid administration was accomplished according to an algorithm designed to favor early colloid administration compared with crystalloid. The final intervention was placement of a plastic wound edge protection device in the incision once the peritoneal cavity was entered.

STANDARD ARM INTERVENTION

The standard arm of this trial consisted of our current practices. These included mechanical bowel preparation with oral antibiotics, intraoperative forced air warming, maintenance of physiologic concentration of inspired oxygen after endotracheal intubation (target fraction of inspired oxygen, 30%), intravenous fluid delivered at the discretion of the anesthesiologist, and no wound edge protectors.

Both arms received intravenous antibiotics prior to the surgical incision according to Surgical Care Improvement Project guidelines. After approximately 1 year, the preferred prophylactic antibiotic was switched from cefoxitin to ertapenem based on evidence from a randomized controlled trial.[15]

Infections were classified according to their location relative to the surgical incision. Infections occurring at or above the fascia were classified as superficial incisional infections. Infections occurring below the fascia were designated as organ/space infections. The Center for Disease Control and Prevention criteria were applied to define infections in these locations.[16] Multiple sites of infection in 1 subject were counted as a single occurrence. Subjects sustaining both superficial incisional infections and organ/space infections were counted as organ/space infections. The primary outcome measure for this trial was overall infection rate at 30 days after surgery (superficial incisional infection rate plus organ/space infection rate = overall SSI rate). Secondary outcome measures were the location of the SSI (superficial incisional or organ/space) and the time to identification of the infection. Subjects who completed the study were reviewed independently by blinded, certified infection control coordinators (K.H. and J.M.) who applied the study definitions to determine whether or not the subject had sustained an SSI, the timing of the identification of the SSI, and whether the SSI was a superficial incisional or organ/space in location. Evaluations were made by the infection control coordinators at the time of discharge and/or by electronic medical record review at 30 days after surgery.

DATA COLLECTION

Clinical and demographic information was collected including age, sex, indication for surgery, comorbid conditions, and preoperative laboratory values. Perioperative data collected included American Society of Anesthesiologists class, type and timing of intravenous prophylactic antibiotic given, skin preparation used, surgery performed, estimated level of contamination, wound classification, estimated blood loss, length of operation, blood work (including arterial blood gas), and type and volume of fluids given. In addition to the study end points, postoperative variables collected included subject temperature in the recovery unit and postoperative blood work. If an SSI was identified, data was collected on the timing from surgery and the location of the infection.

STATISTICAL ANALYSIS

We theorized that the bundled interventions included in the extended arm of this study would significantly reduce overall SSI. Based on a 50% reduction in overall SSI from the baseline rate (ie, 25% baseline to 12.5% after intervention) with α set at .05 and power of 0.9, it was estimated that 334 subjects were required (167 in each arm) and, planning for a 5% attrition rate, the total sample size estimated to complete the study was calculated to be 350 subjects.

The trial opened in April 2007, closed in January 2010, and successfully recruited 211 subjects. The study was terminated after a planned second interim analysis suggested that continuing the study to its originally designated sample size was unlikely to result in a significant improvement in overall SSI rate. Conditional power analysis of the study results at this junction suggested a less than 1% chance of identifying a statistically positive effect of the extended arm interventions on SSI rate if the study was taken to its original accrual goal.

The resulting database was analyzed in SPSS version 16.0 (SPSS Inc, Chicago, Illinois). All analyses were performed according to intention to treat. Univariate analysis of categorical variables was performed using Fisher exact or Pearson χ^2 tests. Normally distributed continuous variables were analyzed using the *t* test. Nonparametric variables were assessed using the Mann-Whitney *U* test. All *P* values were calculated with 2-tailed tests. All variables trending toward significance (ie, where $P \leq .20$) in univariate analysis were included in multivariate analysis. A forward stepwise logistic regression was used to identify factors associated with occurrence of SSI.

RESULTS

The trial enrolled and randomized a total of 211 subjects. A single subject withdrew consent; thus, 210 consenting, randomized subjects underwent a surgical procedure. Thirteen subjects were excluded from the analysis because they did not have incisions at risk for SSI (12 subjects had their surgical wounds left open to heal by secondary intention [7 standard and 5 extended] and a single subject had transrectal resection of a rectal tumor). Thus, there were 197 subjects considered in the intent-to-treat analysis(**Figure**).

All but 9 subjects were male, with an average age of 63.8 years (range, 30-87). Of the characteristics present prior to surgery, only serum albumin, creatinine, and hematocrit were significantly different between the standard and extended arms of the study. Although statistically significant, these values were not felt to represent clinically important imbalances. **Table 2** and **Table 3** summarize preoperative and perioperative variables for subjects in the extended and standard arms of the trial. Of note, operations performed on patients in the standard arm where shorter in duration than operations performed on patients in the extended arm (mean [SD],

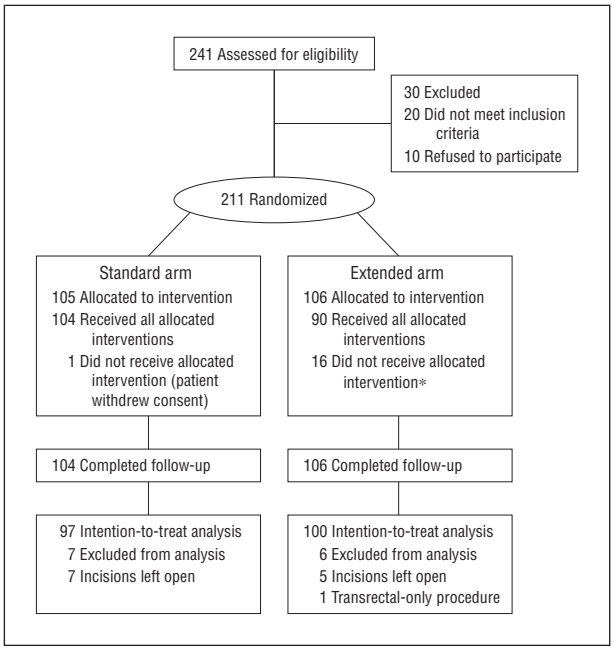

Figure. Subject enrollment and randomization. *Sixteen patients did not receive the allocated interventions in the extended arm: 6 had fluids in excess of protocol; 3, fraction of inspired oxygen of less than 80%; 3, no heating blanket; and 5, no wound protector; 105 of 106 received at least 4 of 5 interventions.

Table 2. Preoperative Variables for Subjects Randomized to Standard and Extended Study Arms

Variable	No./Total (%)		*P* Value[a]
	Standard Arm	Extended Arm	
Age, mean (SD), y	63.8 (10.8)	63.8 (7.5)	.99
DM	30/97 (31)	29/100 (29)	.88
Insulin-dependent DM	9/97 (9)	7/100 (7)	.61
CAD/MI/CABG	10/97 (10)	14/100 (14)	.52
COPD	13/97 (13)	17/100 (17)	.55
Current alcohol use	22/97 (23)	25/100 (25)	.74
Current tobacco use	29/97 (30)	27/100 (27)	.75
Body mass index, mean (SD)[b]	28.3 (5.7)	29.7 (6.1)	.11
Cancer or polyp as indication for surgery	76/97 (78)	81/100 (81)	.64
ASA risk class ≥3	75/97 (77)	81/100 (81)	.60
Hematocrit, mean (SD), %	38.3 (5.6)	40.1 (4.7)	.01
White blood cell count, mean (SD), No. in thousands/mm^3	7.2 (2.3)	7.6 (3.4)	.36
Serum albumin, mean (SD), g/dL	3870 (520)	4060 (390)	.004
Serum creatinine, mean (SD), mg/dL	0.97 (0.26)	1.05 (0.26)	.04

Abbreviations: ASA, American Society of Anesthesia; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD: chronic obstructive pulmonary disease; DM, diabetes mellitus; MI, myocardial infarction.

SI conversion factors: To convert hematocrit to proportion of 1.0, multiply by 0.01; albumin to grams per liter, multiply by 10; creatinine to micromoles per liter, multiply by 88.4.

[a] Categorical variables assessed by Fischer exact test. Continuous variables assessed by *t* test.

[b] Calculated as weight in kilograms divided by height in meters squared.

150 [101] vs 170 [92] minutes; $P = .03$). The most common indication for surgery was to remove an adenomatous polyp or colorectal malignancy (80% of operations overall). The most common surgical procedure performed was right hemicolectomy (39% of all operations) (**Table 4**). There was no mortality among the participants in this trial; therefore, 30 days of follow-up were completed for the entire cohort.

Table 3. Perioperative Variables for Subjects Randomized to Standard and Extended Study Arms

Variable	No./Total (%)		*P* Value[a]
	Standard Arm	Extended Arm	
Chlorhexidine/alcohol skin preparation	89/97 (92)	98/100 (98)	.06
SCIP-approved antibiotic	92/97 (95)	99/100 (99)	.12
Antibiotic delivery within 1 hour of incision	97/97 (100)	99/100 (99)	.98
Laparoscopic approach	18/97 (19)	27/100 (27)	.18
Operation below peritoneal reflection	21/97 (22)	29/100 (29)	.26
Surgical time, median (IQR), min	150 (101)	170 (92)	.03
Estimated blood loss, median (IQR), mL	100 (205)	120 (200)	.44
Total fluid given during operation, median (IQR), mL	2500 (1850)	1800 (1300)	.001
Crystalloid given during operation, median (IQR), mL	2250 (1500)	1500 (928)	<.001
Intraoperative blood transfusion	7/97 (7)	6/100 (6)	.78
Intraoperative Pao_2, mm Hg	139 (73)	261 (96)	<.001
Significant contamination	5/97 (5)	9/100 (9)	.41
Ostomy: creation, reversal, or revision	26/97 (27)	22/100 (22)	.51
Immediate postoperative temperature, °C	36.3 (0.44)	36.7 (0.47)	<.001
NHSN risk category			
0	25	19	.26
1	47	44	
2	24	34	
3	1	3	

Abbreviations: IQR, interquartile range; NHSN, National Healthcare Safety Network; SCIP: Surgical Care Improvement Project.

[a] Categorical variables assessed by Fisher exact test except for NHSN risk category; Pearson χ^2 used in this case. Continuous variables assessed by *t* test or, in the case of comparison of median surgical time, median estimated blood loss, median total fluids given during operation, and median crystalloid given during operation, the Mann-Whitney *U* test.

Table 4. Colorectal Procedures Performed by Study Assignment

Type of Surgery	Standard Arm (n=97)	Extended Arm (n=100)
Not colorectal	6	1
Right hemicolectomy	40	37
Left hemicolectomy	3	8
Sigmoid colectomy	12	14
Low anterior resection	12	17
Subtotal colectomy	4	4
Colostomy reversal	4	8
Abdominoperineal resection	3	6
Colostomy	7	1
Other	6	4

Overall compliance with Surgical Care Improvement Project guidelines for timing and appropriateness of antibiotic choice was 99% and 96%, respectively. There was not a significant difference in the rate of SSI based on the type of prophylactic antibiotic delivered. The overall rate of infection for subjects who received cefoxitin was 37% (32 of 87), and the rate for those receiving ertapenem as prophylaxis was 34% (34 of 99; $P=.76$). One hundred percent of subjects in both arms had their abdominal wall hair clipped. A chlorhexidine-alcohol preparation was used to clean the surgical site in 187 subjects (95%), and povidone-iodine was used in the remaining 10 subjects.

For subjects considered in the intention-to-treat analysis, complete compliance with all of the 5 interventions comprising the extended arm of the study was 84% (84 of 100). Ninety-nine percent of subjects received at least 4 of 5 of the extended interventions. Of the individual components of the extended arm interventions, compliance was most difficult for the fluid restriction algorithm (94%). Compliance with the other intended interventions was greater than 95% in each case. In 5 cases, subjects in the standard arm did not receive the intended mechanical bowel preparation; otherwise, there was no evidence of contamination of the standard arm with interventions intended for the extended arm.

Considering the intention-to-treat population, the overall rate of SSI identified was 35% (69 of 197). The intention-to-treat analysis identified a significantly higher rate of infection for subjects in the extended arm of the study (intention-to-treat rates: standard arm, 24% vs extended arm, 45%; $P=.003$). Most of this effect occurred owing to a difference in the rate of superficial incisional infections. The superficial incisional infection rate for subjects enrolled in the standard arm was 19%, whereas subjects enrolled in the extended arm had a rate of 36% ($P=.004$). The rate of organ/space infections was not significantly different between the 2 groups (standard arm, 6% vs extended arm, 9%; $P=.59$).

Univariate analysis failed to reveal any significant associations between overall SSI rate and a wide range of perioperative variables except for study arm assignment (**Table 5** and **Table 6**). Logistic regression considering factors trending toward significant association with overall SSI in univariate analysis (American Society of Anesthesiologists class ≥3, laparoscopic approach, operation below peritoneal reflection, operative time, and body mass index) and study arm assignment demonstrated that only allocation to the extended arm of this trial was independently associated with SSI. Allocation to the extended arm of this study conferred a 2.49-fold (95% confidence interval, 1.36-4.56; $P=.003$) increased risk of developing a SSI.

The median time to identification of infection was the ninth postoperative day (3-24 days). Although there was no difference in time to identification of infection between the 2 groups (median time to infection: standard arm, 9 days [range, 3-20]; extended arm, 10 days [range, 3-24]; $P=.71$), more infections were identified after discharge in the extended arm. A total of 32 (46%) infections were identified after the subject had been discharged from the hospital. In the extended arm, 51% of infections were identified after discharge and in the standard arm, 38% ($P=.006$).

Table 5. Associations Between Perioperative Variables and Overall Surgical Site Infection Rates Within Intention-to-Treat Population

Variable	No./Total (%): Overall SSI Rate in Population With Variable Present	No./Total (%): Overall SSI Rate in Population With Variable Absent	*P* Value[a]
Diabetes mellitus	19/59 (32)	50/138 (36)	.63
CAD/MI/CABG	7/24 (29)	62/173 (36)	.65
COPD	14/30 (47)	55/167 (33)	.15
Current alcohol consumption	19/47 (40)	50/150 (33)	.39
Current tobacco use	20/56 (36)	49/141 (35)	.89
Cancer or polyp as indication for surgery	55/157 (35)	14/40 (35)	.99
ASA class ≥ 3	59/156 (38)	10/41 (24)	.11
SCIP antibiotic guideline compliance	68/191 (36)	1/6 (17)	.67
Ostomy: creation, reversal, or revision	19/48 (40)	50/149 (34)	.49
Laparoscopic approach	20/45 (44)	49/152 (32)	.16
Operation below peritoneal reflection	22/50 (44)	47/147 (32)	.13
Extended study arm assignment	45/100 (45)	24/97 (25)	.004

Abbreviations: ASA, American Society of Anesthesia; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; SCIP, Surgical Care Improvement Project; SSI, surgical site infection.
[a] Fisher exact test.

COMMENT

Infections after colorectal surgery result in substantial morbidity and mortality. Despite greater awareness of the negative consequences of SSI and the widespread adoption of process measures directed at reducing SSIs, they remain stubbornly persistent. This study was designed to build on the process improvements already in place in an attempt to reduce SSI rates among subjects who have colorectal surgical procedures. A previous retrospective review of our practice identified an SSI rate of 24.5% for subjects who had colorectal operations despite careful adherence to prophylactic intravenous antibiotic recommendations.[17] Subsequent review of the available literature identified 5 additional evidenced-based practices that reduced SSI rates in subjects who had colorectal surgical procedures. While each of these practices had a modest ability to reduce SSI, we hypothesized that incorporating these strategies into a single treatment bundle would have a synergistic effect on reducing infection rates in colorectal surgery subjects. Not only did this prove to be false but, counterintuitively, the bundled intervention resulted in significantly more SSIs.

There are several limitations of the study that may explain this result. First, the design does not allow for the identification of the contribution of individual measures to the overall outcome. Thus, it is possible that 1 or more of the measures included in this study may, singly or in combination, have a favorable affect on SSIs. Although aware of this issue, we felt justified in designing

Table 6. Associations Between Perioperative Variables and Overall Surgical Site Infection Rates Within Intention-to-Treat Population

Variable	Mean (SD) If Infection Absent	Mean (SD) If Infection Present	*P* Value[a]
Body mass index[b]	28.6 (5.7)	29.9 (6.1)	.14
Preoperative hematocrit, %	39.0 (5.3)	39.6 (5.2)	.46
Preoperative white blood cell count, No. in thousands/mm^3	7.3 (0.20)	7.7 (3.9)	.37
Preoperative serum albumin, g/dL	0.0039 (0.00051)	0.0040 (0.00040)	.25
Preoperative creatinine, mg/dL	1.0 (0.28)	0.98 (.24)	.14
Surgical time, minutes	170 (87)	193 (77)	.06
Estimated blood loss, mL	227 (448)	246 (222)	.70
Total fluid given during operation, mL	2412 (1616)	2664 (1733)	.32
Crystalloid given during operation, mL	2043 (1311)	2260 (1545)	.33
Intraoperative Pao_2, mm Hg	218 (111)	199 (96)	.26
Immediate postoperative temperature, °C	36.5 (0.50)	36.6 (0.50)	.17

Abbreviations: SSI, surgical site infection.
SI conversion factors: To convert albumin to grams per liter, multiply by 10; creatinine to micromoles per liter, multiply by 88.4.
[a] By *t* test.
[b] Calculated as weight in kilograms divided by height in meters squared.

a study in which multiple interventions were bundled in an attempt to improve an outcome because this closely resembles current practices in the era of process improvements and performance measures.

Second, 2 additional studies have been published since this trial was begun that call into question the utility of some of the measures included in the extended arm of this study. An updated Cochrane review and the report of the PROXI trial have suggested that omission of bowel preparation and the use of supplemental oxygen may not exert as positive an influence on SSI as was originally believed.[14,18] A further limitation is the methodology used to define the main outcome. Although this was intended to be prospective and blinded, medical record review at 30 days was often used to define the main outcome; thus, some degree of observer bias was possible. It is also notable that several risk factors that have been traditionally associated with SSI (eg, body mass index, operative time, and National Healthcare Safety Network category) were imbalanced in the 2 arms of this study, perhaps contributing to the observed results.

Finally, although the lack of mortality in this population suggests quality perioperative care, the overall rate of SSI identified in this study is higher than previously described and brings into question the generalizability of the results. The overall rate of infection was 36%, with almost 80% of the infections occurring within the surgical incision and nearly 50% of these identified after the subject was discharged from the hospital. This rate is likely a reflection of many factors including the broad inclusion criteria (for example, the present study included subjects with stomas, a population typically excluded from studies of SSI); the general lack of physiologic reserve of the population (80% were American Society of Anesthesiologists class 3 or 4); complete subject follow-up allowing accurate capture of infections (especially the high number of infections occurring after hospital discharge); use of blinded evaluators; and rigid application of unambiguous definitions of SSI. The effect of additional factors such as the teaching nature of our program, the specific sex and age distributions of our subject population, variations in surgical practice, and some of the imbalances in risk factors (For example, in the extended arm there were more subjects with NHSN risk scores of 2 and 3, longer operative times, and greater number of operations performed below the peritoneal reflection.) may also explain this result. It should be noted, however, that despite the high rate of SSI overall, the rate within the standard arm was identical to our previous article and similar to the rate reported in several recent publications.[15,17,19] Therefore, while the overall rate of infection reported in this study appears high, this is attributable to the bundled interventions in the extended-arm. We speculate that the higher-than-expected rate of infection among the subjects who received extended arm treatments is the result of unanticipated interactions between individual components that made up the extended arm of the trial. For example, perhaps increasing subject temperature coupled with reduced intraoperative fluids resulted in diminished blood flow and tissue oxygenation within the peri-incisional tissues, reducing immune surveillance and facilitating bacterial growth. It is also possible that the degree of diligence required to successfully adhere to multiple interventions diverted surgeon attention from the technical aspects of the procedures that are more important in limiting SSI.

Regardless of the specific reasons for the increased rate of infection in the extended arm of this study, these interventions seem to be ineffective when used as a bundle. However, we believe the more important implication of this study pertains to the common practice of adopting bundled interventions to improve outcome. The assumption that single measures identified by randomized controlled trials can be grouped into a bundle and effect an outcome in a predictable and positive fashion is not supported by the findings of this study. This, in turn, suggests a more cautious approach when it comes to adopting bundled measures that have not formally been tested in the target population.

In summary, we elected to take a scientifically unconventional but clinically common approach to the problem of SSI after colorectal surgery and attempted to show that an intervention bundle consisting of evidence-supported practices would positively affect SSI. The results of study demonstrated, however, that the bundle of interventions used (omission of mechanical bowel preparation, preoperative and intraoperative warming designed to maintain normothermia, increased inspired oxygen during and immediately after surgery, limiting fluid administration during surgery, and the use of surgical wound protectors) increased the risk of SSI 2.49-fold when compared with our standard practice. The use of this

bundle of interventions is not warranted and raises significant questions concerning the general wisdom of adopting bundled approaches in other clinical situations to minimize negative outcomes when these bundles have not formally been tested in controlled clinical trials.

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Author Contributions: Dr Anthony had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Anthony, Lenkovsky, and Huerta. *Acquisition of data:* Anthony, Murray, Sum-Ping, Lenkovsky, Vornik, Parker, McFarlin, and Hartless. *Analysis and interpretation of data:* Anthony, Sum-Ping, McFarlin, Hartless, and Huerta. *Drafting of the manuscript:* Anthony, Parker, Hartless, and Huerta. *Critical revision of the manuscript for important intellectual content:* Anthony, Murray, Sum-Ping, Lenkovsky, Vornik, McFarlin, and Huerta. *Statistical analysis:* McFarlin, and Hartless. *Obtained funding: Administrative, technical, and material support:* Anthony, Murray, Parker, and Huerta. *Study supervision:* Anthony, Murray, Sum-Ping, and Lenkovsky.
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