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Oversight

The full protocol was initially approved by the University of Virginia Institutional Review Board (IRB), the Data and Safety Monitoring Board, and the assigned National Institute of Health Program Officer (Sara Dunsmore, PhD). Local IRB approval was required prior to initiation of the study at the individual sites. The independent four person data safety and monitoring board (Chair: Andrew F. Shorr, MD, Washington, DC; William D. Dupont, PhD, Nashville, TN; Kevin P. High, MD, Winston-Salem, NC; John C. Magee, MD, Ann Arbor, MI) reviewed the initial protocol, six-monthly cumulative safety data, a midpoint interim analysis, and the final data and manuscript, granting approval for continuation at each step. The first author wrote the first and subsequent drafts of the manuscript with approval of the local investigators. All the authors of the paper vouch for the accuracy of the data and confirm that the contents of the article adhere to the specifications of the protocol.

Table S1. Baseline Patient and Index Infection Characteristics

<u>Demographics and Comorbidities</u>	Control Group (N=260)	Experimental Group (N=258)
Age - yr	52.2 ± 1.0	52.2 ± 1.0
Male sex - no. (%)	145 (55.8)	144 (55.8)
Race - no. (%) [†]		
White	208 (80.0)	196 (76.0)
Black	43 (16.5)	51 (19.8)
Asian	5 (1.9)	6 (2.3)
American Indian/ Alaskan Native	2 (0.8)	1 (0.4)
Other	2 (0.8)	4 (1.6)
Hispanic - no. (%) [†]	20 (7.8)	15 (5.8)
Body mass index (kg/m ²)	28.4 ± 0.5	29.5 ± 0.6
<u>Classification of index infection - no. (%)</u>		
Community-acquired	166 (63.8)	155 (60.0)
Healthcare-associated	94 (36.2)	102 (40.0)
Hospital-acquired	31 (11.9)	38 (14.7)
Prior red cell transfusion - no. (%)	22 (8.5)	21 (8.1)
Any major medical co-morbidity - no. (%)	135 (51.9)	144 (55.8)
<u>Medical history - no. (%)</u>		
Diabetes mellitus	41 (15.8)	37 (14.3)
Cardiac disease	37 (14.2)	33 (12.8)
Malignancy	28 (10.8)	31 (12.0)
Inflammatory bowel disease	24 (9.2)	29 (11.2)
Pulmonary disease	23 (8.8)	29 (11.2)
Chronic corticosteroid use	16 (6.2)	15 (5.8)
Cerebrovascular disease	12 (4.6)	7 (2.7)
Peripheral vascular disease	10 (3.8)	16 (6.2)
Cirrhosis	10 (3.8)	7 (2.7)
<u>Characteristics of Index Infection</u>		
APACHE II score	9.9 ± 0.4	10.3 ± 0.4
Maximum white blood cell count - k/ml	15.6 ± 0.4	17.1 ± 0.7
Maximum temperature - °C	37.8 ± 0.1	37.7 ± 0.1
<u>Organ of origin - no. (%)</u>		
Colon or rectum	80 (30.8)	97 (37.6)
Appendix	34 (13.3)	39 (15.1)
Small bowel	31 (11.9)	42 (16.3)
Biliary tree including gall bladder	31 (11.9)	25 (9.7)

Stomach	20 (7.7)	11 (4.3)
Liver	13 (5.0)	5 (1.9)
Pancreas	12 (4.6)	4 (1.6)
Duodenum	9 (3.5)	14 (5.4)
Abdominal wall	5 (1.9)	8 (3.1)
Esophagus	2 (0.8)	1 (0.4)
Other/multiple/unknown	23 (8.8)	11 (4.3)
Source control procedure – no. (%)		
Percutaneous drainage	86 (33.1)	86 (33.3)
Resection and anastomosis or closure	69 (26.5)	64 (24.8)
Surgical drainage only	55 (21.1)	54 (20.9)
Resection and proximal diversion	27 (10.4)	37 (14.3)
Simple closure	20 (7.7)	12 (4.7)
Surgical drainage and diversion	3 (1.2)	4 (1.6)
Management of wound – no. (%)		
Primary closure	87 (33.5)	72 (27.9)
None (percutaneous drainage)	86 (33.1)	86 (33.3)
Secondary intention	47 (18.1)	51 (19.8)
Delayed primary closure	24 (9.2)	32 (12.4)
Close port sites only	16 (6.2)	16 (6.2)
Most commonly isolated pathogens – no. (%)		
<i>Escherichia coli</i>	46 (17.7)	33 (12.8)
<i>Streptococcus</i> species	42 (16.2)	37 (14.3)
<i>Bacteroides</i> species	29 (11.2)	40 (15.5)
<i>Enterococcus</i> species	29 (11.2)	23 (8.9)
<i>Candida albicans</i>	23 (11.2)	18 (7.0)
No culture obtained	56 (21.5)	51 (19.8)
Most commonly used antimicrobials – no. (%)		
Piperacillin-tazobactam	144 (55.4)	139 (53.9)
Metronidazole	83 (31.9)	80 (31.0)
Ciprofloxacin	73 (28.1)	68 (26.4)
Vancomycin	57 (21.9)	74 (28.7)
Fluconazole	40 (15.4)	36 (14.0)
Ertapenem	29 (11.2)	24 (9.3)

* Values listed are Mean ± SEM or No. (%).

† Race and ethnicity were designated by the subject or surrogate.

No differences between groups were significant at the p <0.05 level.

Table S2. Outcomes in key subgroups.

Subgroup	No.	Days of antimicrobials Median/IQR	Surgical site infections no. (%)	Recurrent intra-abdominal infections no. (%)	Deaths no. (%)	Surgical site infection, recurrent intra-abdominal infection, or death no. (%)	Difference for composite outcome p^{\ddagger}
Protocol fulfilled							
Control	189	7 (5-10)*	16 (8.5%)	18 (9.5%)	1 (0.5%)	33 (17.5%)	
Experimental	211	4 (4-5)	14 (6.7%)	24 (11.4%)	2 (1.0%)	37 (17.6%)	0.97
Protocol not fulfilled							
Control	71	11 (7-17)	7 (9.9%)	18 (25.4%)	1 (1.4%)	25 (35.2%)	
Experimental	47	11 (8-19)	3 (6.4%)	16 (34.0%)	1 (2.1%)	18 (38.3%)	0.88
APACHE II \geq 10							
Control	120	8 (5-10)*	14 (11.7%)	23 (19.2%)	1 (0.8%)	36 (30.0%)	
Experimental	122	4 (4-5)	7 (5.7%)	20 (16.4%)	2 (1.6%)	27 (22.1%)	0.21
Healthcare-associated							
Control	94	8 (5-10)*	9 (9.6%)	14 (14.9%)	0 (0.0%)	22 (23.4%)	
Experimental	102	4 (4-5)	6 (5.9%)	17 (16.7%)	2 (2.0%)	23 (22.5%)	0.87
Percutaneous drainage							
Control	86	8 (5-10)*	-	14 (16.3%)	0 (0.0%)	14 (16.3%)	
Experimental	86	4 (4-5)	-	14 (16.3%)	0 (0.0%)	14 (16.3%)	1.0
Surgical drainage							
Control	174	8 (5-10)*	23 (13.2%)	22 (12.6%)	2 (1.1%)	44 (25.3%)	
Experimental	171	4 (4-5)	17 (9.9%)	26 (15.2%)	3 (1.8)	41 (24.0%)	0.87
Appendiceal source							

Control	34	8 (5-10)†	1 (2.9%)	6 (17.6%)	0 (0.0%)	7 (20.6%)	
Experimental	39	5 (4-6)	2 (5.1%)	7 (17.9%)	0 (0.0%)	9 (23.1%)	0.80
Non- appendiceal source							
Control	226	8 (5-10)*	22 (9.7%)	30 (13.3%)	2 (0.9%)	51 (22.6%)	
Experimental	218	4 (4-5)	15 (6.9%)	33 (15.1%)	3 (1.4%)	46 (21.1%)	0.80

* p <0.01 for difference between clinical response and four day groups by Wilcoxon test

† p <0.05 for difference between clinical response and four day groups by Wilcoxon test

‡ Difference between clinical response and four day groups by Chi-square test with Yates' correction

None of the individual outcomes were different between groups at the 0.05 significance level

Table S3. Logistic regression analysis of predictors of the primary composite outcome.

Variable	Wald Chi-square	Odds Ratio*	P Value
Experimental group versus control group	0.049	0.95 (0.63-1.45)	0.82
Age in years	1.12	0.99 (0.98-1.01)	0.29
Female versus male	0.021	0.97 (0.63-1.49)	0.86
APACHEII per point	6.68	1.05 (1.01-1.09)	0.0098
Percutaneous drainage versus surgical drainage	1.98	0.69 (0.42-1.15)	0.16
Site = appendix versus non-appendix	0.026	1.05 (0.57-1.96)	0.87
Healthcare-acquired versus community-acquired infection	1.07	0.75 (0.43-1.30)	0.30

* Odds ratio with 95% confidence interval

C-statistic = 0.603, Hosmer-Lemeshow goodness-of-fit test = 0.729