Supplementary materials

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Supplementary Methods

Eligibility Criteria, COMBINE Trial

Inclusion criteria

1.1 Adult (18 years or older) patients admitted to the participating center
1.2 Scheduled to undergo laparoscopic or open elective colorectal surgery
1.3 From whom written informed consent is obtainable.

Exclusion criteria

1.1 Non-elective colorectal surgery (emergent surgery and/or reintervention or revision of a previous colorectal procedure)
1.2 Relevant concomitant surgical procedure (e.g., resection of liver metastasis)
1.3 Active bacterial infection at the time of surgery
1.4 Recent antimicrobial therapy (within 2 weeks) before surgery
1.5 Inflammatory bowel disease
1.6 Body-mass index greater than 35 kg/m^2
1.7 Known hypersensitivity to β-lactams or imidazoles
1.8 Preoperative renal function impairment (defined by a glomerular filtration rate lower than 30 $mL/min/1.73\ m^2$)
1.9 Known infection or colonization by multidrug-resistant digestive bacteria (especially multidrug-resistant Gram-negative bacteria)
1.10 Known allergy to lactose, galactose intolerance, lactase deficit or glucose and/or galactose malabsorption
1.11 Pregnancy, breastfeeding, or childbearing potential without effective contraception
1.12 Major protected (guardianship)
1.13 Refusal to participate or inability to provide informed consent

Phone contact form

(To be used each week after hospital discharge until day 30 after surgery)

Patient's first name: ……

Patient's last name: ……

Date of birth: ……...

Randomization number: I__I__I__I

Date of surgery: I__I__I – I__I__I- I__I__I

Date of phone call: I__I__I – I__I__I- I__I__I **Call:** weekly: ❒ day 30 ❒

Questionnaire

Since hospital discharge,

1. Do you feel pain and/or a sensation of warmth at the surgical scar? YES ❒ NO ❒

2. Have you noticed local redness and/or abnormal swelling at and/or around the surgical scar? YES ❒ NO ❒

3. Have you noticed a dehiscence of the surgical scar? YES ❒ NO ❒

4. Is there a cloudy discharge from the surgical scar? YES ❒ NO ❒

5. Do you have fever*? YES ❒ NO ❒
(* Temperature >38°C)

6. Have you seen a physician for one or more of these symptoms? YES ❒ NO ❒

Trial definitions for study outcomes

Primary outcome

The occurrence of any surgical-site infection (SSI) within 30 days after the index colorectal surgical procedure, defined according to the Centers for Disease Control and Prevention criteria,[1] as:

- Superficial incisional SSI:
  Patient must meet the followings:
  - Infection occurs within 30 days after an operative procedure

  AND
  - Involves only the skin and subcutaneous tissue of the incision

  AND
  - At least one of the following:
    a) Diagnosis of a superficial incisional SSI by the surgeon or attending physician
    b) Purulent drainage from the superficial incision.
    c) Organisms isolated from an aseptically-obtained culture from the superficial incision or subcutaneous tissue.
    d) Superficial incision that is deliberately opened and is culture positive or NOT cultured (a negative surgical culture result means that SSI cannot be confirmed at this decision point but may still be diagnosed at points a., b., or c.)

  AND
  - At least one of the following signs or symptoms:
    a) Pain or tenderness
    b) Localized swelling
    c) Erythema
    d) Heat

- Deep incisional SSI:
  Patient must meet the followings:
  - Infection occurs within 30 days after an operative procedure

  AND
  - Involves deep soft tissues of the incision (e.g., fascial and muscle layers)

  AND
  - At least one of the following:
    a) Purulent drainage from the deep incision.
    b) An abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam, or imaging test.
    c) A deep incision that spontaneously dehisces, or is deliberately opened or aspirated and is culture positive or NOT cultured (a negative surgical culture result means that a Deep SSI cannot be confirmed at this decision point but may still be diagnosed at points a. or b.)

  AND
  - At least one of the following signs or symptoms:
    a) Fever (>38°C)
    b) Localized pain or tenderness

- Organ-Space SSI:
  Patient must meet the followings:
  - Infection occurs within 30 days after an operative procedure

  AND
  - Infection involves any part of the body deeper than the fascial/muscle layers, that is opened or manipulated during the operative procedure

  AND
  - At least one of the following:
    a) Purulent drainage from a drain that is placed into the organ/space (e.g., closed suction drainage system, open drain, T-tube drain, CT guided drainage)
    b) Organisms isolated from an aseptically-obtained culture of fluid or tissue in the organ/space
    c) An abscess or other evidence of infection involving the organ/space that is detected on gross anatomical or histopathologic exam, or imaging test

Secondary outcomes

1. Occurrence of any type of SSI (superficial, deep, or organ-space infections) within 30 days after the index colorectal surgery assessed individually
2. Postoperative surgical complications within 30 days after the index colorectal surgery:
   - Major surgical complication grade, classified as Clavien-Dindo grade III or higher[2]:

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
Grade II	Requiring pharmacological treatment - Blood transfusions and total parenteral nutrition
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IV	Life-threatening complication requiring intermediate care or intensive care unit management
Grade V	Death of a patient

   - Anastomotic leakage within 30 days after the index colorectal surgical procedure
   - Need for abdominal reoperation and/or radiological intervention for any reason within 30 days after the index colorectal surgical procedure

3. Postoperative non-surgical complications within 30 days after the index colorectal surgery (any of the following):
   - Systemic inflammatory response syndrome (SIRS), sepsis, and septic shock, defined according to consensus definitions[3 4]

SIRS criteria:
Two or more of the following:

a) Core temperature >38°C or <36°C. (Core temperature is rectal or tympanic). If oral, inguinal or axillary temperatures are used, add 0.5°C to the measured value. The most deranged value recorded will be used.
b) Heart rate >90 beats/minute. If patient had an atrial arrhythmia, record the ventricular rate. If patients have a known medical condition or are receiving treatment that would prevent tachycardia (for example, heart block or beta blockers), they must meet two of the remaining three SIRS criteria. The most deranged value recorded will be used.
c) Respiratory rate > 20 breaths per minute or a $PaCO_2$ <4.3 kPa (32 mmHg) or mechanical ventilation for an acute process. The most deranged respiratory rate or $PaCO_2$ recorded will be used.
d) White Blood Cell (WBC) count of >12 x 109/l or <4 x 109/l or > 10% immature neutrophils (band forms). The most deranged value recorded will be used.

Sepsis and septic shock criteria:
Sepsis is defined as a

a) Defined focus of infection and
b) At least two SIRS criteria.

Defined focus of infection is indicated by either an organism grown in blood or a sterile site, or an abscess, or infected tissue (e.g., pneumonia, peritonitis, urinary tract, vascular line infection, soft tissue, etc.).

Septic shock is sepsis-induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities.

- Cardiovascular complication: major cardiac cardiovascular event (new arrhythmia, myocardial infarction or acute heart failure)
- Pulmonary complication: pneumonia, defined according to the CDC criteria;[1] need for postoperative ventilation (tracheal intubation or curative non-invasive mechanical ventilation) for acute respiratory failure
- Kidney dysfunction, defined according defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification[5]

4. Need for hospital readmission within 30 days after the index colorectal surgery
5. Unplanned intensive-care-unit (ICU) admission within 30 days after the index colorectal surgery
6. Duration of hospital stay (including hospital stay of patients who are readmitted after surgery) within 30 days after the index colorectal surgery
7. Hospital-free days (censored at 30 days following surgery), defined as the number of days spent alive and outside of any healthcare facility through day 30 after the index colorectal surgery
8. Death from any cause within 30 days and 90 days after surgery

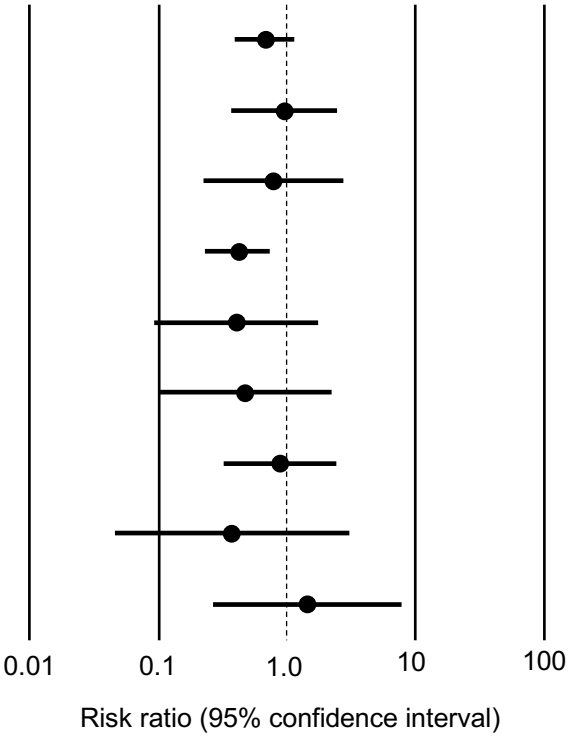
Safety outcomes

incidence of serious adverse events (SAE), defined as any adverse event assessed by study investigators as being potentially related to study drug and that is fatal (results

in deaths) or is felt to be life-threatening, requires in-patient hospitalization or prolongation of an existing hospitalization, results in significant disability or incapacity

Supplementary Figure S1. Treatment Effect on Surgical Site Infection Across Sites

Study site	Risk ratio	Lower limit	Upper limit
001	0.67	0.40	1.12
002	0.94	0.37	2.36
003	0.78	0.23	2.68
004	0.42	0.24	0.72
005	0.40	0.09	1.73
006	0.47	0.10	2.23
007	0.88	0.33	2.38
010	0.37	0.05	2.95
011	1.43	0.27	7.61



P value=0.98 for homogeneity of effect across sites, calculated with a robust random-effect Poisson generalized linear mixed regression model with adjustment for stratification variables (study center, the surgical technique [laparoscopic vs. open surgery], skin antisepsis [chlorhexidine–alcohol vs. povidone-iodine alcoholic solution]), randomization group, male sex, and surgical duration. Two study sites did not report SSI events.

Supplementary Table S1. Blood sample results (modified intention-to-treat population)

Variable		Oral prophylaxis (N=463)		Placebo (N=463)	P Value
	No. assessed†	Value	No. assessed†	Value	
Preoperative					
CRP, mg/L	236	3.2 (2.9-10)	206	3.4 (2.9-9.2)	0.96
Serum creatinine, μmol/L	426	74 (63-87)	420	76 (65-88)	0.04
BUN, mmol/L	406	6.3 (4.8-8.1)	401	6.3 (5-7.8)	0.47
Hemoglobin, g/dL,	440	13.3 (12.1-14.5)	429	13.5 (12.2-14.7)	0.22
Platelets, $\times 10^3/mm^3$	440	259 (218-312)	428	258 (210-311)	0.58
WBC, $\times 10^3/mm^3$	433	7.3 (5.8-8.9)	422	7 (5.8-8.3)	0.06
Postoperative day 1					
CRP, mg/L	294	58 (35-94)	292	61 (37-92)	0.60
Serum creatinine, μmol/L	367	71 (58-81)	375	71 (62-83)	0.10
BUN, mmol/L	353	5.1 (3.9-6.8)	359	5 (3.8-6.6)	0.24
Hemoglobin, g/dL,	373	11.7 (10.6-12.9)	384	12.2 (11.1-13.1)	0.006
Platelets, $\times 10^3/mm^3$	372	224 (184-268)	380	219 (179-271)	0.63
WBC, $\times 10^3/mm^3$	373	11.2 (9.1-13.2)	384	10.7 (8.3-12.8)	0.07
Postoperative day 2					
CRP, mg/L	214	103 (59-164)	214	112 (60-168)	0.62
Serum creatinine, μmol/L	227	67 (53-79)	243	71 (57-80)	0.08
BUN, mmol/L	225	4 (3-5.6)	242	4.2 (3-5.9)	0.43
Hemoglobin, g/dL,	235	11.4 (10.2-12.7)	243	11.9 (10.2-12.9)	0.34
Platelets, $\times 10^3/mm^3$	235	209 (170-252)	242	211 (170-255)	0.94
WBC, $\times 10^3/mm^3$	235	9.6 (7.8-11.5)	243	9.4 (7.6-11.3)	0.19
Postoperative day 3					
CRP, mg/L	308	85 (47-148)	289	91 (55-155)	0.22
Serum creatinine, μmol/L	327	62.2 (53.1-79)	312	68.7 (58.6-80)	0.01
BUN, mmol/L	317	3.9 (2.8-5.5)	304	4.4 (3.2-5.8)	0.03
Hemoglobin, g/dL,	332	11.9 (10.5-13.2)	317	12 (10.6-13.3)	0.74
Platelets, $\times 10^3/mm^3$	333	231 (188-278)	316	228 (178-274)	0.49
WBC, $\times 10^3/mm^3$	332	8.2 (6.8-10.4)	317	8.5 (6.4-10.6)	0.51

Values are medians (interquartile range) among participants with available data.

BUN denotes blood urea nitrogen, CRP C-reactive protein, and WBC white blood cells.

† Number of patients for whom the measurements were documented in source data.

Supplementary Table S2. Univariable and multivariable analysis of factors associated with the primary outcome

	Univariable Analysis		Multivariable Analysis	
Variable	**Odds ratio (95%CI)**	**P Value**	**Odds ratio (95%CI)**	**P Value**
Intervention (Reference: placebo group)	0.54 (0.38–0.77)	0.001	0.55 (0.38–0.78)	0.001
Male sex (Reference: female sex)	2.21 (1.51–3.24)	<0.001	1.92 (1.30–2.84)	0.001
Age/year	1.00 (0.99–1.02)	0.59		
ASA physical status classification III-IV (Reference: ASA class I-II)	1.33 (0.89–1.99)	0.17		
Cancer diagnosis (Reference: no cancer)	1.42 (0.92–2.18)	0.11		
Current smoker (Reference: non-smoker)	0.96 (0.60–1.53)	0.86		
Diabetes (Reference: no diabetes)	1.38 (0.88–2.15)	0.16		
Coronary artery disease (Reference: no)	1.94 (1.17–3.20)	0.01		
Chlorhexidine-alcohol skin preparation (Reference: povidone iodine-alcohol skin preparation)	0.94 (0.52–1.68)	0.83		
Laparoscopy-assisted surgery (Reference: open surgery)	0.59 (0.41–0.84)	0.004	0.58 (0.40–0.84)	0.004
Blood transfusion (Reference: none)	1.70 (0.75–3.87)	0.21		
Mechanical bowel preparation (Reference: no mechanical bowel preparation)	1.30 (0.91–1.85)	0.15		
Surgical duration >2 hours (Reference: ≤2 hours)	4.36 (1.57–12.09)	0.005	4.27 (1.52–11.99)	0.006
Inspired fraction of oxygen/% (per log increment)	1.34 (0.74–2.43)	0.34		
Stapled anastomosis (Reference: hand-sewn anastomosis)	0.95 (0.63–1.43)	0.81		

CI denotes confidence intervals.

Multiple logistic mixed regression was used to identify variables associated with the primary outcome. Variables tested in the model were selected if the P value was <0.10 and according to clinical relevance, in addition to the stratification variables (center, skin preparation, type of procedure).

Supplementary Table S3. Results of the adjusted analyses of outcomes in the modified intention-to-treat population*

Outcome	Unadjusted Relative Risk (95% CI)	P Value	Adjusted Relative Risk (95% CI)	P Value
Primary outcome				
Any surgical-site infection – no. (%)	0.60 (0.45 to 0.80)	0.001	0.62 (0.44 to 0.86)	0.005
Secondary outcomes‡				
Superficial incisional infection – no. (%)	0.56 (0.29 to 1.09)	0.09	0.59 (0.30 to 1.15)	0.12
Deep incisional infection – no. (%)	0.54 (0.31 to 0.92)	0.03	0.56 (0.32 to 0.96)	0.04
Organ-space infection – no. (%)	0.53 (0.31 to 0.91)	0.02	0.52 (0.30 to 0.89)	0.02
SIRS – no. (%)	0.79 (0.62 to 0.99)	0.045	0.80 (0.68 to 0.94)	0.005
Sepsis or septic shock – no. (%)	0.62 (0.39 to 0.99)	0.046	0.62 (0.49 to 0.80)	<0.001
Arrhythmia – no. (%)	1.11 (0.83 to 1.47)	0.49	1.12 (0.99 to 1.27)	0.07
Acute hear failure – no. (%)	NA		NA	
Myocardial infarction – no. (%)	NA		NA	
Pneumonia – no. (%)	2.17 (0.83 to 5. 65)	0.11	2.24 (1.20 to 4.19)	0.01
Postoperative mechanical ventilation	0.60 (0.27 to 1.36)	0.22	0.60 (0.29 to 1.22)	0.16
Acute kidney injury	0.97 (0.70 to 1.34)	0.85	1.0 (0.61 to 1.65)	0.99
Surgical complications				
Clavien-Dindo class grade I-II – no. (%)	0.98 (0.74 to 1.29)	0.86	0.98 (0.73 to 1.32)	0.89
Clavien-Dindo class grade III or higher – no. (%)	0.63 (0.41 to 0.97)	0.03	0.64 (0.48 to 0.85)	0.02
Anastomotic leakage	0.59 (0.36 to 0.99)	0.046	0.59 (0.45 to 0.79)	<0.001
Reintervention	0.71 (0.47 to 1.08)	0.11	0.75 (0.54 to 1.03)	0.08
Surgical or endoscopic drainage	0.43 (0.11 to 1.65)	0.20	0.45 (0.12 to 1.72)	0.24
Time from randomization to initiation of adjuvant chemotherapy – days‡	Between-group difference (95% CI) -2.1 (-5.5 to 1.3)	0.22	Between-group difference (95% CI) -2.5 (-5.6 to 0.6)	0.12
Unplanned hospital readmission – no. (%)	1.00 (0.61 to 1.63)	1	1.03 (0.76 to 1.41)	0.84
Unplanned ICU admission – no. (%)	0.20 (0.02 to 1.71)	0.14	0.26 (0.03 to 2.69)	0.26
Median duration of stay in hospital (IQR) – days	Between-group difference (95% CI) -0.06 (-0.13 to 0.05) (per-log increment in days)	0.07	Between-group difference (95% CI) -0.05 (-0.11 to 0.01) (per-log increment in days)	0.11
Median hospital-free days by day 30 (IQR) – days	Between-group difference (95% CI) 0.13 (0.05 to 0.20) (per-log increment in days)	0.001	Between-group difference (95% CI) 0.12 (0.05 to 0.19) (per-log increment in days)	0.001

Outcome	Unadjusted Relative Risk (95% CI)	P Value	Adjusted Relative Risk (95% CI)	P Value
Death – no. (%)				
At 30 days	0.40 (0.08 to 2.05)	0.27	0.37 (0.07 to 1.91)	0.24
At 90 days	0.50 (0.17 to 1.45)	0.20	0.50 (0.20 to 1.23)	0.13

* Adjusted analyses were performed using robust random-effect Poisson regression with robust variance for binary outcomes, random-effect multinomial logistic regression for categorical outcomes, and random-effect linear regression for continuous outcomes. Variables in the adjusted analyses included the following: stratification variables (study center, the surgical technique [laparoscopic vs. open surgery], skin antisepsis [chlorhexidine–alcohol vs. povidone-iodine alcoholic solution]), randomization group, male sex, and surgical duration.

ICU denotes intensive care unit, IQR interquartile range, and SIRS systemic inflammatory response syndrome.

‡ Data on the time from randomization to initiation of adjuvant chemotherapy were for 9 patients in the oral prophylaxis group and 8 patients in the placebo group.

Supplementary Table S4. Baseline characteristics in the per-protocol population

Characteristic	Oral prophylaxis (N = 432)	Placebo (N = 436)
Age – yr	63±13	63±13
Male sex – no. (%)	245 (57)	274 (63)
Weight – kg	74±15	75±15
Body-mass index	26±4	26±4
ASA physical status classification – no./total no. (%)		
1	94/431 (22)	97/434 (22)
2	254/431 (59)	245/434 (56)
3	80/431 (19)	88/434 (20
4	3/431 (1)	4/434 (1)
Coexisting conditions – no. (%)		
Hypertension	185 (43)	186 (43)
Diabetes mellitus	65 (15)	67 (15)
Coronary artery disease	29 (7)	50 (11)
Chronic pulmonary disease	21 (5)	28 (6)
Current smoker	69 (16)	71 (16)
Any alcohol intake	34 (8)	37 (8)
Disease-related malnutrition§	28 (6)	20 (5)
History of multidrug-resistant bacteria – no. (%)	2 (1)	3 (1)
Antibiotic use within 3 months before surgery – no. (%)	45 (10)	50 (11)
Adjuvant chemotherapy or radiotherapy – no. (%)	107 (25)	94 (22)
Medication at the time of surgery – no. (%)		
Corticosteroid	11 (3)	14 (3)
Non-steroidal anti-inflammatory drug	4 (1)	12 (3)
Indication for surgery – no. (%)		
Colon cancer	195 (55)	198 (45)
Rectal cancer	133 (31)	134 (31)
Diverticulitis	73 (17)	68 (16)
Other condition	31 (7)	36 (8)
Skin preparation – no. (%)		
Chlorhexidine-alcohol	39 (9)	46 (11)
Povidone iodine-alcohol	393 (91)	390 (89)
Mechanical bowel preparation – no. (%)		
Polyethylene glycol	61 (42)	50 (35)
Senna solution	83 (58)	94 (65)
Received retrograde enema – no. (%)	185 (43)	192 (44)

* Plus-minus values are means ±SD. Percentages may not total 100 because of rounding.

The per-protocol population was defined as participants in the modified intention-to-treat population except those who would not have been eligible for randomization according to inclusion/non-inclusion criteria OR those who accidentally would have received the wrong intervention (oral ornidazole or placebo and vice versa) OR those in whom surgical intervention would not have been done.

Supplementary Table S5. Surgical and Other Perioperative Characteristics in the Per Protocol Population

Characteristic	Oral prophylaxis (N = 432)	Placebo (N = 436)
Median time from oral antibiotic or placebo dose to skin incision (IQR) – hr	12.9 (12.5-13.4)	12.9 (12.5-13.4)
Median time from intravenous antimicrobial prophylaxis to skin incision (IQR) – min	35 (28-48)	35 (28-48)
Type of surgery – no./total no. (%)		
Colectomy	278/432 (64)	286/436 (66)
Right hemicolectomy	114/278 (41)	108/286 (38)
Left hemicolectomy	151/278 (54)	162/286 (57)
Transverse colectomy	26/278 (9)	21/286 (7)
Total colectomy	6/278 (2)	12/286 (4)
Rectal resection	154/432 (36)	150/436 (34)
Surgical method – no. (%)		
Open	54 (12)	53 (12)
Laparoscopic-assisted	315 (73)	328 (75)
Laparoscopy converted to open	63 (15)	55 (13)
Type of anastomosis – no./total no. (%)		
Stapled anastomosis	310/413 (75)	320/415 (77)
Hand-sewn anastomosis	103/413 (25)	95/415 (23)
Ileostomy or colostomy performed – no. (%)	141 (33)	143 (33)
Abdominal surgical drain used – no. (%)	187 (43)	181 (42)
Median duration of surgery (IQR) – min	217 (160-282)	210 (160-270)
Median volume of intravenous fluid (IQR) – ml		
Crystalloid	2000 (1500-2500)	2000 (1500-2500)
Colloid	500 (500-1000)	500 (500-1000)
Median infusion rate (IQR) – ml/kg/hr	7.6 (5.9-10.3)	7.9 (5.9-10.8)
Cardiac output monitoring used – no./total no. (%)	88/432 (20)	107/436 (25)
Median FiO_2 during surgery (IQR) – %		
Start of surgery	44 (40-50)	45 (40-50)
End of surgery	45 (40-51)	45 (39-51)
Core temperature at the end of surgery – °C	36±1	36±1
Received dexamethasone – no. (%)	299 (69)	302 (69)
Received intravenous lidocaine – no. (%)	329 (76)	316 (72)
Median intraoperative blood loss (IQR) – ml	150 (100-300)	150 (100-300)
Red-cell transfusion during surgery – no. (%)	16 (4)	12 (3)
Postoperative lidocaine used – no. (%)	141 (33)	131 (30)
Postoperative epidural analgesia used – no. (%)	53 (12)	53 (12)
Planned postoperative care in HDU or ICU – no. (%)	113 (26)	104 (24)

Plus-minus values are means ±SD. Percentages may not total 100 because of rounding. FiO_2 denotes inspired fraction of oxygen, HDU high-dependency unit, ICU intensive care unit, and IQR interquartile range.

The per-protocol population was defined as participants in the modified intention-to-treat population except those who would not have been eligible for randomization according to inclusion/non-inclusion criteria OR those who accidentally would have received the wrong

intervention (oral ornidazole or placebo and vice versa) OR those in whom surgical intervention would not have been done.

Supplementary Table S6. Results of the primary analysis in the per-protocol population.

Outcome	Oral ornidazole (N = 432)	Placebo (N = 436)	Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)†
Any surgical-site infection – no. (%)	56 (12.9)	93 (21.3)	0.61 (0.45 to 0.82) P=0.001	0.62 (0.43 to 0.87) P=0.006
Superficial incisional infection – no. (%)	13 (3.0)	21 (4.8)	0.56 (0.28 to 1.15) P=0.11	0.56 (0.28 to 1.14) P=0.11
Deep incisional infection – no. (%)	22 (5.1)	36 (8.3)	0.58 (0.32 to 0.97) P=0.037	0.58 (0.33 to 1.01) P=0.054
Organ-space infection – no. (%)	21 (4.9)	36 (8.3)	0.53 (0.30 to 0.93) P=0.027	0.51 (0.29 to 0.91) P=0.021

† Adjusted analyses were performed using robust random-effect Poisson regression with robust variance for binary outcomes and random-effect multinomial logistic regression for categorical outcomes. Variables in the adjusted analyses included stratification variables (study center, the surgical technique [laparoscopic vs. open surgery], skin antisepsis [chlorhexidine–alcohol vs. povidone-iodine alcoholic solution]), randomization group, male sex, and surgical duration.

The per-protocol population was defined as participants in the modified intention-to-treat population except those who would not have been eligible for randomization according to inclusion/non-inclusion criteria OR those who accidentally would have received the wrong intervention (oral ornidazole or placebo and vice versa) OR those in whom surgical intervention would not have been done.

Supplementary Table S7. Microbiology of surgical-site infection with documented isolated pathogens according to study group

	Oral ornidazole		Placebo	
	n	%	n	%
Gram-positive aerobic cocci	47	15.3	67	21.8
Staphylococcus aureus	5	1.6	4	1.3
Staphylococcus coagulase negative	7	2.2	16	5.2
Enterococcus bovis	2	0.6	1	0.3
Enterococcus faecalis	25	8.1	29	9.4
Enterococcus faecium	1	0.3	4	1.3
Enterococcus gallinarium	1	0.3	1	0.3
Enterococcus sp.	0	0	2	0.6
Rothia sp.	1	0.3	0	0
Streptococcus anginosus	0	0	2	0.6
Streptococcus anginosus	0	0	2	0.6
Streptococcus bovis	2	0.6	1	0.3
Streptococcus constellatus	0	0	1	0.3
Streptococcus mitis	2	0.6	3	0.3
Streptococcus pneumoniae	1	0.3	0	0
Streptococcus sanguis	0	0	1	0.3
Gram-positive aerobic bacilli	1	0.3	4	1.3
Bacillus cereus	0	0	1	0.3
Corynebacterium amylocolatum	1	0.3	0	0
Corynebacterium tuberculostearicum	0	0	1	0.3
Gram positive bacilli species†	0	0	2	0.6
Gram-negative aerobic bacilli	73	23.8	85	27.7
Acinetobacter pitii	0	0	1	0.3
Citrobacter freundii	1	0.3	0	0
Citrobacter koseri	2	0.6	1	0.3
Enterobacter aerogenes	1	0.3	3	1
Enterobacter cloacae	8	2.6	7	2.2
Escherichia coli	34	12.1	38	12.4
Gram negative bacilli species†	1	0.3	0	0
Hafnia alvei	1	0.3	0	0
Hemophilus parainfluenzae	1	0.3	0	0
Klebsiella oxytoca	3	1	0	0
Klebsiella pneumoniae	6	2	9	3
Klebsiella variicola	2	0.6	1	0.3
Morganella morganii	6	2	2	0.6
Proteus mirabilis	3	1	3	1
Proteus vulgaris	0	0	1	0.3
Pseudomonas aeruginosa	3	1	18	5.9
Serratia marcescens	0	0	1	0.3
Stenotrophomonas maltophilia	1	0.3	0	0
Gram-negative anaerobic cocci	1	0.3	0	0
Veillonella atypica	1	0.3	0	0
Gram-positive anaerobic bacilli	2	0.6	5	1.6
Bifidobacterium longum	0	0	1	0.3
Clostridium innoculum	0	0	1	0.3
Clostridium perfringes	1	0.3	0	0
Clostridium ramosum	0	0	1	0.3
Eggerthella lenta	1	0.3	0	0
Paenibacillus glucanolyticus	0	0	1	0.3

Propionebacterium acnes	0	0	1	0.3
Gram-negative anaerobic bacilli	4	1.3	16	5.2
Bacteroides faecis	0	0	1	0.3
Bacteroides fragilis	3	1	12	3.9
Bacteroides ovatus	1	0.3	1	0.3
Bacteroides uniformis	0	0	1	0.3
Parabacteroides distasonis	0	0	1	0.3
Yeasts	0	0	2	0.6
Candida albicans	0	0	2	0.6
Total	128	41.7	179	58.3

The numbers are the counts of pathogens documented across all patients/pathogens. This number may be greater than the number of patients, as some patients had more than one pathogen.

†Species not specified

Post hoc analysis of the primary outcome

Post hoc analysis of heterogeneity of treatment effect according to study periods in relation to the primary outcome

At the time of the French clinical practice recommendations update (June 21, 2018), 629 patients (312 patients in the oral prophylaxis group and 317 in the placebo group) had been enrolled in the trial. Of the 297 patients enrolled after the update, 12 patients (4.0%) received 1g intravenous metronidazole in addition to the 2g intravenous cefoxitine (6 in the oral prophylaxis group and 6 in the placebo group).

There was no evidence of an interaction between trial group and updated guidelines implementation regarding the primary outcome. Surgical-site infection within 30 days occurred in 37 of 312 patients (11.9%) in the oral prophylaxis group and in 64 of 317 patients (20.2%) in the placebo group (absolute difference, -8.0%; 95% CI, -14.0 to -2.6; relative risk, 0.59; 95%CI, 0.40-0.85) before the guideline update compared with 23 of 151 patients (15.2%) in the oral prophylaxis group and 36 of 146 patients (24.7%) in the placebo group (absolute difference, -9.4%; 95% CI, -18.5 to -0.3; relative risk, 0.62; 95%CI, 0.39-0.99) before the guideline update (P=0.87 for interaction). Thus, the guideline update had little impact on the main study findings.

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