APPENDIX E1

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APPENDIX E2

Radiology Methods

Imaging studies were first interpreted by an on-call attending radiologist, which was the interpretation used to decide patient eligibility. Subsequently, imaging was reviewed by a full-time radiologist who recorded findings on a standardized form.

Computed tomography (CT) was performed on a multi-detector row CT scanner (Somatom Definition Flash 64 [Siemens Healthcare, Forcheim, Germany]), using a standard imaging protocol: 120 kVp, 24 x 1.2-mm collimation, pitch of 1, 90-second delay after intravenous contrast administration at 3 mL/sec (Omnipaque 350 mgl/mL [GE Healthcare, Little Chalfont, UK]). Tube current modulation (CARE kv) was used on each case with a quality reference mAs setting of 250, which corresponds to a default $CTDI_{vol}$ of 16 mGy. Pediatric CT protocols were utilized for patients less than 18 years of age. Intravenous contrast agent was administered unless contraindicated by decreased glomerular filtration rate less than 30 ml/min or history of severe allergic reaction to iodinated contrast. Enteric contrast material was not administered according to our standard protocol for abdominal CT studies performed in the emergency department. Images were reconstructed in the axial plane at 5-mm and in the coronal plane at 2-mm section thickness, and interpreted on a picture archiving and communication system (PACS) station by a staff radiologist. CT imaging findings were described/dictated using standardized definitions (see below). Ultrasound was performed by using the graded compression technique with a curved 3.5 to 5.0-MHz array and linear 10-MHz array transducers.

We used 4 methods to decrease the radiation dose. We decreased the radiation dose by: (1) Performing a CT abdomen and pelvis with IV contrast only and eliminated the non-contrast CT liver part of the study, which accounts for 40% to 60% of the total radiation dose of a CT of the abdomen and pelvis with and without contrast; (2) Using tube current (mAs) modulation software Siemens CARE Dose4D in acquisition of CT studies, which adjusts the tube current (mAs) based on the size and shape of the patient; (3) Using tube voltage (kV) modulation software Siemens CARE kV, which adjusts the tube voltage based on the patient's topogram and the selected examination protocol; and (4) Providing CT coronal reformations obtained at 2-mm intervals for all studies, which has been shown to improve confidence in visualization of the appendix and in diagnosis or exclusion of appendicitis, avoiding potential interpretations of equivocal for appendicitis, which may lead to repeat imaging and increased radiation dose.[1]

CT studies were reviewed for the following: appendiceal diameter (maximum wall-to-wall); hyperemia (increased appendiceal wall enhancement relative to adjacent bowel wall); periappendiceal fluid, non-physiologic; periappendiceal stranding, presence, and degree (mild [perceptible haziness or increased attenuation in the mesoappendix or retroperitoneal fat], moderate [significantly increased attenuation and/or stranding of the mesenteric fat at the right side of the pelvis], and severe [extensively increased attenuation and/or stranding of the mesenteric fat at the right side of the pelvis and/or lower part of the abdomen]); phlegmon (diffuse and substantial inflammation of the peri-appendiceal fat with ill-defined fluid, with or without air collections); abscess (discrete fluid, with or without an air collection, with well-defined wall); appendicolith; extraluminal (free air); and mucocele (dilated appendix >15 mm without signs of appendicitis, ie, hyperemia, fat stranding, free fluid, free air, peri-appendiceal phlegmon, or abscess).

Ultrasound studies were interpreted for the following: visualization of the appendix, appendiceal diameter, compressibility of the appendix, peri-appendiceal or right lower quadrant fluid collection, and appendicolith. Appendiceal diameter was measured from serosal to serosal surface while imaging the appendix in the transverse plane. Compressibility was defined as measurable change in the caliber of the lumen of the appendix. A fluid collection had a definable wall and mass effect. Appendicolith was defined as an echogenic, well-defined focus within the appendix with posterior acoustic shadowing.

In addition to recording diagnostic characteristics for each case, each reviewer provided an impression of one of the following: normal appendix, acute uncomplicated appendicitis, acute complicated appendicitis, and equivocal for appendicitis. For CT interpretation, an additional diagnostic option was equivocal for uncomplicated versus complicated appendicitis. The imaging criteria for the final

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diagnosis were derived from a review of literature and included those features previously reported to have diagnostic value.[2-9]

APPENDIX E3

Sample Size Calculation

The current operative approach to appendicitis is associated with serious adverse complications in approximately 3% of patients,[1,2] resulting in recovery without serious complications in 97% of cases. Existing trials demonstrate similar rates of recovery among patients treated with primary antibiotic therapy.[3] The rate of uneventful recovery among a relatively healthy population eligible for inclusion in this study is likely to be higher than that observed in the general population. Thus, assuming recovery rates without serious complications in 97% of cases for both treatment arms, and assuming a 5% limit of indifference, a noninferiority trial with a power of 95% and statistical significance of 5% could be completed with 662 patients (331 patients assigned to each arm). Assuming that 10% of patients are unable to complete the study (due to lack of follow-up, protocol violations, and other unforeseen events), the study may need to enroll as many as 736 patients. It has been suggested that pilot studies should include 30 patients or 3% of the sample size for the actual trial, whichever is greater.[4] Under this principle, our estimated sample size for the pilot study is 30 patients (4.5% of the projected sample).

Our limit of indifference of 5% comes from the following analysis. The potential for cost savings drives the use of antibiotics to treat acute uncomplicated appendicitis. Surgical treatment, including emergency department evaluation, physician fees, laboratory and imaging fees, and operating and hospital costs, currently approaches $8,000 per patient.[1,5,6] Primary treatment with antibiotics eliminates many hospital admissions and operation expenses, and reduces costs by 50% to $4,000 per case.[7] However, because primary treatment with antibiotics is associated with failure in up to 30% of cases,[3] the costs for treating patients who require surgical rescue is actually $500 greater than the cost of primary surgery.[7] This effect raises the overall costs of antibiotic treatment with surgical rescue to an average of $5,350 per patient, which still represents cost savings of $2,650 per case.

It is possible that initial cost-savings from the use of primary antibiotic treatment could be eroded through increased cost required to treat patients who experience major complications as a result of this treatment. The average cost of treating patients who experience a major complication following appendectomy is $38,000.[2] This is equivalent to the cost-savings that might be recognized through treating 14 patients with primary antibiotic therapy, and corresponds to a 7% increase in the rate of major complications. Consequently, primary treatment with antibiotic therapy with surgical rescue will present cost advantages provided the associated rate of major complications with this treatment does not exceed the major complication rate of primary surgical treatment by more than 7%.

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Table E1. Baseline characteristics of 30 participants with the diagnosis of acute uncomplicated appendicitis by treatment group.*

Characteristic	Appendectomy (n = 14)	Antibiotics-First (n = 16)
Age, median years (IQR, range)	36 (33-46; 24-65)	31 (25-40; 9-73)
Male sex	9 (64.3)	9 (56.3)
Race		
White	12 (85.7)	13 (81.3)
Black	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)
Hawaiian/Pacific Islander	0 (0.0)	1 (6.3)
American Indian/Alaska Native	0 (0.0)	0 (0.0)
Other	1 (7.1)	2 (12.5)
Unknown	1 (7.1)	0 (0.0)
Hispanic ethnicity	12 (85.7)	14 (87.5)
Comorbidities		
Diabetes	0 (0.0)	1 (6.3)
HIV	0 (0.0)	0 (0.0)
COPD	0 (0.0)	0 (0.0)
CHF	0 (0.0)	0 (0.0)
Cancer	0 (0.0)	0 (0.0)
Body mass index, median kg/m^2 (IQR; range)	28.0 (24.6-29.8; 21.0-31.8)	27.3 (25.1-33.0; 22.3-43.3)
Prior abdominal/pelvic surgery	3 (21.4)	3 (18.8)
Cholecystectomy	0 (0.0)	1 (6.3)
Colectomy	0 (0.0)	0 (0.0)
Hysterectomy	1 (7.1)	0 (0.0)
Exploratory laparotomy	0 (0.0)	0 (0.0)
Other	3 (21.4)	2 (12.5)
Symptoms		
Subjective fever	4 (28.6)	2 (12.5)
Measured fever	1 (7.1)	0 (0.0)
Anorexia	10 (71.4)	11 (68.8)
Nausea	13 (92.9)	12 (75.0)
Vomiting	11 (78.6)	8 (50.0)
Right lower quadrant pain	13 (92.9)	14 (87.5)
Duration of pain, median days (IQR; range)	1.0 (0.5- 3.0; 0.5-5.0)	1.0 (1.0-2.5; 0.5-5.0)
Severity of pain		
Mild	1 (7.1)	3 (19.8)
Moderate	6 (42.9)	11 (68.8)
Severe	7 (50.0)	2 (12.5)
Maximal pain prior 24 hours†, median (IQR; range)	10 (8-10; 5-10)	8 (8-10; 4-10)
Signs		
Localized rebound tenderness	10 (71.4)	8 (50.0)
Localized guarding	6 (42.9)	6 (37.5)
Triage pulse, median beats/min (IQR; range)	75 (70-82; 62-124)	78 (68-95; 56-107)
Triage SBP, median mm Hg (IQR; range)	112 (107-125; 87-135)	121 (107-131; 99-154)
Triage DBP, median mm Hg (IQR; range)	65 (62-72; 53-78)	68 (58-77; 48-91)
Triage respirations, median beats/min (IQR; range)	17 (17-18; 16-20)	18 (17-18; 16-20)
Triage temperature, median °C (IQR; range)	36.9 (36.6-36.7; 36.5-38.1)	36.8 (36.7-37.2; 36.4-37.3)
Computed tomographic findings‡		
Appendicolith§	3 (21.4)	2 (12.5)
Appendiceal diameter, median mm (IQR; range)	9 (9-12; 7-8)	10 (9-12; 7-14)
Periappendiceal stranding		
None	0 (0.0)	2 (12.5)
Mild	7 (50.0)	11 (68.8)
Moderate	6 (42.9)	1 (6.3)
Severe	1 (7.1)	0 (0.0)
NA	0 (0.0)	1 (6.3)
Hyperemia		
Yes	14 (100.0)	11 (68.8)
No	0 (0.0)	4 (25.0)
NA	0 (0.0)	1 (6.3)

Table E1. Continued.

Characteristic	Appendectomy (n = 14)	Antibiotics-First (n = 16)
Periappendiceal fluid		
Yes	3 (21.4)	2 (12.5)
No	11 (78.6)	13 (81.3)
NA	0 (0.0)	1 (6.3)
Laboratory results		
WBC count, $x10^3/\mu L$, median (IQR; range)	15.3 (11.0-18.4; 8.1-23.1)	14.2 (11.3-17.0; 6.2-19.2)
Neutrophils, median % (IQR; range)	83.8 (81.7-89.2; 60.2-94.4)	82.7 (79.8-90.9; 49.8-92.9)
Lactate, median mmol/L (IQR; range)‖	1.0 (0.9-1.4; 0.6-1.6)	1.1 (0.9-1.5; 0.7-2.3)
CRP, median mg/L (IQR; range)‖	64.8 (42.6-101.6; 8.2-256.4)	25.9 (10.8-64.8; 3.8-202.6)
Alvarado score¶, median (IQR; range)	8 (7-9; 4-10)	8 (7-9; 4-10)
Received first parenteral antibiotic dose <6 hours prior to enrollment	4 (28.6)	5 (31.3)
Appendix pathology findings		
Normal	1 (7.1)	
Acute uncomplicated	9 (64.3)	
Suppurative and/or gangrenous	4 (28.6)	
Quality-of-life measures		
SF-12v2 Physical Component Score#, median (IQR; range)	52.0 (47.4-57.0; 25.4-61.4)	55.9 (54.4-57.1; 41.7-64.1)
SF-12v2 Mental Component Score#, median (IQR; range)	57.0 (41.9-61.2; 31.6-68.4)	49.4 (38.8-61.1; 35.5-62.1)

COPD, chronic obstructive pulmonary disease; *CHF*, congestive heart failure; *NA*, not available; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure.

*Data are presented as No. (%) unless otherwise indicated.

†Pain was rated on a scale of 0 to 10.

‡One pediatric participant randomized to antibiotics-first did not receive a CT scan, so results are only presented for the 15 adult participants who did.

§Radiographic identification of an appendicolith was initially an exclusion criterion but was later allowed (after 11 of 30 participants were enrolled) because of lack of consistent evidence of this being a risk factor for antibiotic failure.

‖Two participants in the appendectomy group were missing results for lactate and CRP.

¶The Alvarado score[28] consists of the following components (points): right lower quadrant tenderness (0/2); elevated temperature ($\geq$37.3°C or 99.1°F) (0/1); rebound tenderness (0/1); migration of pain to the right lower quadrant (0/1); anorexia (0/1); nausea or vomiting (0/1); leukocytosis >10,000 cells/μL (0/2); polymorphonuclear cells >75% (0/1).

#SF-12v2® Health Survey Acute version[24] (1-week recall) was utilized for adult (14 appendectomy and 15 antibiotic-first) participants to assess baseline quality of life prior to their appendicitis symptoms.

Table E2. Baseline characteristics of qualifying enrolled and nonenrolled patients with the diagnosis of acute uncomplicated appendicitis.*

Characteristic	Enrolled n=30	Non-Enrolled n=18
Median age, years (IQR, range)	33 (29-45; 9-73)	29 (21-35; 12-55)
Male sex	16 (60.0)	13 (72.2)
Race		
White	25 (83.3)	18 (100.0)
Black	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)
Hawaiian/Pacific Islander	1 (3.3)	0 (0.0)
American Indian/Alaska Native	0 (0.0)	0 (0.0)
Other	3 (10.0)	0 (0.0)
Unknown	1 (3.3)	0 (0.0)
Hispanic ethnicity	26 (86.7)	17 (94.4)
Symptoms		
Subjective fever	6 (20.0)	3 (16.7)
Anorexia	21 (68.8)	7 (38.9)
Nausea	25 (75.0)	14 (77.8)
Vomiting	19 (50.0)	8 (44.4)
Right lower quadrant pain	27 (87.5)	17 (94.4)
Duration of pain, median days (IQR; range)	1.0 (1.0-3.0; 0.5-5.0)	1.0 (1.0-1.5; 0.5-4.0)
Severity of pain		
Mild	4 (19.8)	2 (11.1)
Moderate	17 (68.8)	13 (72.2)
Severe	9 (12.5)	3 (16.7)
Signs		
Triage temperature, median °C (IQR; range)	36.9 (36.7-37.2; 36.4-38.1)	36.9 (36.7-37.3; 36.6-38.2)
Computed tomographic findings†		
Appendicolith‡	5/29 (17.2)	1/17 (5.9)
Appendiceal diameter, median mm (IQR; range)	10 (9-12; 7-18)	11 (10-14; 7-20)
Periappendiceal stranding		
None	2 (6.9)	0 (0.0)
Mild	18 (62.1)	12 (70.6)
Moderate	7 (24.1)	4 (23.5)
Severe	1 (3.4)	1 (5.9)
NA	1 (3.4)	0 (0.0)
Hyperemia		
Yes	24 (82.8)	16 (94.1)
No	4 (13.8)	1 (5.9)
NA	1 (3.4)	0 (0.0)
Periappendiceal fluid		
Yes	5 (12.5)	4 (23.5)
No	24 (82.8)	13 (76.5)
NA	1 (3.4)	0 (0.0)
Laboratory results		
WBC count, median $\times 10^3/\mu L$ (IQR; range)	15.0 (11.3-17.0; 6.2-23.1)	15.1 (11.9-17.2; 9.4-19.1)
Neutrophils, median % (IQR; range)	83.9 (81.1-89.7; 49.8-94.4)	81.8 (72.1-85.9; 57.8-94.8)
Alvarado score§, median (IQR; range)	8 (7-9; 4-10)	8 (6-8; 3-9)
Appendix pathology findings		
Normal	1/14 (7.1)	0 (0.0)
Acute uncomplicated	9/14 (64.3)	12 (70.6)
Suppurative and/or gangrenous	4/14 (28.6)	5 (29.4)
Perforated	0/14 (0.0)	1 (5.9)
Received appendectomy	14/14 (100)	17 (94.4)
Open	5 (35.7)	6/17 (35.2)
Laparoscopic	9 (64.3)	11/17 (64.7)
Major complications	3 (10.0)	0 (0.0)

*Data are presented as No. (%) unless otherwise indicated.
†One patient of pediatric age in each group did not get a computed tomography scan.
‡Radiographic identification of an appendicolith was initially an exclusion criterion but was later allowed (after 11 of 30 participants were enrolled) because of lack of consistent evidence of this being a risk factor for antibiotic failure.
§The Alvarado score[24] consists of the following components (points): right lower quadrant tenderness (0/2); elevated temperature (≥37.3°C or 99.1°F) (0/1); rebound tenderness (0/1); migration of pain to the right lower quadrant (0/1); anorexia (0/1); nausea or vomiting (0/1); leukocytosis >10,000 cells/μL (0/2); polymorphonuclear cells >75% (0/1).

Randomized to Surgery

Complication - Unplanned intubation due to retroperitoneal trocar-related injury with ICU admission on day 1

A 34-year old male with no major co-morbidities or past surgeries presented with a half-day history of severe abdominal pain with anorexia, nausea, and vomiting, and examination findings of localized right lower quadrant abdominal tenderness without rebound or guarding. His WBC count was 17.0 x10^3/μL and his computed tomography (CT) scan revealed a 9-mm diameter appendix and mild stranding with hyperemia. He underwent laparoscopic appendectomy, which demonstrated appendicitis with no purulent fluid, gangrene, perforation, or abscess. Intraoperatively, a retroperitoneal hematoma was observed. Intubation was maintained, the participant was admitted for one day to the ICU for observation, and recovered without need for blood transfusion.

Complications - Organ space infection (pelvic abscess diagnosed 2 days after discharge) and unplanned hospitalization on day 5

A 59-year-old female with no major co-morbidities and prior Caesarian section presented with a 5-day history of severe abdominal pain with anorexia and nausea, and examination findings of right lower quadrant abdominal rebound tenderness and guarding. Her WBC count was 8.1 x 10^3/μL and her CT scan revealed a 7-mm diameter appendix with an appendicolith and moderate stranding and hyperemia, and no periappendiceal fluid. She underwent open appendectomy and inflammation of the cecum was observed, but the appendix appeared normal and was normal on pathology review. The participant returned on day 5 (2 days after being discharged from the hospital) complaining of suprapubic pain and a CT scan revealed a 5-cm fluid collection with an enhancing wall in the pelvis consistent with an abscess. The participant received percutaneous drainage and antibiotics and recovered.

Randomized to Antibiotics-First

Complication - Organ space infection and unplanned hospitalization due to recurrent perforated appendicitis on day 18

A 37-year-old female with no other major co-morbidities or past surgeries presented with a 4-day history of moderate abdominal pain with chills and anorexia, and examination findings of right lower quadrant abdominal rebound tenderness without guarding. Her WBC count was 11.9 x 10^3/μL and her CT scan revealed a 9-mm diameter appendix and moderate stranding and hyperemia and no appendicolith. The participant gradually improved, and on day 11 reported no pain and had no abdominal tenderness. On day 18, the participant returned with right lower quadrant pain and a CT revealed a 10-mm appendix with an associated phlegmon and 1.3-cm fluid collection. The participant wished to avoid surgery. She was treated with antibiotics and recovered. She was offered and declined interval appendectomy.

Figure E1. Summary of major complications.

Table E3. Pain, analgesic use, activity, and quality-of-life outcomes of 30 participants with the diagnosis of acute uncomplicated appendicitis by treatment group.*

Characteristic	Appendectomy (n=14)	Antibiotics-First (n=16)
Number of participants pain-free		
At day 2†	0 (0.0)	5 (31.3)
Day 3-5	1 (7.1)	10 (62.5)
Two weeks	2 (14.3)	12 (75.0)
One month	9 (64.3)	14 (87.5)
Total days on analgesics, median (IQR; range)		
Through day 2	1.0 (0.0-1.0; 0.0-1.0)	0.5 (0.0 -1.0; 0.0-1.0)
Day 3-5	2.0 (1.0-2.0; 0.0-3.0)	1.0 (0.0-1.0; 0.0-3.0)
Two weeks	4.0 (2.0-6.0; 1.0-10.0)	1.0 (0.0-1.0; 0.0-12)
One month	4.5 (3.0-8.0; 1.0-24.0)	1.0 (0.0-1.5; 0.0-12)
Maximal pain score‡ prior 24 hours, median (IQR; range)		
Day 2	9.0 (7.0-9.0; 4.0-10.0)	4.5 (3.0-6.5; 1.0-9.0)
Day 3-5	4.5 (4.0-6.0; 2.0-8.0)	2.0 (0.5-5.5; 0.0-7.0)
Two weeks	3.5 (1.0-4.0; 0.0-8.0)	0.0 (0.0-2.0; 0.0-7.0)
One month	1.0 (0.0-4.0; 0.0-8.0)	0.0 (0.0-2.0; 0.0-6.0)
Total days missed normal activities, median (IQR; range)		
Through day 2	1.0 (1.0-1.0; 0-1.0)	1.0 (0.0-1.0; 0.0-1.0)
Day 3-5	2.0 (2.0-3.0; 1.0-4.0)	1.0 (0.5-2.5; 0.0-4.0)
Two weeks	2.5 (2.0-9.0; 1.0-13)	1.0 (0.5-2.5; 0.0-6.0)
One month	4.0 (2.0-9.0; 1.0-28)	1.0 (0.5-2.5; 0.0-6.0)
Unable to perform normal activities		
At day 2	14/14 (100.0)	10/16 (62.5)
Day 2 to 3-5	12/14 (85.7)	7/16 (43.8)
Day 3-5 to two weeks	6/14 (42.9)	1/15 (6.7)
Two weeks to one month	2/13 (15.4)	0/15 (0.0)
Total days missed work or school, median (IQR; range)	n=8§	n=13§
Through day 2	1.0 (0.5-1.0; 0.0-1.0)	1.0 (1.0-1.0; 0.0-1.0)
Day 3-5	2.5 (1.5-3.0; 0.0-4.0)	1.0 (1.0-3.0; 0.0-3.0)
Two weeks	3.5 (2.0-10; 1.0-13)	2.0 (1.0-3.0; 0.0-7.0)
One month	3.5 (2.5-22; 2.0-28)	2.0 (1.0-3.0; 0.0-7.0)
Missed any work or school		
At day 2	8/8 (100)	10/13 (76.9)
Day 2 to 3-5	6/8 (75.0)	7/13 (53.8)
Day 3-5 to two weeks	5/8 (62.5)	4/12 (33.3)
Two weeks to one month	4/8 (50.0)	0/12 (0.0)
Quality-of-life meaures		
SF-12v2 Physical Component Score‖, median (IQR; range)		
At two weeks	44 (36-51; 31-56)	54 (52-58; 38-63)
One month	47 (40-53; 32-55)	56 (47-57; 33-62)
SF-12v2 Mental Component Score‖, median (IQR; range)		
At two weeks	58 (48-61; 17-68)	55 (53-59; 38-61)
One month	56 (43-58; 37-68)	55 (49-57; 36-63)
PEDsQL Physical Health Score¶		
At two weeks		97
One month		97
PEDsQL Psychosocial Health Score¶		
At two weeks		95
One month		95

*Data are presented as No. (%) unless otherwise indicated.
†Follow-up visits occurred at day 2, day 3-5, two weeks (day 10-18) and one month (day 25-35) after enrollment (day 1).
‡Pain was rated on a scale of 0-10, 10 being the most pain.
§Not all participants worked or went to school, so were omitted from these descriptions. Denominators are indicated.
‖SF-12v2® Health Survey Acute version[24] (1-week recall) was utilized for adult (14 appendectomy and 15 antibiotic-first) participants at two weeks and the 4-week recall version at one month.
¶The PEDsQL™ Survey Acute version[27] child report for ages 8-12 years (1-week recall) was utilized for the pediatric participant (randomized to antibiotics-first) at two weeks and the 4-week recall version at one month.

Table E4. Number of adverse events by severity* and treatment group through 1 month for 30 participants with the diagnosis of acute uncomplicated appendicitis.

		Appendectomy			Antibiotics-First	
Adverse Event	**All**	**Mild**	**Moderate**	**Life- Threatening**	**Mild**	**Moderate**
Diarrhea	14	1	1	0	11	1
Back pain	14	9	0	0	5	0
Subjective fever/chills	11	5	0	0	6	0
Nausea	9	2	0	0	7	0
Headache	9	1	0	0	6	2
Anorexia	7	2	0	0	5	0
Constipation	6	1	1	0	4	0
Abdominal pain (new)	4	1	0	0	1	2
Rash	4	2	0	0	2	0
Dizziness	3	1	0	0	2	0
All other†	22	4	3	1	13	1
Total events	**103**	**29**	**5**	**1**	**62**	**6**
Number per participant, median (IQR; range)	3 (1-4; 0-9)	2 (1-3; 0-6)			4 (1-7; 1-9)	

*All adverse events were graded for severity as follows: mild (Grade 1), events that required minimal or no treatment and did not interfere with the participant's daily activities; moderate (Grade 2), events that resulted in a low level of inconvenience or concern with the therapeutic measures, and may have caused some interference with functioning; severe (Grade 3), events that interrupted a participant's usual daily activity and may have required systemic drug therapy or other treatment, and were incapacitating; and life-threatening (Grade 4), any adverse drug experience that placed the participant at immediate risk of death, not including a reaction that had it occurred in a more severe form, might have caused death.[29]

†Other adverse events graded as mild in the antibiotics-first group were fatigue (1), metallic smelling mouth (1), gastritis (2), bloating (1), yeast infection (1), chest pressure (1), right leg and testicular numbness (1), vaginal itchiness (1), irritation with bowel movements (1), itching (1), inability to pass gas/bloating (1), and burning on urination (1). The adverse event graded as moderate in the antibiotics-first group was a phlegmon. Adverse events graded as mild in the appendectomy group were abdominal cramping (1), chest pain (1), testicular pain (1), and double vision (1), and adverse events graded as moderate were intraabdominal abscess (1), sore throat (1), and numbness in abdomen (1). The adverse event graded as life-threatening in the appendectomy group was a trochar-related injury causing a retroperitoneal hematoma that required prolonged intubation and ICU admission for observation but no blood transfusions.