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Antibiotic prophylaxis for acute cholecystectomy: PEANUTS II multicentre randomized non-inferiority clinical trial

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Abstract

Background: Guidelines recommending antibiotic prophylaxis at emergency cholecystectomy for cholecystitis were based on low-quality evidence. The aim of this trial was to demonstrate that omitting antibiotics is not inferior to their prophylactic use.

Methods: This multicentre, randomized, open-label, non-inferiority clinical trial randomly assigned adults with mild-to-moderate acute calculous cholecystitis (immediate cholecystectomy indicated) to 2 g cefazolin administered before incision or no antibiotic prophylaxis. The primary endpoint was a composite of all postoperative infectious complications in the first 30 days after surgery. Secondary endpoints included all individual components of the primary endpoint, other morbidity, and duration of hospital stay.

Results: Sixteen of 226 patients (7.1 per cent) in the single-dose prophylaxis group and 29 of 231 (12.6 per cent) in the no-prophylaxis group developed postoperative infectious complications (absolute difference 5.5 (95 per cent c.i. −0.4 to 11.3) per cent). With a non-inferiority margin of 10 per cent, non-inferiority of no prophylaxis was not proven. The number of surgical-site infections was significantly higher in the no-prophylaxis group (5.3 *versus* 12.1 per cent; $P = 0.010$). No differences were observed in the number of other complications, or duration of hospital stay.

Conclusion: Omitting antibiotic prophylaxis is not recommended.

Introduction

Acute calculous cholecystitis generally mandates emergency cholecystectomy[1]. Postoperative infectious complications, both surgical-site and distant infections, occur in approximately 17 per cent of patients undergoing emergency cholecystectomy[2]. To reduce infectious complications after surgery, it is common practice to administer perioperative antibiotic prophylaxis[3]. The Dutch guideline[4] recommends prophylaxis in patients with an increased risk of contaminated bile: those with acute cholecystitis, elderly patients, or patients who have recently had an endoscopic or radiological biliary intervention. Antimicrobial prophylaxis for patients undergoing cholecystectomy for acute cholecystitis is also recommended internationally by the Surgical Infection Society[5] and the Tokyo Guidelines[3]. Nonetheless, all these recommendations are based on low-quality evidence, and the actual benefit of preoperative antibiotic prophylaxis remains unclear. Consequently, the use and the type and dose of prophylactic antibiotics in emergency cholecystectomy varies greatly among surgeons and hospitals.

For patients undergoing elective cholecystectomy for uncomplicated gallstone disease, there is high-level evidence that antibiotic prophylaxis does not reduce the incidence of postoperative infectious complications[6–13]. Therefore, the use of preoperative prophylaxis is discouraged in these patients. Two recent randomized trials[2,14] demonstrated that prolonging antibiotics after cholecystectomy for acute cholecystitis did not reduce the risk of postoperative infectious complications, compared with the administration of a single dose of antibiotic prophylaxis. The question arises whether or not antibiotic prophylaxis has an additional value in preventing infectious complications. The aim of this study was to assess the influence of antibiotic prophylaxis on postoperative infectious

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complications in patients undergoing emergency cholecystectomy for mild or moderate acute calculous cholecystitis.

Methods

Study design and participants

The PEANUTS II trial was a multicentre, randomized, open-label, non-inferiority clinical trial conducted in six hospitals (5 large teaching hospitals and 1 academic hospital) in the Netherlands. All adult patients presenting with acute calculous cholecystitis in whom the intention was to perform immediate cholecystectomy were assessed for eligibility. The diagnosis of acute cholecystitis was established according to the Tokyo Guidelines[15]. Patients who presented with severe cholecystitis received antibiotics in the sepsis protocol and were therefore excluded. Additional exclusion criteria were acalculous cholecystitis, already receiving or needing antibiotic treatment for a concomitant infection or sepsis, proven allergy to cefazolin, pregnancy, or an indication for endoscopic retrograde pancreatocholangiography (ERCP) on admission. The full study protocol is available[16]. The PEANUTS II trial was conducted in accordance with the Declaration of Helsinki and Dutch law regarding research involving human subjects. The study protocol was approved by the Medical Research Ethics Committee of St Antonius Hospital, Nieuwegein, the Netherlands, followed by approval from the executive boards of all participating centres.

The study protocol was registered after enrolment of the first participant with the Netherlands Trial Register at www.trialregister.nl (registration number NTR5802) on 31 May 2016. Written informed consent was obtained from each participant before any trial-related procedures were carried out. The study protocol was written according to the SPIRIT 2013 statement for reporting a clinical trial protocol[17]. A data and safety monitoring board (DSMB) consisting of three independent members was appointed to assess patient safety. The DSMB had unblinded access to all data. The first assessment took place after 20 patients had been included, and subsequently patient safety was assessed once after every 50 included patients. All adverse events were recorded and reported to the Dutch Central Committee on Research Involving Human Subjects using the committee's online module (http://www.toetsingonline.nl).

Randomization

Patients were assigned randomly to the prophylaxis or no-prophylaxis group. Randomization was performed by the study coordinator using an online randomization module (ALEA2.2; https://www.aleaclinical.eu/; Academic Medical Centre, Amsterdam, the Netherlands) and stratified according to centre. Computer-generated permuted bl ock randomization with varying block sizes was used with a maximum block size of six patients. The sequence of the different bl ocks was predetermined by an independent programmer and concealed to all investigators.

Intervention and procedures

Patients in the prophylaxis group received 2 g first-generation cephalosporin administered intravenously 15–30 min before surgery. Patients in the no-prophylaxis group did not receive any antibiotic prophylaxis. Cholecystectomy was performed within 24 h after randomization.

Laparoscopic cholecystectomy was carried out using the four-trocar technique according to the guidelines of the Dutch Society of Surgery, which included establishing the critical view of safety[18]. The surgical procedure was performed by, or under the supervision of, an experienced laparoscopic surgeon. During surgery, the severity of cholecystitis was scored by the surgeon on a scale from 1 (no inflammation) to 10 (severe inflammation), and bile cultures were obtained from the gallbladder during surgery. The presence of empyema and bile spillage was registered, as were duration of surgery and reason for conversion. Patients were discharged based on their clinical condition, and at the discretion of the treating physician. If patients in either group developed infectious complications, treatment was chosen as deemed appropriate. On the day of discharge, a case record form was completed with information on the occurrence of infectious complications, and the manner by which the infection was diagnosed and treated. One week after discharge, the study coordinator contacted the patients by telephone. One month after discharge, the patients were either called or seen in the outpatient clinic by a surgeon. The patient's clinical condition, the development of infectious complications, and visits to the emergency room were documented.

Data collection and outcome measures

Each patient received an anonymous study number that was used for the study record forms and database. On admission, baseline characteristics, including age, sex, BMI, ASA physical status grade, co-morbidity, and clinical data on admission (temperature, white blood cell (WBC) count, C-reactive protein (CRP) level, and duration of symptoms), were documented by the admitting physician or (local) study coordinator. The (preoperative) severity grade of cholecystitis was assessed using the Tokyo Guideline criteria for severity assessment[15].

The primary endpoint was a composite endpoint consisting of all postoperative infectious complications occurring during the first 30 days after cholecystectomy. *Table 1* provides an overview of the definitions of the complications that were registered. Surgical-site infections were defined according to the criteria of the Centers for Disease Control and Prevention[19]. Secondary endpoints included the individual components of the primary endpoint, the number of non-infectious complications, and total duration of postoperative hospital stay defined as the sum of number of days in hospital from surgery to the day of discharge and those of readmission. All (non-)infectious complications were graded according to the Clavien–Dindo classification[20]. After the last patient had completed follow-up, raw data were presented to an adjudication committee consisting of three surgeons, a clinical microbiologist, and the study coordinator to determine whether the endpoints (infectious complications) met the criteria specified in *Table 1*. Each member of the committee was blinded to the treatment allocation and assessed the potential endpoints individually. Disagreement was resolved in a plenary consensus meeting.

Statistical analysis

Sample size calculations were derived from a recently published RCT[2] that reported a postoperative infectious complication rate of 17 per cent in patients with mild or moderate acute calculous cholecystitis undergoing laparoscopic cholecystectomy. A non-inferiority margin of 10 per cent was chosen based on recommendations of the US Food and Drug Administration for anti-infective trials. With a one-sided risk of 2.5 per cent and a power of 80 per cent, a total of at least 454 patients was required in this trial.

The final analysis was performed according to the intention-to-treat principle. Additionally, a per-protocol analysis was performed in which all patients were analysed according to the treatment received.

Table 1 Definitions of postoperative infectious complications

Complication	Definition
Superficial incisional infection	Localized signs such as redness, pain, heat, or swelling at site of incision or by drainage of pus
Deep incisional infection	Presence of pus or abscess, fever with tenderness of wound, or separation of edges of incision exposing deeper tissues
Organ or space infection	Fever and/or raised CRP level/WBC count and intra-abdominal fluid collection visualized by CT or ultrasound imaging
Pneumonia	Coughing or dyspnoea, radiography with infiltrative abnormalities, or raised levels of infection parameters in combination with positive sputum culture
Urinary tract infection	Dysuria, raised WBC count, and/or presence of nitrate in urine sediment in combination with positive urine culture
Bacteraemia	Presence of at least one positive blood culture test result for the same pathogen

CRP, C-reactive protein; WBC white blood cell.

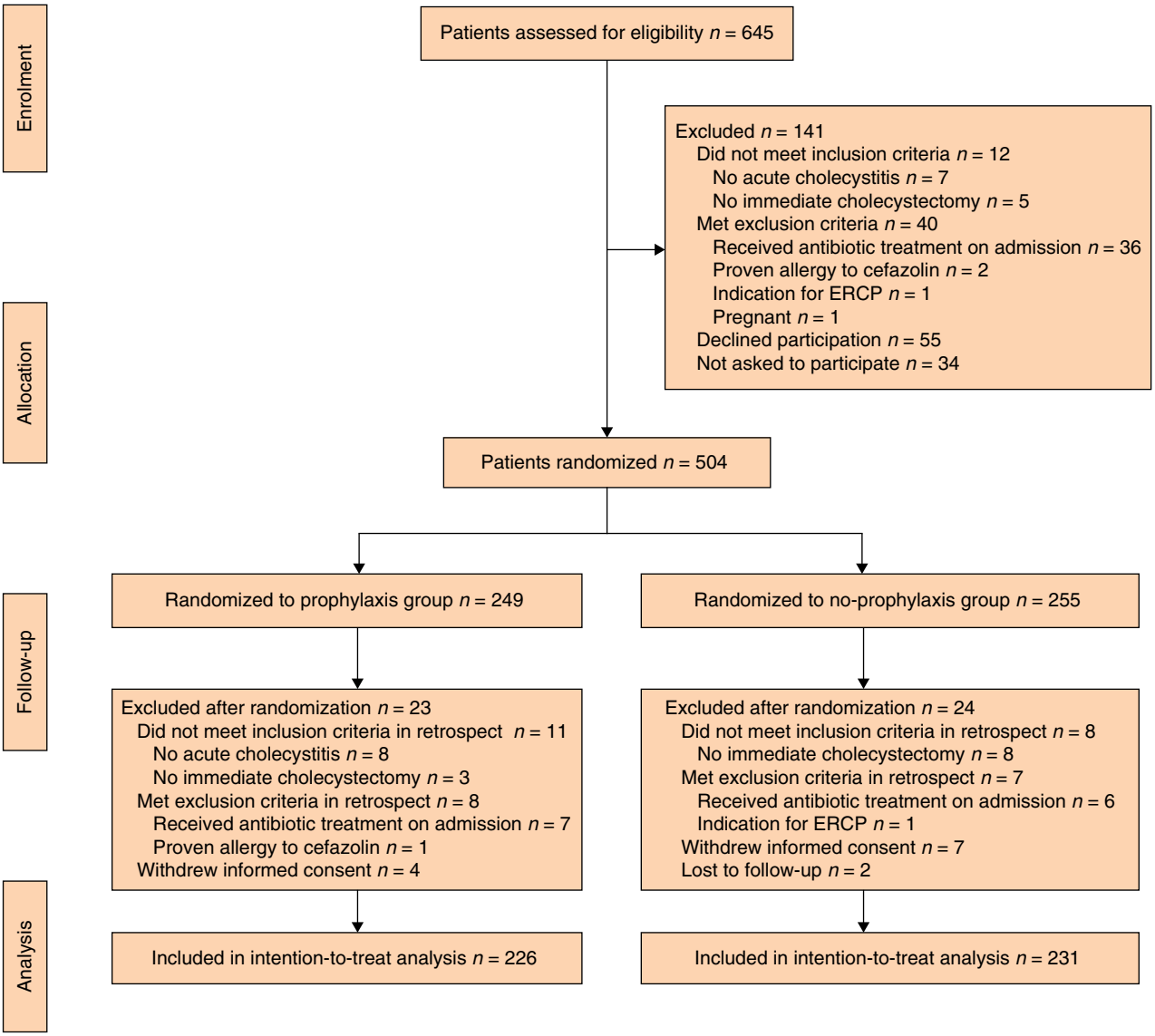

Fig. 1 CONSORT diagram for trial

ERCP, endoscopic retrograde cholangiopancreatography

Dichotomous data and counts are presented as frequencies. Continuous data are presented as mean(s.d.), or as median (i.q.r.) if the distribution was skewed. Differences between groups were assessed using the Student's *t* test for normally distributed continuous data, and the Mann–Whitney *U* test for non-normally distributed data. The χ^2 test was used to analyse group differences for dichotomous and categorical variables. Two-tailed $P < 0.050$ was considered statistically significant. Non-inferiority was

assessed by calculating the 95 per cent confidence interval for the absolute difference in the incidence of the primary endpoint. Formal hypothesis testing regarding non-inferiority was undertaken using the Westlake–Shuirmann test. A binomial logistic regression analysis was performed to identify risk factors associated with the development of postoperative infectious complications. Variables included in the model were treatment allocation, conversion, severity grade, and outcome of bile culture. Subgroup analyses were conducted to identify differences in treatment effects using multivariable models to test for interaction. Variables included in this model were sex, BMI, age, WBC count, CRP level, severity score, severity grade, result of bile culture, and presence of bile spillage and empyema. Statistical analysis was carried out using SPSS® version 26 (IBM, Armonk, NY, USA) and R (R Project for Statistical Computing, Vienna, Austria, https://www.R-project.org/).

Results

Patients

Between March 2016 and February 2020, a total of 645 patients with mild or moderate acute calculous cholecystitis, as defined according to the Tokyo Guidelines, were assessed for eligibility. Five hundred and four patients were randomized to either the prophylaxis or no-prophylaxis group. After randomization, 47 patients were excluded from the final analysis, 11 for not receiving an immediate cholecystectomy and eight for having cholangitis or pancreatitis (*Fig. 1*).

Table 2 Baseline characteristics of patients in single-dose antibiotic prophylaxis and no-prophylaxis groups

	Single-dose antibiotic prophylaxis ($n = 226$)	No antibiotic prophylaxis ($n = 231$)
Age (years)*	58.0 (13.9)	57.5 (14.6)
Sex		
M	107 (47.3)	117 (50.6)
F	119 (52.7)	114 (49.4)
BMI (kg/m^2)*‡	28.8 (5.2)	28.7 (5.1)
ASA fitness grade§		
I	65 (28.8)	69 (29.9)
II	113 (50.0)	111 (48.1)
III	32 (14.2)	29 (12.5)
Co-morbidities		
None	79 (35)	97 (42.0)
Cardiovascular disease	95 (42)	84 (36.4)
Diabetes mellitus	32 (14.2)	15 (6.5)
Previous abdominal surgery	65 (28.8)	63 (27.3)
Pulmonary disease	28 (12.4)	33 (14.3)
Other relevant history	11 (4.9)	7 (3)
Temperature on admission (°C)*¶	37.4 (0.7)	37.4 (0.7)
CRP on admission (mg/l)†	82.5 (27.0–180.3)	69.0 (32.0–149.8)
WBC count on admission (10^9/l)*#	13.5 (4.9)	14.4 (8.9) with outlier 13.9 (4.9) without outlier
Duration of complaints (days)†**	3 (1.5–4)	2 (1–4)
Severity grade††		
Grade I, mild	134 (59.3)	138 (59.7)
Grade II, moderate	92 (40.7)	93 (40.3)

Values in parentheses are percentages unless indicated otherwise; values are *mean(s.d.) and †median (i.q.r.). ‡Assessed for 206 patients in prophylaxis group and 217 in no-prophylaxis group. §Reported in 210 patients in prophylaxis group and 209 in no-prophylaxis group. ¶Registered in 225 patients in prophylaxis group and 230 in no-prophylaxis group. #Registered in all patients in prophylaxis group and 229 in no-prophylaxis group. **Reported in 225 patients in prophylaxis group and 230 in no-prophylaxis group. ††Tokyo Guidelines criteria for severity assessment. CRP, C-reactive protein; WBC, white blood cell.

Table 3 Operative details of laparoscopic cholecystectomy

	Single-dose antibiotic prophylaxis ($n = 226$)	No antibiotic prophylaxis ($n = 231$)
Duration of operation (min)*†	68 (26)	71 (29)
Conversion	1 (0.4)	8 (3.5)
Inability to identify anatomy safely owing to severe inflammation	1 (0.4)	2 (0.9)
Intraoperative haemorrhage	0 (0)	2 (0.9)
Adhesions	0 (0)	3 (1.3)
Duodenal perforation	0 (0)	1 (0.4)
Primary open cholecystectomy	0 (0)	1 (0.4)
Bile spillage‡	131 (60)	132 (57.1)
Empyema§	47 (20.8)	46 (19.9)
Severity*¶	6.7 (2.1)	6.8 (2.2)
Bile culture obtained	179 (79.2)	183 (79.2)
Positive bile culture	79 (44.1)	85 (46.4)

Values in parentheses are percentages unless indicated otherwise; values are *mean(s.d.). †Registered in 219 patients in prophylaxis group and 226 in no-prophylaxis group. ‡Reported in 207 patients in prophylaxis group and 211 in no-prophylaxis group. §Reported in 183 patients in prophylaxis group and 186 in no-prophylaxis group. ¶Perioperative severity of cholecystitis as scored by surgeon on a scale from 1 (no inflammation) to 10 (severe inflammation); reported in 177 patients in each group.

Table 4 Postoperative infectious complications in intention-to-treat and per-protocol analyses

	Intention-to-treat analysis			Per-protocol analysis			
	Single-dose antibiotic prophylaxis ($n = 226$)	No antibiotic prophylaxis ($n = 231$)	P*	Single-dose antibiotic prophylaxis ($n = 225$)	No antibiotic prophylaxis ($n = 232$)	P*	Clavien–Dindo classification
Surgical-site infection	12 (5.3)	28 (12.1)	0.010	9 (4.0)	31 (13.4)	<0.001	
Superficial wound infection	6 (2.7)	11 (4.8)	0.234	7 (3.1)	10 (4.3)	0.498	I, II
Deep wound infection	0 (0)	3 (1.3)	0.086	0 (0)	3 (1.3)	0.087	I, II
Organ or space infection	6 (2.7)	14 (6.1)	0.075	2 (0.9)	18 (7.8)	<0.001	IIIa
Distant infection	4 (1.8)	1 (0.4)	0.170	4 (1.8)	1 (0.4)	0.166	
Pneumonia	1 (0.4)	1 (0.4)	0.988	1 (0.4)	1 (0.4)	0.983	II
Urinary tract infection	1 (0.4)	0 (0)	0.311	1 (0.4)	0 (0)	0.309	II
Bacteraemia	2 (0.9)	0 (0)	0.152	2 (0.9)	0 (0)	0.150	II
Total	16 (7.1)	29 (12.6)	0.052	13 (5.8)	32 (13.8)	0.004	

Values in parentheses are percentages. *χ^2 test.

A total of 457 patients were included in the final data analysis, 226 in the prophylaxis group and 231 in the no-prophylaxis group. Baseline characteristics and operative details are summarized in *Tables 2* and 3 respectively. More patients in the prophylaxis group had diabetes mellitus. Eight laparoscopic cholecystectomies were converted to an open procedure in the no-prophylaxis group compared with one conversion in the prophylaxis group.

Adherence to study protocol

In 414 patients (90.6 per cent), the treatment received was according to the treatment allocation at randomization. In the prophylaxis group, 204 patients (90.3 per cent) received antibiotic prophylaxis before surgery. Prophylaxis was not administered in 22 patients. In the no-prophylaxis group, the treatment allocation was adhered to in 210 patients (90.9 per cent). However, 21 patients did receive antibiotic prophylaxis, either unintentionally before incision (11 patients) or because of intraoperative observation of severe inflammation, gangrenous gallbladder, or necrotizing cholecystitis (10). Eleven patients, of whom four were allocated to the no-prophylaxis group, received extended antibiotic treatment. In all patients, the indication for postoperative antibiotic treatment was peroperative findings suggestive of severe infection such as perforated gallbladder or empyema, or conversion to open cholecystectomy.

Primary endpoint

Of 226 patients in the prophylaxis group, 16 (7.1 per cent) developed postoperative infectious complications *versus* 29 (12.6 per cent) of 231 in the no-prophylaxis group (absolute difference 5.5 (95 per cent c.i. −0.4 to 11.3) per cent; $P = 0.052$). As the non-inferiority margin was set at 10 per cent, non-inferiority of omitting antibiotic prophylaxis compared with administering a single dose of antibiotic prophylaxis for the development of postoperative infectious complications was not reached.

Secondary endpoints

Postoperative infectious complications

There was no significant difference between the two groups in the number of individual postoperative infectious complications (*Table 4*). However, there were more surgical-site infections in the no-prophylaxis group than in the prophylaxis group (12.1 *versus* 5.3 per cent; $P = 0.010$). All patients with an organ or space infection needed radiological catheter drainage of the intra-abdominal fluid collection. Additionally, two patients in the prophylaxis group underwent ERCP. One patient who developed a deep wound infection after laparoscopic cholecystectomy converted to an open procedure was treated with negative pressure wound therapy. All other infectious complications were either treated with antibiotics, or conservative management without any pharmacological treatment. In the per-protocol analysis, the incidence of infectious complications was significantly higher in the no-prophylaxis group ($P = 0.004$). The number of surgical-site infections and, in particular, the number of organ or space infections was significantly higher in the no-prophylaxis group ($P < 0.001$).

Non-infectious complications

The total number of other (non-infectious) complications in the prophylaxis and no-prophylaxis groups was 30 (13.2 per cent) and 42 (18.2 per cent) respectively ($P = 0.150$) (*Table S1*). The majority of complications was graded Clavien–Dindo I or II, and resolved either spontaneously or with pharmacological treatment. In total, four patients (1.8 per cent) in the prophylaxis group and five (2.2 per cent) in the no-prophylaxis group developed postoperative bile leakage either from the cystic duct or the duct of Luschka. One patient with bile leakage developed severe sepsis and died on postoperative day 12. Although this patient was allocated to the no-prophylaxis group, the surgeon decided on peroperative administration of 2 g cefazolin. All other patients with postoperative bile leakage recovered without any sequelae.

Duration of hospital stay

No statistically significant difference in the total length of hospital stay was observed between the two groups, with a median of 1 day (range 0–45 days in prophylaxis group and 0–21 days in no-prophylaxis group). The overall readmission rate was 5.8 per cent in the prophylaxis group and 10.0 per cent in the no-prophylaxis group, both in the intention-to-treat and per-protocol analyses ($P = 0.186$). Readmissions for procedure-related complications were comparable between the two groups ($P = 0.270$).

Bile cultures

Bile cultures were obtained from 362 patients, of which 164 (45.3 per cent) were positive. The rate of positive bile cultures was similar in the two groups. In 56 patients, two or more organisms were isolated from bile cultures. The most common organisms isolated were *Escherichia coli* (53.1 per cent), *Klebsiella pneumoniae* (11.0 per cent), *Streptococcus* spp. (27.4 per cent), and *Enterococcus* spp. (11.0 per cent) (*Table S2*).

Risk factors

Omitting antibiotic prophylaxis and a positive bile culture were significantly associated with the development of a surgical-site infection; odds ratios were 3.74 (95 per cent c.i. 1.71 to 8.15) and 3.76 (1.61 to 8.76) respectively. Subgroup analysis to assess the treatment effect (prophylaxis or no prophylaxis) on the development of postoperative infectious complications revealed no significant interaction effect in a particular subgroup (*Fig. S1*).

Discussion

Recently, an RCT[21] was published in which patients with acute cholecystitis undergoing laparoscopic cholecystectomy were allocated to either 4 g piperacillin/tazobactam or placebo administered intravenously before surgery. The observed infection rate was 19 per cent in the prophylaxis group (29 per cent in placebo group). Another trial[2] reported a postoperative infection rate of 17 per cent in patients with acute calculous cholecystitis treated with preoperative antibiotic prophylaxis only. The rates of postoperative infections in the present study were lower, but there may be variation in the definition and timing of endpoints. Conversion to open cholecystectomy and cholecystitis severity grade were not significant predictors of developing a postoperative infection in the present study. The difference in the number of surgical-site infections was greater than expected. The per-protocol analysis revealed a significantly higher rate of organ or space infections in the no-prophylaxis group. Multivariable analysis showed that omitting antibiotic prophylaxis and a positive bile culture were associated with surgical-site infections, in line with previous studies[22,23].

It was not possible to assess whether empyema, severity of cholecystitis, or bile spillage was associated with surgical-site infections because these data were missing for one in five patients. In an analysis of the treatment effect on postoperative infectious complications in subgroups defined by preoperative and peroperative characteristics, no significant interaction effect was observed. Although the results were not significant, all groups seemed to benefit from antibiotic treatment. This suggests that it is not possible to select a specific group of patients based on preoperative or peroperative characteristics who would (nor would not) benefit from antibiotic prophylaxis. The number needed to treat to prevent a serious postoperative infectious complication (requiring hospitalization and radiological intervention) is 15.

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Supplementary material

Supplementary material is available at *BJS* online.

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