



Effect of oral antimicrobial prophylaxis on surgical site infection after elective colorectal surgery: multicentre, randomised, double blind, placebo controlled trial

Emmanuel Futier, Samir Jaber, Matthias Garot, Marie Vignaud, Yves Panis, Karem Slim, Jean-Christophe Lucet, Gilles Lebuffe, Alexandre Ouattara, Younes El Amine, et al.

► To cite this version:

Emmanuel Futier, Samir Jaber, Matthias Garot, Marie Vignaud, Yves Panis, et al.. Effect of oral antimicrobial prophylaxis on surgical site infection after elective colorectal surgery: multicentre, randomised, double blind, placebo controlled trial. *BMJ - British Medical Journal*, In press, 379, pp.e071476. <10.1136/bmj-2022-071476>. <hal-03839446>

HAL Id: hal-03839446

<https://hal.science/hal-03839446v1>

Submitted on 4 Nov 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY 4.0 - Attribution - International License

Effect of oral antimicrobial prophylaxis on surgical site infection after elective colorectal surgery: multicentre, randomised, double blind, placebo controlled trial

Emmanuel Futier,^{1,2} Samir Jaber,^{3,4} Matthias Garot,⁵ Marie Vignaud,¹ Yves Panis,⁶ Karem Slim,⁷ Jean-Christophe Lucet,^{8,9} Gilles Lebuffe,⁵ Alexandre Ouattara,^{10,11} Younes El Amine,¹² Philippe Couderc,¹³ Aurélien Dupré,^{14,15} Audrey De Jong,³ Sigismond Lasocki,¹⁶ Marc Leone,¹⁷ Julien Pottecher,¹⁸ Bruno Pereira,¹⁹ Catherine Paugam-Burtz,²⁰ on behalf of the COMBINE study group

ABSTRACT OBJECTIVE

To investigate whether oral antimicrobial prophylaxis as an adjunct to intravenous antibiotic prophylaxis reduces surgical site infections after elective colorectal surgery.

DESIGN

Multicentre, randomised, double blind, placebo controlled trial.

SETTING

11 university and non-university hospitals in France between 25 May 2016 and 8 August 2019.

PARTICIPANTS

926 adults scheduled for elective colorectal surgery.

INTERVENTION

Patients were randomised to receive either a single 1 g dose of ornidazole (n=463) or placebo (n=463) orally 12 hours before surgery, in addition to intravenous antimicrobial prophylaxis before surgical incision.

MAIN OUTCOME MEASURES

The primary outcome was the proportion of patients with surgical site infection within 30 days after surgery. Secondary outcomes included individual types of surgical site infections and major postoperative complications (Clavien-Dindo classification grade 3 or higher) within 30 days after surgery.

RESULTS

Of the 960 patients who were enrolled, 926 (96%) were included in the analysis. The mean age of participants was 63 years and 554 (60%) were men.

Surgical site infection within 30 days after surgery occurred in 60 of 463 patients (13%) in the oral prophylaxis group and 100 of 463 (22%) in the placebo group (absolute difference -8.6%, 95% confidence interval -13.5% to -3.8%; relative risk 0.60, 95% confidence interval 0.45 to 0.80). The proportion of patients with deep infections was 4.8% in the oral prophylaxis group and 8.0% in the placebo group (absolute difference -3.2%, 95% confidence interval -6.4% to -0.1%). The proportion of patients with organ space infections was 5.0% in the oral prophylaxis group and 8.4% in the placebo group (absolute difference -3.4%, -6.7% to -0.2%). Major postoperative complications occurred in 9.1% patients in the oral prophylaxis group and 13.6% in the placebo group (absolute difference -4.5%, -8.6% to -0.5%).

CONCLUSION

Among adults undergoing elective colorectal surgery, the addition of a single 1 g dose of ornidazole compared with placebo before surgery significantly reduced surgical site infections.

TRIAL REGISTRATION

ClinicalTrials.gov NCT02618720.

Introduction

Surgical site infection is among the most common healthcare related infections¹ and is associated with increases in morbidity, readmission rates, mortality, and attributable healthcare costs.²⁻⁴ Patients who undergo colorectal surgery are particularly at risk of surgical site infection, with reported incidence rates of up to 26%.^{5,6}

Intravenous antimicrobial prophylaxis against both aerobic and anaerobic bacteria is recommended to prevent surgical site infection after colorectal surgery.⁷⁻⁹ Several large retrospective database studies¹⁰⁻¹² and meta-analyses^{13,14} reported that oral antimicrobial prophylaxis as an adjunct to intravenous antibiotic prophylaxis may help to further reduce surgical site infections after elective colorectal surgery. The results, however, have been controversial because many of these studies used oral antibiotics in addition to mechanical bowel preparation, making it unclear if the reduced infection was related to the oral antibiotics or the additional use of bowel preparation. Moreover, absence of benefit of mechanical bowel preparation compared with no bowel preparation, and concerns about possible harmful effects and discomfort for

Correspondence to: E Futier
Département de Médecine
Périopératoire, Anesthésie
Réanimation, Clermont-Ferrand
cedex 1, France
efutier@chu-clermontferrand.fr
(ORCID 0000-0002-6454-271X)

WHAT IS ALREADY KNOWN ON THIS TOPIC

Intravenous antimicrobial prophylaxis is recommended in patients who undergo colorectal surgery—a patient population that is particularly at risk of surgical site infections

In a recent network meta-analysis, the use of oral antimicrobial prophylaxis in addition to intravenous antibiotics in patients undergoing colorectal surgery was associated with a statistically significant reduction in surgical site infections

The supporting evidence for that finding, however, remains limited

WHAT THIS STUDY ADDS

Compared with placebo, oral antimicrobial prophylaxis using a single dose of 1 g ornidazole 12 hours before surgery as an adjunct to intravenous antibiotic prophylaxis resulted in significantly lower surgical site infections within 30 days

patients, led to recommendations against the routine use of bowel preparation for colonic surgery.^{15 16} Furthermore, one randomised trial of 417 patients who had colonic surgery identified no benefit from combined oral antibiotic prophylaxis and mechanical bowel preparation over no bowel preparation.¹⁷

Whether oral antimicrobial prophylaxis effectively prevents surgical site infection after colorectal surgery remains unclear, with differences in recommendations between organisations.^{7 8} A recently published network meta-analysis of randomised trials showed that the addition of oral antimicrobial prophylaxis to intravenous antibiotics was the best option to prevent surgical site infections after elective colorectal surgery, resulting in a reduction by more than 50%; suggesting that this issue is not definitively resolved.¹⁸ However, the supporting evidence is limited by the number of studies and patients included. Because evidence of a clear clinical benefit is lacking, we conducted the Comparison of Intravenous versus Combined Oral and Intravenous Antimicrobial Prophylaxis (COMBINE) trial to assess the effectiveness of oral antimicrobial prophylaxis as an adjunct to intravenous antibiotic prophylaxis to reduce surgical site infections after colorectal surgery compared with placebo.

Methods

Trial design and setting

We conducted a pragmatic, multicentre, randomised, double blind, placebo controlled trial in 11 academic teaching and non-academic hospitals in France from May 2016 to August 2019. The study protocol and statistical analysis plan were published before the end of enrolment.¹⁹ Written informed consent was obtained from all eligible patients before inclusion in the study. An independent data and safety monitoring board oversaw the conduct of the study and reviewed the interim analysis results so that the trial investigators were blinded. This study followed the consolidated standards of reporting trials (CONSORT) guideline.

Adults who were scheduled for elective laparoscopic or open colorectal surgery were eligible for participation. Patients were excluded if they were to undergo a concomitant surgical procedure (eg, hepatic resection for liver metastasis), had active bacterial infection at the time of surgery or had received antimicrobial treatment within two weeks before surgery, had inflammatory bowel disease, had a body mass index of 35 or higher, had known allergy to β lactams or imidazole antibiotics, had chronic kidney disease (glomerular filtration rate <30 mL/min/1.73 m²), had a known allergy or intolerance to lactose or galactose, and were pregnant or breastfeeding. The supplementary file provides the complete list of exclusion criteria.

Randomisation and trial procedures

Eligible patients were randomly assigned (1:1) to receive a preoperative oral dose of either ornidazole—a nitroimidazole with activity against anaerobic bacteria, or placebo. Randomisation was performed centrally

through a dedicated, password protected web based system. Treatment assignments were stratified with the use of a minimisation algorithm according to trial site, surgical technique (laparoscopic or open surgery), and skin antisepsis (chlorhexidine-alcohol or povidone-iodine alcoholic solution). Study pharmacists prepared the ornidazole and placebo in identical opaque blister packs. All other staff, including investigators and research staff, clinical staff, surgeons, and patients were unaware of the trial group assignments.

Patients received a single 1 g dose of ornidazole or placebo orally 12 hours before surgery. A nurse controlled the receipt of the trial drug. All patients received the same intravenous antimicrobial prophylaxis, using a second generation cephalosporin with anaerobic activity (cefoxitin 2 g) as recommended,^{20 21} administered to all patients at least 30 minutes before skin incision, and readministered intraoperatively if the procedure lasted two hours or more. On 21 June 2018, after 629 patients had been enrolled, an update to French national clinical practice guidelines on antibiotic prophylaxis, external to the trial, substantially modified previous recommendations suggesting the addition of a single intravenous dose of 1g metronidazole to cefoxitin.²² The data and safety monitoring board, the members of which were unaware of treatment assignments and outcome data, did not recommend stopping the trial or changing its conduct.

Site staff were instructed not to prepare the bowel before colonic surgery; however, given the pragmatic nature of the protocol, the operating surgeon ultimately made the decision about whether or not to perform bowel preparation. For rectal surgery, bowel preparation and retrograde rectal enema were recommended the day before surgery,²³ and done according to the expertise of the staff at each study site and to routine clinical practice. All patients received skin preparation with an alcohol based antiseptic agent before surgical incision. All centres followed the enhanced recovery after surgery protocol.²⁴ Laparoscopic and open surgery were allowed; the technique was not standardised. Additional patient care followed local protocols and established guidelines.

Outcome measures

The primary outcome was the proportion of patients with any surgical site infection within 30 days after surgery, as defined by the US Centers for Disease Control and Prevention criteria,²⁵ and classified as superficial incisional, deep incisional, or organ space infection. The operating surgeons assessed surgical site infection during the hospital stay and at each follow-up visit. For patients discharged before day 30, trial staff performed weekly assessments during structured telephone interviews and arranged for in-person clinical evaluations if infection was suspected (see supplementary material for further details). Whenever possible, clinically relevant microbiological samples were cultured.

The secondary outcomes included the proportion of patients with individual types of surgical

site infection; the proportion of patients with postoperative complications, defined as Clavien-Dindo classification²⁶; the proportion of patients with postoperative systemic inflammatory response syndrome or sepsis or septic shock within 30 days; postoperative cardiovascular complications within 30 days; postoperative respiratory complications within 30 days; postoperative acute kidney injury within 30 days, defined according to the Kidney Disease: Improving Global Outcomes criteria; postoperative cardiovascular complications (arrhythmia, myocardial infarction, and acute cardiac failure) within 30 days; postoperative anastomotic leakage, reoperation, and surgical or endoscopic drainage within 30 days; the

time to initiation of adjuvant chemotherapy; the need for unplanned hospital readmissions; unexpected admission to the intensive care unit; duration of hospital stay; hospital-free days to day 30; and all cause mortality within 30 and 90 days after surgery (see supplementary material for definitions of end points). Clinicians and research staff, who were unaware of the trial group assignments, obtained the data for outcome measures.

Statistical analysis

Assuming a 15% rate of surgical site infections with placebo,^{5 6 13} we estimated that enrolling 920 patients would provide 80% power to detect a 40%

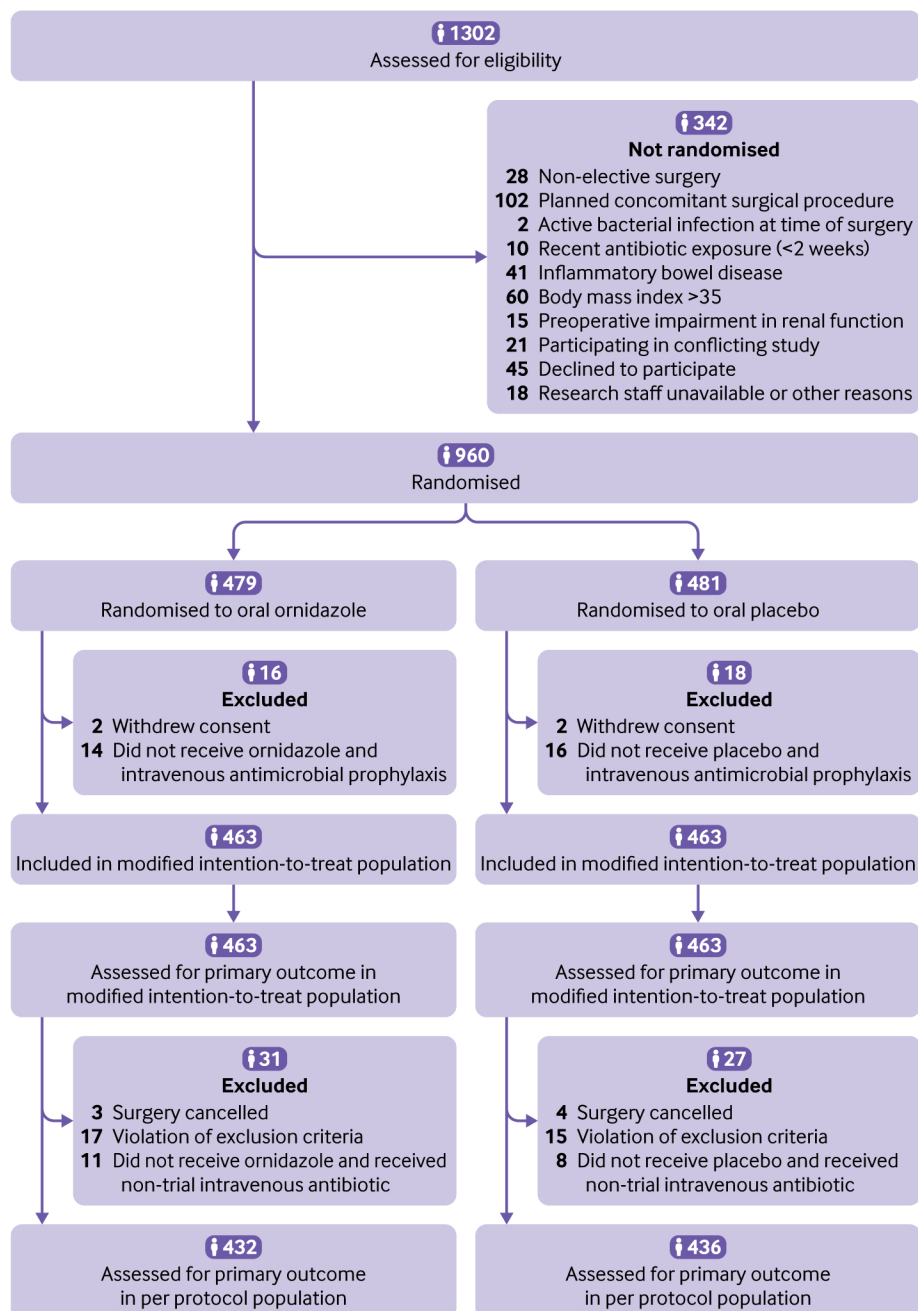


Fig 1 | Flow of participants through study. The per protocol population included patients from the modified intention-to-treat population, except those with one or more major protocol violations

Table 1 | Baseline characteristics of participants in modified intention-to-treat population. Values are numbers (percentages) unless stated otherwise

Characteristics	Oral prophylaxis group (n=463)	Placebo group (n=463)
Mean (SD) age (years)	63 (13)	63 (13)
Men	262 (57)	292 (63)
Mean (SD) weight (kg)	74 (15)	75 (15)
Mean (SD) body mass index	26 (4)	26 (4)
ASA physical status classification*:		
1	101/462 (22)	101/461 (22)
2	272/462 (59)	260/461 (56)
3	86/462 (18)	94/461 (20)
4	3/462 (1)	6/461 (2)
Medical history:		
Hypertension	199 (43)	198 (43)
Diabetes mellitus	69 (15)	71 (15)
Coronary artery disease	32 (7)	56 (12)
Chronic pulmonary disease	22 (5)	33 (7)
Current smoker	71 (15)	78 (17)
Any alcohol intake	34 (7)	39 (8)
Disease related malnutrition	31 (7)	20 (4)
History of multidrug resistant bacteria	2 (1)	3 (1)
Antibiotic use within 3 months before surgery	53 (11)	56 (12)
Adjuvant chemotherapy or radiotherapy	113 (24)	110 (24)
Drugs used at time of surgery:		
Corticosteroid	11 (2)	15 (3)
Non-steroidal anti-inflammatory drug	5 (1)	13 (3)
Indication for surgery:		
Colorectal cancer	351 (76)	356 (77)
Diverticulitis	78 (17)	70 (15)
Other condition	34 (7)	37 (8)
Skin preparation:		
Chlorhexidine-alcohol	43 (9)	48 (10)
Povidone-iodine alcohol	420 (91)	415 (90)
Mechanical bowel preparation:	153 (33)	160 (35)
Polyethylene glycol	64/151 (42)	57/157 (36)
Senna solution	87/151 (58)	100/157 (64)
Retrograde enema	199 (43)	210 (45)

ASA=American Society of Anesthesiology.

Only male sex (P=0.04) and coronary artery disease (P=0.007) differed significantly.

Percentages may not total 100 because of rounding.

*Data on the ASA physical status class were missing for two participants in the placebo group and one participant in the oral prophylaxis (ornidazole) group.

relative between group difference in the incidence of the primary outcome (ie, 15% in the placebo group and 9% in the oral ornidazole group),¹³ with a 5% two sided type I error. We inflated the sample size to 960 patients to account for a 5% loss to follow-up. As prespecified in the study protocol, one interim analysis was planned after the enrolment of the first 460 patients. The data and safety monitoring board did not recommend stopping the trial, and 960 patients were therefore included.

The planned approach to statistical analysis is published elsewhere.¹⁹ We analysed data in the modified intention-to-treat population, which was prespecified as all randomised patients who received a trial drug plus intravenous antimicrobial prophylaxis, with the exception of those who withdrew consent. We also analysed one per protocol population, which included patients from the modified intention-to-treat population except those with one or more major protocol violations.

An unadjusted χ^2 test was used to compare the primary outcome between the two groups. Other binary outcomes were tested using an unadjusted χ^2

test or Fisher's exact test as appropriate. Results are reported as absolute differences and relative risks with 95% confidence intervals. Multivariable logistic mixed regression was used to identify prespecified covariates with a known association with the primary outcome (selected if the P value was <0.10 in the bivariable analysis) in addition to the stratification variables. We assessed multicollinearity between variables by computing the variance inflation factor and using the Farrar-Glauber test. The Akaike information criterion and bayesian information criterion were calculated and used as model diagnostics to determine how well the model fit improved after the addition of covariates. Adjusted analyses were performed with the use of robust random effect Poisson generalised linear mixed model regression with robust variance for binary outcomes,²⁷ multinomial logistic mixed model for categorical outcomes, and linear mixed regression for continuous outcomes, with study site as a random effect. Time to event was compared between the two groups using the Kaplan-Meier method. A marginal Cox proportional hazards model was used to estimate hazard ratios and corresponding 95% confidence intervals. The proportional hazard hypothesis was evaluated using the Schoenfeld test and plotting residuals.

We conducted two prespecified subgroup analyses of the primary outcome in subgroups with mechanical bowel preparation versus without and with colonic surgery versus rectal surgery. Interaction terms in the random effect regression model were used to test for heterogeneity of effect between subgroups.

A post hoc analysis was conducted to test for a difference in treatment effect during the conduct of the trial in relation to publication of the update to French guidelines (before versus after publication update). We also conducted a post hoc analysis to investigate a potential treatment effect resulting from non-compliance with bowel preparation. No correction for multiple testing was applied in the analyses of secondary outcomes or subgroups. Complete case analysis was performed for all outcomes. We did not compensate for dropouts. A two sided P value of <0.05 was considered to indicate statistical significance. All analyses were generated with the use of Stata software, version 15.0 (StataCorp).

Patient and public involvement

Except for providing written informed consent before participation, patients and members of the public were not involved in the design or conduct of this study, because it was not customary for them to be involved in the design of scientific studies when the study was started. Patients will be consulted to assist with the dissemination of the study findings.

Results

From 25 May 2016 to 8 August 2019, 960 patients provided informed consent and were enrolled in the trial: 479 were randomly assigned to oral prophylaxis and 481 to placebo. After withdrawals (16 patients

Table 2 | Surgical and other perioperative characteristics of participants in modified intention-to-treat population. Values are numbers (percentages) unless stated otherwise

Characteristics	Oral prophylaxis group (n=463)	Placebo group (n=463)
Mean (SD) time from intervention dose to skin incision (hours)	13.0 (1.3)	13.1 (1.2)
Mean (SD) time from intravenous antimicrobial prophylaxis to skin incision (minutes)*	36.8 (22.0)	37.7 (24.2)
Type of surgery:		
Colectomy	301/463 (65)	296/463 (64)
Right hemicolectomy	121/301 (40)	110/296 (37)
Left hemicolectomy	164/301 (54)	169/296 (57)
Transverse colectomy	28/301 (9)	23/296 (8)
Total colectomy	8/301 (3)	12/296 (4)
Rectal resection	162/463 (35)	167/463 (36)
Surgical method:		
Open	60 (13)	57 (12)
Laparoscopic assisted	337 (73)	344 (74)
Laparoscopy converted to open	66 (14)	62 (14)
Type of anastomosis:		
Stapled	326/437 (75)	331/430 (77)
Handsewn	111/437 (25)	99/430 (23)
Ileostomy or colostomy performed	154 (33)	153 (33)
Abdominal surgical drain used	200 (43)	192 (41)
Median (IQR) duration of surgery (minutes)†	211 (160-280)	201 (159-270)
Median (IQR) volume of intravenous fluid (mL):		
Crystalloid	2000 (1500-2500)	2000 (1500-2500)
Colloid	500 (500-1000)	500 (500-1000)
Median (IQR) infusion rate (mL/kg/h)	7.6 (6.0-10.3)	8.0 (6.0-11.0)
Cardiac output monitoring used	94/463 (20)	112/463 (24)
Median (IQR) FiO ₂ (%):		
Start of surgery	44 (40-50)	45 (40-50)
End of surgery	45 (40-51)	45 (39-51)
Mean (SD) core temperature at end of surgery (°C)	36 (1)	36 (1)
Received dexamethasone	314 (68)	320 (69)
Received intravenous lidocaine	351 (76)	330 (71)
Median (IQR) intraoperative blood loss (mL)	150 (100-300)	150 (100-300)
Red blood cell transfusion during surgery	17 (4)	14 (3)
Postoperative lidocaine used	150 (32)	133 (29)
Postoperative epidural analgesia used	57 (12)	60 (13)
Planned postoperative care in HDU or ICU	117 (25)	110 (24)

FiO₂=fraction of inspired oxygen; HDU=high dependency unit; ICU=intensive care unit; IQR=interquartile range; SD=standard deviation.

Percentages may not total 100 because of rounding.

*Data were missing for 25 patients in the oral prophylaxis group and 20 patients in the placebo group.

†Data were missing for three patients in the placebo group.

in the oral prophylaxis group and 18 in the placebo group), 926 patients (463 assigned to oral prophylaxis and 463 assigned to placebo) were included in the analysis (fig 1). Baseline characteristics of both groups, with the exception of men and coronary artery disease both of which were more frequent in the placebo group, and other aspects of perioperative management were comparable (table 1 and table 2, also see supplementary table S1). In the overall population, 64% of patients underwent colon resection and 36% underwent rectal resection; 74% of the surgical procedures were performed laparoscopically. Among the 597 patients (301 in the oral prophylaxis group and 296 in the placebo group) who underwent colon surgery, 103 (17.3%) received bowel preparation (53 patients in the oral prophylaxis group and 50 patients in the placebo group). The mean time from oral prophylaxis or placebo to skin incision was 13 hours and from intravenous antimicrobial prophylaxis

to skin incision was 37 minutes, without significant differences between the groups.

Primary outcome

Surgical site infections within 30 days after surgery occurred in 60 of 463 patients (13.0%) with oral prophylaxis and in 100 of 463 patients (21.6%) with placebo (absolute difference −8.6%, 95% confidence interval −13.5% to −3.8%; relative risk 0.60, 95% confidence interval 0.45 to 0.80). Supplementary table S2 shows the results of associated univariable and multivariable analyses. The result was unaffected by adjustment for stratification variables and covariates (adjusted relative risk 0.62, 95% confidence interval 0.44 to 0.46) (see supplementary table S3). Similar results were obtained in the per protocol population (see supplementary tables S4-S6). Figure 2 shows the times to surgical site infection.

Secondary outcomes

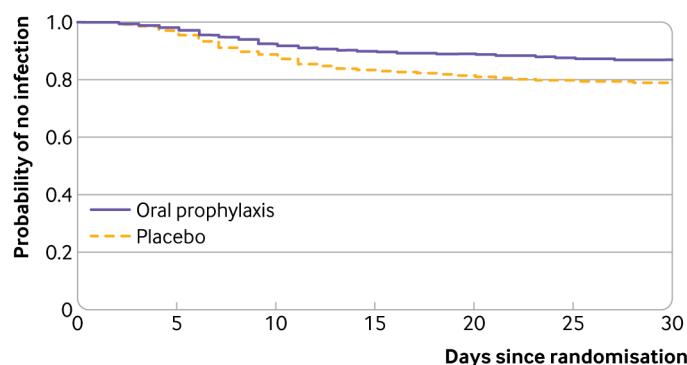
Table 3 shows predefined secondary outcomes. Significant differences were found between the oral prophylaxis and placebo groups for occurrence of deep infections (4.8% v 8.0%; relative risk 0.54, 95% confidence interval 0.31 to 0.92) and organ space infections (5.0% v 8.4%; 0.53, 0.31 to 0.91). Adjusted analyses yielded similar results (see supplementary table S3). Fewer patients in the oral prophylaxis group than placebo group developed major (Clavien-Dindo grade ≥3) complications within 30 days after surgery (relative risk 0.67, 0.46 to 0.96). Similarly, clinically meaningful between group differences were found for anastomotic leakage and sepsis or septic shock (table 3). Death within 30 days did not differ between the two groups. No serious adverse event from trial drugs was reported by the investigator in either group. Supplementary table S7 shows the spectrum of pathogens isolated from patients with surgical site infection.

Heterogeneity existed between the oral prophylaxis and placebo groups and bowel preparation for surgical site infection (9.8% v 29.3%; difference −19.6% (95% confidence interval −28.1% to −11.1%)) in patients who received mechanical bowel preparation and 14.5% v 17.5%; difference −2.9% (−8.8% to 2.8%) in patients who did not receive mechanical bowel preparation; P for interaction=0.006) (fig 3). We found no evidence of a differential effect according to type of surgery (colon versus rectum resection; P for interaction=0.49).

Post hoc analysis

We found no significant interaction between treatment groups in relation to update of the French guidelines (before versus after publication update) for surgical site infection (P for interaction=0.87) (see supplementary materials).

We also conducted a post hoc analysis to investigate a potential treatment effect resulting from non-compliance with bowel preparation. Similar results to the primary analysis were found in a per protocol analysis excluding all patients (30 patients in



Oral prophylaxis	463	455	429	418	413	407	403
Placebo	463	450	412	387	378	370	363

Fig 2 | Kaplan-Meier probability of surgical site infection (modified intention-to-treat population). Raw data for the Kaplan-Meier probability of surgical site infection were censored at 30 days after surgery (hazard ratio with oral prophylaxis versus placebo 0.57, 95% confidence interval 0.43 to 0.78). The Cox proportional-hazards model was unadjusted

the oral prophylaxis group and 35 patients in the placebo group) who did not fully comply with bowel preparation (12.7% v 22%; unadjusted relative risk 0.58, 95% confidence interval 0.43 to 0.78; adjusted relative risk 0.59, 95% confidence interval 0.46 to

0.77). Detection of a treatment effect would have suggested uncontrolled confounding.

Discussion

Principal findings

In this multicentre pragmatic double blind randomised trial involving patients undergoing elective colorectal surgery, adding a single dose of 1 g ornidazole 12 hours before surgery as an adjunct to intravenous antibiotic prophylaxis resulted in a significantly lower rate of surgical site infection within 30 days after surgery compared with placebo. Compared with those assigned to placebo, participants assigned to oral prophylaxis had a 40% lower relative risk of surgical site infection; in addition, the oral prophylaxis group had lower rates of other secondary outcomes, including major postoperative surgical complications (33% lower relative risk). The findings suggest that the effect of oral prophylaxis versus placebo was attributed mostly to a reduction in the rates of deep and organ space surgical site infections.

Comparison with other studies

The overall incidence of surgical site infection in our study (17.3%) was slightly higher than hypothesised but consistent with rates reported in previous trials (ranging from 7% to 26%).^{5 6 17 28} A possible explanation is the 35.5% proportion of rectal procedures in this

Table 3 | Primary and secondary outcomes of participants in modified intention-to-treat population. Values are numbers (percentages) unless stated otherwise

Outcomes	Oral prophylaxis group (n=463)	Placebo group (n=463)	Relative risk (95% CI)*	P value
Primary outcome				
Any surgical site infection within 30 postoperative days	60 (13.0)	100 (21.6)	0.60 (0.45 to 0.80)	0.001
Secondary outcomes†				
Superficial incisional infection	15 (3.2)	24 (5.2)	0.56 (0.29 to 1.09)	0.09
Deep incisional infection	22 (4.8)	37 (8.0)	0.54 (0.31 to 0.92)	0.03
Organ space infection	23 (5.0)	39 (8.4)	0.53 (0.31 to 0.91)	0.02
SIRS	96 (20.7)	122 (26.4)	0.79 (0.62 to 0.99)	0.045
Sepsis or septic shock	26 (5.6)	42 (9.1)	0.62 (0.39 to 0.99)	0.046
Arrhythmia	84 (18.1)	76 (16.4)	1.11 (0.83 to 1.47)	0.49
Acute heart failure	1 (0.2)	0 (0.0)	NA	1.00
Myocardial infarction	0 (0.0)	1 (0.2)	NA	1.00
Pneumonia	13 (2.8)	6 (1.3)	2.17 (0.83 to 5.65)	0.11
Postoperative mechanical ventilation	9 (1.9)	15 (3.2)	0.60 (0.27 to 1.36)	0.22
Acute kidney injury	61 (13.2)	63 (13.6)	0.97 (0.70 to 1.34)	0.85
Clavien-Dindo classification grade:				
1 or 2	188 (40.6)	181 (39.1)	0.98 (0.74 to 1.29)	0.86
≥3	42 (9.1)	63 (13.6)	0.63 (0.41 to 0.97)	0.03
Anastomotic leakage	22 (4.8)	37 (8.0)	0.59 (0.36 to 0.99)	0.046
Reoperation	35 (7.6)	49 (10.6)	0.71 (0.47 to 1.08)	0.11
Surgical or endoscopic drainage	3 (0.7)	7 (1.5)	0.43 (0.11 to 1.65)	0.20
Mean (SD) time from randomisation to adjuvant chemotherapy initiation (days)	20 (5)	22 (6)	NA	0.47
Unplanned hospital readmission	30 (6.5)	30 (6.5)	1 (0.61 to 1.63)	1.00
Unplanned admission to ICU	1 (0.2)	5 (1.1)	0.20 (0.02 to 1.71)	0.14
Median (IQR) duration of hospital stay (days)	6 (5-10)	7 (5-11)	NA	0.48
Median (IQR) hospital-free days at 30 days (days)	24 (20-25)	23 (19-25)	NA	0.48
Death:				
At 30 days	2 (0.4)	5 (1.1)	0.40 (0.08 to 2.05)	0.27
At 90 days	5 (1.1)	10 (2.2)	0.50 (0.17 to 1.45)	0.20

CI=confidence interval; ICU=intensive care unit; IQR=interquartile range; NA=not applicable; SIRS=systemic inflammatory response syndrome.

*Relative risk is for oral prophylaxis group compared with placebo group. Confidence intervals were not adjusted for multiple comparisons of other secondary outcomes; thus these analyses are exploratory and should not be used to infer definitive treatment effects. Supplementary table S3 shows the results of adjusted outcome analyses.

†All secondary outcomes, except 90 day mortality, were assessed up to 30 days after surgery.

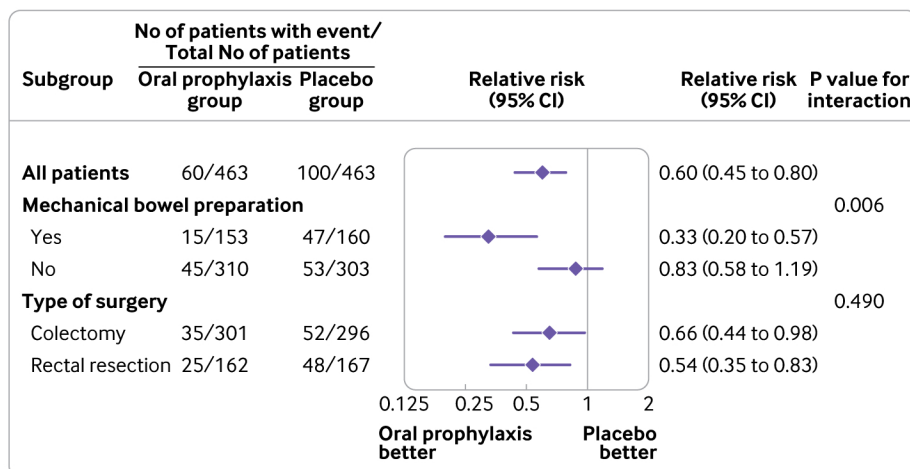


Fig 3 | Relative risks with 95% confidence intervals for the primary outcome of surgical site infection within 30 days after surgery in the oral prophylaxis group and placebo group, among all patients and in the two predefined subgroups. The widths of the confidence intervals for subgroup analyses were not adjusted for multiplicity and should not be used to infer definitive treatment effects. Mechanical bowel preparation consisted of polyethylene glycol or senna solution

study. Rectal resection is associated with a higher risk of anastomotic leakage and surgical site infections than would be expected after intraperitoneal colon resection.²⁹

Previous meta-analyses of randomised trials have suggested that use of oral antibiotics, whether alone or in combination with mechanical bowel preparation, is associated with lower rates of surgical site infections.^{13 14 30} These trials had several limitations however, including the main use of open surgery, which may be associated with a greater risk of surgical site infection than laparoscopic surgery,³¹ and, in many of these trials, the postoperative continuation of antibiotic prophylaxis—a strategy that is no longer recommended.³² Also, the oral antibiotics, dosages, and timings varied across studies, making the results difficult to translate into clinical practice. Several antibiotic regimens have been previously evaluated for oral prophylaxis.¹³ Although nitroimidazole derivatives in combination with aminoglycosides were frequently used, no clear evidence exists on which preferred type and dosage of oral antibiotics should be used before colorectal surgery.⁸ Antibiotics with the narrowest possible spectrum should be used to produce as little inadvertent damage as possible to the endogenous microflora, which provides a natural resistance to colonisation, and to reduce the emergence of resistant organisms. In our study, we assessed the effect of a single preoperative oral dose of 1 g ornidazole, which has a spectrum of activity extended to most anaerobes encountered in the colon and the rectum, has a longer elimination half life than other nitroimidazole derivatives (especially metronidazole)—the pharmacokinetic profile of which allows a single dose to be administered the day before surgery, and is widely available. Additionally, no serious adverse event was recorded in our study.

A major component of the controversy about oral antimicrobial prophylaxis is the use of mechanical bowel preparation. In our pragmatic randomised study,

bowel preparation was used in accordance with current practice, which states that bowel preparation should be avoided before colonic surgery but might be beneficial in patients having rectal resections.²³ However, the treatment effect showed heterogeneity, suggesting that in patients who received mechanical bowel preparation, an excess risk of surgical site infection might be associated with placebo (versus ornidazole). In patients who did not undergo bowel preparation, we found no evidence of a difference in risk of surgical site infection between placebo and ornidazole. Finally, the combination of ornidazole and mechanical bowel preparation seems to be associated with the lowest risk of surgical site infection. The findings in the present study contrast with those of the recent MOBILE study in patients having elective colon resection, in which mechanical and oral antibiotic bowel preparation was not associated with a reduced rate of surgical site infections or overall morbidity compared with no bowel preparation.¹⁷ In another multicentre, single blind, randomised trial of 565 patients who did not receive bowel preparation, oral antibiotic prophylaxis was associated with a reduced rate of surgical site infections; this study did not, however, include rectal surgery.³³ In our study, the effects of oral prophylaxis in the prespecified subgroup analysis did not differ between the groups who underwent colonic surgery and rectal surgery. The number of patients who had rectal surgery was, however, too low to draw definite conclusions.^{8 9}

Strengths and limitations of this study

The strengths of our study include the large sample size and the multicentred and pragmatic design with maintenance of usual care, including compliance with the programme for early recovery after surgery. Moreover, unlike previously available published studies, our trial was not restricted to colonic surgeries, allowing the findings to be generalisable to colorectal surgery overall.

Limitations must also be considered. Firstly, protocol deviations could have biased the analyses. Non-adherence to the allocated trial intervention is unlikely to have affected the results, however, because the per protocol analysis, from which these patients were excluded, supported the primary analysis. Mechanical bowel preparation may potentially have biased the estimate of treatment effect in our trial. However, our results were robust in an analysis excluding patients who did not fully comply with bowel preparation. Secondly, we did not assess all cointerventions during the trial that might have influenced the risk of surgical site infection, such as glycaemic control or preoperative bathing during the trial period. The trial was, however, blinded and randomisation was stratified; it is less likely that any imbalance in cointerventions affected the results. Thirdly, although cefoxitin has both aerobic and anaerobic activity, because of increasing resistance of anaerobes (including *Bacteroides*) to second generation cephalosporins, its use for intravenous antibiotic prophylaxis could have been suboptimal. This may limit external validity, as currently guidelines for preoperative prophylaxis include enhanced anaerobic coverage. Whether the effect for the oral antimicrobial prophylaxis results from improved anaerobic coverage or from an additional decrease in the bioburden from oral antibiotics deserves further evaluation. Fourthly, one third of the participants had rectal surgery. Although the exclusion of participants who were candidates for rectal surgery might have enhanced the study design, we aimed to evaluate whether the intervention effect would be consistent across colorectal procedures. The subgroup analysis suggested that oral antibiotic prophylaxis might be equally beneficial to patients having colon and rectal procedures. A further anticipated limitation, owing to possible pharmacokinetic and pharmacodynamic modifications, was the exclusion of patients with a body mass index of 35 or higher, even though obese patients are at increased risk of surgical site infection. However, the participants in our trial had baseline characteristics, including mean body mass index, that were similar to those of participants in previous studies. Finally, generalisability to populations not included in the trial, such as patients with inflammatory bowel diseases, remains to be evaluated.

Conclusion

In this large pragmatic multicentre trial in patients undergoing elective colorectal surgery, the use of oral antimicrobial prophylaxis with a single oral dose of 1 g ornidazole compared with placebo as an adjunct to intravenous antibiotic prophylaxis resulted in a significantly lower rate of surgical site infection within 30 days after surgery.

AUTHOR AFFILIATIONS

¹Département Anesthésie et Réanimation, Centre Hospitalier Universitaire de Clermont-Ferrand, Hôpital Estaing, Clermont-Ferrand, France

²Inserm U-1103, CNRS UMR 6293, Université Clermont Auvergne, Clermont-Ferrand, France

³Département Anesthésie et Réanimation B, Centre Hospitalier Universitaire de Montpellier, Hôpital Saint-Eloi, Montpellier, France

⁴Inserm U-1046, Université Montpellier, Montpellier, France

⁵Pôle Anesthésie Réanimation, Centre Hospitalier Universitaire de Lille, Hôpital Claude Huriez, Lille, France

⁶Département de Chirurgie Colorectale, Assistance publique-Hôpitaux de Paris, Pôle des Maladies de l'Appareil Digestif, Hôpital Beaujon, Clichy, France

⁷Service de Chirurgie Digestive et Hépatobiliaire, Centre Hospitalier Universitaire de Clermont-Ferrand, Hôpital Estaing, Clermont-Ferrand, France

⁸Unité d'Hygiène et de Lutte Contre les Infections Nosocomiales, Assistance Publique-Hôpitaux de Paris, Hôpital Bichat-Claude Bernard, Paris, France

⁹IAME, Université Paris Sorbonne Nord, UMR 1137 Inserm, Paris, France

¹⁰Service Anesthésie et Réanimation, Centre Medico-chirurgical Magellan, Centre Hospitalier Universitaire de Bordeaux, Pessac, France

¹¹Biologie des Maladies Cardiovasculaires, Université de Bordeaux, UMR 1034 Inserm, Pessac, France

¹²Département Anesthésie et Réanimation, Centre Hospitalier de Valenciennes, Valenciennes, France

¹³Service de Chirurgie Viscérale et Digestive, Centre Hospitalier de Pau, Pau, France

¹⁴Département de chirurgie oncologique, Centre Léon Bérard, Lyon, France

¹⁵Inserm, LabTAU, Université Claude Bernard Lyon 1, Lyon, France

¹⁶Département Anesthésie et Réanimation, Centre Hospitalier Universitaire de Angers, Angers, France

¹⁷Service Anesthésie et Réanimation, Assistance Publique Hôpitaux de Marseille, Aix Marseille Université, Hôpital Nord, Marseille, France

¹⁸Service d'Anesthésie Réanimation et Médecine Périopératoire, Hôpitaux Universitaires de Strasbourg, Hôpital Hautepierre, Strasbourg, France

¹⁹Direction de la Recherche Clinique, Centre Hospitalier Universitaire de Clermont-Ferrand, Biostatistics Unit, Clermont-Ferrand, France

²⁰Département Anesthésie Réanimation, Assistance publique-Hôpitaux de Paris, Hôpitaux Universitaires Paris Nord Val de Seine, Hôpital Beaujon, Clichy, France

A list showing members of the COMBINE study group is in the supplementary materials.

Contributors: Ef and SJ are joint first authors. EF obtained funding from the French Ministry of Health to undertake the study. He is the guarantor and accepts full responsibility for the work. EF and CPB conceived the study. EF, SJ, JCL, and CPB designed the study. MG, MV, YP, KS, GL, AO, YEA, PC, AD, SL, ML, and JP acquired the data. EF, SJ, ADJ, and BP analysed and interpreted the data. EF and SJ wrote the initial draft and contributed equally to this manuscript. All authors critically revised the manuscript and approved the final version. The lead author (EF) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Additional contributors: Justine Bourdier (research technician) and Dominique Morand (administrative support, Direction de la recherche clinique Clermont-Ferrand).

Funding: This study was funded by a grant from the French Ministry of Health under its Clinical Research Program (PHRC-14-0060) and by the Clermont-Ferrand University Hospital. The funders had no role in considering the study design or in the collection, analysis, or interpretation of data, the writing of the report, or the decision to submit the article for publication.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: the study was funded by a grant from the French Ministry of Health under its Clinical Research Program and by Clermont-Ferrand University Hospital; EF reports receiving consulting fees from Drager Medical, GE Healthcare, and Edwards Lifesciences, and honorariums

for presentation from Baxter outside the submitted work; SJ reports receiving consulting fees from Drager Medical, Fisher & Paykel Healthcare, Fresenius Xenios, Medtronic, Baxter, and Mindray outside the submitted work; SL reports receiving consulting fees from Vifor Pharma and Alexys Sante, and honorariums for lectures from Vifor Pharma, Pharmacosmos, Pfizer, and Masimo outside the submitted work; ML reports receiving consulting fees from Gilead, Ambu, and LFB outside the submitted work; AO reports receiving consulting fees from LFB, Orion Pharma, Vifor Pharma, Nordic Pharma, and iSEP, and honorariums for lectures from Orion Pharma, Nordic Pharma, and LFB outside the submitted work. The authors declare no financial relationships with any organisations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This trial was approved for all centres by the South-Est VI Committee for the Protection of Research Subjects (ID: 2015-002559-84) and the French National Agency of Medicine and Health Products Safety.

Data sharing: Deidentified data about the individual participants will be shared with researchers of further studies on reasonable request. Request for data sharing will be handled in line with the data access and sharing policy of Clermont-Ferrand University Hospital.

The lead author (EF) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained

Dissemination to participants and related patients and public communities: After publication, the findings of this study will be disseminated to appropriate audiences, including participating surgical departments, academia, clinicians, and the general public, through various channels, such as blogs, press releases, and social media. The results were also presented at the French Society of Anaesthesiology and Critical Care Medicine and will serve as a support for the update of French guidelines.

Provenance and peer review: Not commissioned; externally peer reviewed.

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

- Fields AC, Pradarelli JC, Itani KMF. Preventing Surgical Site Infections: Looking Beyond the Current Guidelines. *JAMA* 2020;323:1087-8. doi:10.1001/jama.2019.20830.
- Coello R, Charlett A, Wilson J, Ward V, Pearson A, Borriello P. Adverse impact of surgical site infections in English hospitals. *J Hosp Infect* 2005;60:93-103. doi:10.1016/j.jhin.2004.10.019.
- de Lissovoy G, Fraeman K, Hutchins V, Murphy D, Song D, Vaughn BB. Surgical site infection: incidence and impact on hospital utilization and treatment costs. *Am J Infect Control* 2009;37:387-97. doi:10.1016/j.ajic.2008.12.010.
- Keenan JE, Speicher PJ, Thacker JK, Walter M, Kuchibhatla M, Mantyh CR. The preventive surgical site infection bundle in colorectal surgery: an effective approach to surgical site infection reduction and health care cost savings. *JAMA Surg* 2014;149:1045-52. doi:10.1001/jamasurg.2014.346.
- Bennett-Guerrero E, Pappas TN, Koltun WA, et al, SWIPE 2 Trial Group. Gentamicin-collagen sponge for infection prophylaxis in colorectal surgery. *N Engl J Med* 2010;363:1038-49. doi:10.1056/NEJMoa1000837.
- Itani KM, Wilson SE, Awad SS, Jensen EH, Finn TS, Abramson MA. Ertapenem versus cefotetan prophylaxis in elective colorectal surgery. *N Engl J Med* 2006;355:2640-51. doi:10.1056/NEJMoa054408.
- Berrios-Torres SI, Umscheid CA, Bratzler DW, et al, Healthcare Infection Control Practices Advisory Committee. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. *JAMA Surg* 2017;152:784-91. doi:10.1001/jamasurg.2017.0904.
- Allegranzi B, Bischoff P, de Jonge S, et al, WHO Guidelines Development Group. New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. *Lancet Infect Dis* 2016;16:e276-87. doi:10.1016/S1473-3099(16)30398-X.
- Ban KA, Minei JP, Laronga C, et al, American College of Surgeons and Surgical Infection Society: Surgical Site Infection Guidelines, 2016 Update. *J Am Coll Surg* 2017;224:59-74. doi:10.1016/j.jamcollsurg.2016.10.029.
- Morris MS, Graham LA, Chu DI, Cannon JA, Hawn MT. Oral Antibiotic Bowel Preparation Significantly Reduces Surgical Site Infection Rates and Readmission Rates in Elective Colorectal Surgery. *Ann Surg* 2015;261:1034-40. doi:10.1097/SLA.0000000000001125.
- Kiran RP, Murray AC, Chiuzean C, Estrada D, Forde K. Combined preoperative mechanical bowel preparation with oral antibiotics significantly reduces surgical site infection, anastomotic leak, and ileus after colorectal surgery. *Ann Surg* 2015;262:416-25, discussion 423-5. doi:10.1097/SLA.0000000000000146.
- Scarborough JE, Mantyh CR, Sun Z, Migaly J. Combined Mechanical and Oral Antibiotic Bowel Preparation Reduces Incisional Surgical Site Infection and Anastomotic Leak Rates After Elective Colorectal Resection: An Analysis of Colectomy-Targeted ACS NSQIP. *Ann Surg* 2015;262:331-7. doi:10.1097/SLA.0000000000001041.
- Nelson RL, Gladman E, Barbateskovic M. Antimicrobial prophylaxis for colorectal surgery. *Cochrane Database Syst Rev* 2014;CD001181:CD001181. doi:10.1002/14651858.CD001181.pub4.
- Rollins KE, Javanmard-Emamghissi H, Acheson AG, Lobo DN. The Role of Oral Antibiotic Preparation in Elective Colorectal Surgery: A Meta-analysis. *Ann Surg* 2019;270:43-58. doi:10.1097/SLA.0000000000003145.
- Slim K, Vicaut E, Launay-Savary MV, Contant C, Chipponi J. Updated systematic review and meta-analysis of randomized clinical trials on the role of mechanical bowel preparation before colorectal surgery. *Ann Surg* 2009;249:203-9. doi:10.1097/SLA.0b013e318193425a.
- Güenaga KF, Matos D, Wille-Jørgensen P. Mechanical bowel preparation for elective colorectal surgery. *Cochrane Database Syst Rev* 2011;CD001544:CD001544. doi:10.1002/14651858.CD001544.pub4.
- Koskenvuo L, Lehtonen T, Koskensalo S, et al. Mechanical and oral antibiotic bowel preparation versus no bowel preparation for elective colectomy (MOBILE): a multicentre, randomised, parallel, single-blinded trial. *Lancet* 2019;394:840-8. doi:10.1016/S0140-6736(19)31269-3.
- Woodfield JC, Clifford K, Schmidt B, Turner GA, Amer MA, McCall JL. Strategies for Antibiotic Administration for Bowel Preparation Among Patients Undergoing Elective Colorectal Surgery: A Network Meta-analysis. *JAMA Surg* 2022;157:34-41. doi:10.1001/jamasurg.2021.5251.
- Vignaud M, Paugam-Burtz C, Garot M, et al, COMBINE trial management committee. Comparison of intravenous versus combined oral and intravenous antimicrobial prophylaxis (COMBINE) for the prevention of surgical site infection in elective colorectal surgery: study protocol for a multicentre, double-blind, randomised controlled clinical trial. *BMJ Open* 2018;8:e020254. doi:10.1136/bmjopen-2017-020254.
- Martin C, Auboyer C, Dupont H, et al, Société française d'anesthésie et de réanimation. Antibiotrophylaxis in surgery and interventional medicine (adult patients). Actualization 2010. [In French.] *Ann Fr Anesth Reanim* 2011;30:168-90. doi:10.1016/j.annfar.2010.05.012.
- Bratzler DW, Dellinger EP, Olsen KM, et al, American Society of Health-System Pharmacists, Infectious Disease Society of America, Surgical Infection Society, Society for Healthcare Epidemiology of America. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm* 2013;70:195-283. doi:10.2146/ajhp120568.
- Martin C, Auboyer C, Boisson M, et al, Steering committee of the French Society of Anaesthesia and Intensive Care Medicine (SFAR) responsible for the establishment of the guidelines. Antibiotrophylaxis in surgery and interventional medicine (adult patients). Update 2017. *Anaesth Crit Care Pain Med* 2019;38:549-62. doi:10.1016/j.accpm.2019.02.017.
- Bretagnol F, Panis Y, Rullier E, et al, French Research Group of Rectal Cancer Surgery (GRECCAR). Rectal cancer surgery with or without bowel preparation: The French GRECCAR III multicenter single-blinded randomized trial. *Ann Surg* 2010;252:863-8. doi:10.1097/SLA.0b013e3181fd8ea9.
- Gustafsson UO, Scott MJ, Schwenk W, et al, Enhanced Recovery After Surgery (ERAS) Society, for Perioperative Care, European Society for Clinical Nutrition and Metabolism (ESPEN), International Association for Surgical Metabolism and Nutrition (IASMEN). Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *World J Surg* 2013;37:259-84. doi:10.1007/s00268-012-1772-0.
- Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;36:309-32. doi:10.1016/j.ajic.2008.03.002.

- 26 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205-13. doi:10.1097/01.sla.0000133083.54934.ae
- 27 Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004;159:702-6. doi:10.1093/aje/kwh090.
- 28 Darouiche RO, Wall MJ Jr, Itani KM, et al. Chlorhexidine-Alcohol versus Povidone-Iodine for Surgical-Site Antisepsis. *N Engl J Med* 2010;362:18-26. doi:10.1056/NEJMoa0810988.
- 29 Guillaou PJ, Quirke P, Thorpe H, et al, MRC CLASICC trial group. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet* 2005;365:1718-26. doi:10.1016/S0140-6736(05)66545-2.
- 30 Toh JWT, Phan K, Hitos K, et al. Association of Mechanical Bowel Preparation and Oral Antibiotics Before Elective Colorectal Surgery With Surgical Site Infection: A Network Meta-analysis. *JAMA Netw Open* 2018;1:e183226. doi:10.1001/jamanetworkopen.2018.3226.
- 31 Caroff DA, Chan C, Kleinman K, et al. Association of Open Approach vs Laparoscopic Approach With Risk of Surgical Site Infection After Colon Surgery. *JAMA Netw Open* 2019;2:e1913570. doi:10.1001/jamanetworkopen.2019.13570.
- 32 Allegranzi B, Zayed B, Bischoff P, et al, WHO Guidelines Development Group. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. *Lancet Infect Dis* 2016;16:e288-303. doi:10.1016/S1473-3099(16)30402-9.
- 33 Espin Basany E, Solís-Peña A, Pellino G, et al. Preoperative oral antibiotics and surgical-site infections in colon surgery (ORALEV): a multicentre, single-blind, pragmatic, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2020;5:729-38. doi:10.1016/S2468-1253(20)30075-3.