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Bile duct

Extended antibiotic therapy versus placebo after laparoscopic cholecystectomy for mild and moderate acute calculous cholecystitis: A randomized double-blind clinical trial ☆

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ABSTRACT

Background: Acute calculous cholecystitis (ACC) is the most common complication of cholelithiasis. Laparoscopic cholecystectomy (LC) is the gold standard treatment in mild and moderate forms. Currently there is consensus for the use of antibiotics in the preoperative phase of ACC. However, the need for antibiotic therapy after surgery remains undefined with a low level of scientific evidence.

Methods: The CHART (Cholecystectomy Antibiotic Randomised Trial) study is a single-center, prospective, double blind, and randomized trial. Patients with mild to moderate ACC operated by LC were randomly assigned to receive antibiotic (amoxicillin/clavulanic acid) or placebo treatment for 5 consecutive days. The primary endpoint was postoperative infectious complications. Secondary endpoints were as follows: (1) duration of hospital stay, (2) readmissions, (3) reintervention, and (4) overall mortality.

Results: In the per-protocol analysis, 6 of 104 patients (5.8%) in the placebo arm and 6 of 91 patients (6.6%) in the antibiotic arm developed postoperative infectious complications (absolute difference 0.82 (95% confidence interval, −5.96 to 7.61, $P = .81$). The median hospital stay was 3 days. There was no mortality. There were no differences regarding readmissions and reoperations between the 2 groups.

Conclusion: Although this trial failed to show noninferiority of postoperative placebo compared to antibiotic treatment after LC for mild and moderate ACC within a noninferiority margin of 5%, the use of antibiotics in the postoperative period does not seem justified, because it was not associated with a decrease in the incidence of infectious and other types of morbidity in the present study.

The incidence of cholelithiasis in the adult population is 10%, and acute calculous cholecystitis (ACC) is the most common complication.[1,2] Acute cholecystitis affects >20 million Americans annually, with costs in excess of $6.3 billon, constituting a major health burden that has increased >20% in the past 3 decades.[3,4] The diagnostic criteria and severity assessment of ACC were well established in the Tokyo guidelines 2007[5] and updated in 2013.[6] According to this expert consensus, ACC is classified into 3 grades: mild, moderate, and severe. Laparoscopic cholecystectomy (LC) is

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the gold standard treatment in mild and moderate forms.[7] Currently there is consensus for the use of antibiotics in the preoperative phase of ACC, with controversies about its usefulness after the surgical treatment has been completed. Recent guidelines suggest that antibiotics should be administered only up to 24 hours after surgery for mild ACC and 4 to 7 days for moderate or severe forms.[8] It has been suggested that a scheme with β-lactam/inhibitor of β-lactamase combinations would be adequate in patients with mild and moderate ACC, according to most frequently isolated germs.[2,8,9] Despite this, the need for antibiotic therapy after surgery remains ill defined with a lack of high-quality evidence.[10,11] Hence, we conducted a randomized controlled trial in patients undergoing LC for mild and moderate ACC, randomizing patients to receive antibiotics or placebo after surgery. The primary objective of the present trial was to assess whether antibiotic treatment after LC in mild or moderate ACC reduces the incidence of postoperative infectious complications. The hypothesis was that postoperative antibiotic treatment has no positive impact on the patient's outcome and therefore should not be indicated in this subset of patients.

Methods

Study design and ethics

The Cholecystectomy Antibiotic Randomised Trial (CHART) is single-center, randomized, controlled trial with blinded patients and investigators. It compares antibiotic treatment after LC due to mild and moderate ACC versus no antibiotic treatment. The study design has been reported in detail previously.[12] This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice Regulations ICH E6, and applicable regulatory requirements. Written informed consent was obtained from all patients, and the Hospital Italiano de Buenos Aires (HIBA) Institutional Review Board gave ethical approval to perform this study (N° 2111). The CHART has been registered at Clinicaltrial.gov database (ClinicalTrials.gov, identifier: NCT02057679).

Study aims

Primary endpoint

Postoperative infectious complications, defined as any infection occurring within the first 30 postoperative days, classified according to the Clavien-Dindo Classification.[13] Any of the following infectious complications were considered: intra-abdominal collections (abscesses, biloma, subphrenic collection or fluid collection from another location within the abdomen), hepatic abscesses, surgical wound infections presence of erythema and/or phlogosis, turbid or purulent drainage and extra-abdominal infectious complications such as pneumonia or urinary tract infections.

Secondary endpoints

Secondary endpoints included the following: (1) duration of hospital stay: number of days from admission to hospital discharge; (2) readmission: need of readmission due to postoperative complications that require hospital care (hydration, intravenous antibiotics, percutaneous drainage or surgical treatment); (3) reintervention: need of surgical treatment under general anesthesia or percutaneous procedure in complicated patients; and (4) overall mortality: deaths occurring during the first postoperative month.

Study population and study treatment

All consecutive patients from February 2014 with a new diagnosis of mild or moderate ACC according to the Revised Tokyo Guidelines[6] admitted to the HIBA were screened for eligibility to be enrolled in the CHART. Patients received parenteral hydration; gastric protection with proton pump inhibitors; and analgesics and treatment with ampicillin/sulbactam intravenously every 6 hours until surgery, which was carried out within 5 days after admission. Patients were approached for randomized inclusion if they met each of the following inclusion criteria: diagnosis of mild or moderate ACC[6]; willingness to participate in the study; ability to understand the nature of the study and what was required of them; men and nonpregnant, nonlactating women between 18 and 85 years of age who undergo early LC. The main exclusion criteria were as follows: rejection of participation in the trial or the process of informed consent; hypersensitivity to amoxicillin/clavulanic acid (AMC) or lactose (used in placebo); severe ACC; moderate ACC associated with liver and/or gallbladder abscesses, cholangitis, or bile peritonitis; intraoperative findings such as liver cancer, liver metastases, common bile duct stones, or gallbladder carcinoma; conversion to laparotomy; previous treatment with antibiotics for >5 days; active oncologic diseases; AIDS; transplanted patients. If there were no intraoperative criteria for exclusion, patients were randomly assigned to either group of intervention:

1. Experimental group: antibiotic treatment after surgery (AG): received 1,000 mg of AMC orally every 8 hours for 5 days, immediately after surgery.
2. Control group: placebo treatment after surgery (PG): received 1,000 mg of placebo orally every 8 hours for 5 days, immediately after surgery.

Simple randomization was used, and patients were assigned using a randomizer provided by the HIBA statistical department.

The HIBA pharmacy was the only nonblind participant in the study and was in charge of preparing, storing, and distributing the medication, also ensuring that medication was used exclusively for the purposes of the study. Each treatment pack (TP) had a code that was used to identify which group of treatment modalities the patient was assigned. Each TP contained capsules for 5 days of treatment. The antibiotic and placebo capsules were packaged and labeled identically.

Surgical procedure

The American technique for LC was used, as described previously.[14] Intraoperative cholangiography was used as a routine in all patients after having achieved the "critical view of safety."[15]

Safety, tolerability, and follow-up

Any adverse events detected during ambulatory monitoring were recorded and classified according to their severity as mild, moderate, or severe and by relationship to study treatment according to the decision of the blinded investigator. Treatment relationship was determined with a reasonable probability that the event might have been caused by treatment. Each patient received written instructions to mark the intake of each medication as stipulated. Patients were clinically monitored at an outpatient clinic 7 and 30 days after surgery. They received the telephone number of the investigators for any concerns or for the need to report any event. Postoperative adverse events were evaluated according to the Clavien-Dindo classification.[13]

Statistical analysis

Sample size calculation was based on an expected postoperative infection rate of 3% in the antibiotic group,[16-19] following the hypothesis that the absence of postoperative antibiotic treatment would not be inferior to the use of antibiotic treatment after LC for the development of postoperative infections. Assuming a noninferiority margin of 5%, a 1-tailed α error of 5% (instead of 2.5%

because the expected frequency of the event is rare), and a power of 80% to reject the null hypothesis, it was estimated that the required sample size was 150 cases in each group. The main analysis was performed according to per-protocol analysis (PP) and secondarily according to intention-to-treat (ITT) principle.

Categorical variables are described using percentages. Continuous variables are expressed as mean and standard deviation (SD) for those symmetrically distributed and median (interquartile range) for those nonsymmetrically distributed. The association between the outcome and the assigned treatment was assessed using the χ^2 test in categorical variables or Fisher test when appropriate. The risk differences between the 2 arms were estimated, with their respective 95% confidence intervals (CIs). The statistical analysis was performed with the STATA software version 14 (StataCorp LP, TX).

Interim analysis

Due to the primary and secondary endpoints of the protocol, an interim analysis of the results was scheduled once the 50% of the patients were recruited. A nonrelated study investigator presented a report of the interim analysis to the HIBA Ethics Committee, which endorsed early suspension of the protocol. Statistical simulations were performed, following the methodology presented by Bratton et al,[20] to estimate how many samples would include the noninferiority limit in their 95% CI if the sample size were reached according to the initial sample size calculation. Two scenarios were considered, 1 optimistic (equal probabilities to those used for the original sample size calculation) and 1 more conservative (observed probabilities). In both cases, 1,000 samples were generated for both the AG and PG of 150 patients in each branch of each sample, as if the expected sample size had been achieved.

Results

Study participants

Between February 2014 and March 2017, a total of 314 patients were assessed to participate in the CHART. Finally, 201 patients were randomized, 105 in the PG and 96 in the AG (ITT population). One patient from the PG and 5 from the AG were excluded from the PP analysis (Fig). No patient was lost during the 30-day follow-up. Only 1 patient did not complete all medication intakes and discontinued treatment on the fourth day due to cutaneous rash in the PG, while 4 patients discontinued medication in the AG. Of these, 2 patients discontinued on the second day due to digestive intolerance and the remaining 2 on the third and fourth day of treatment due to digestive intolerance and cutaneous rash, respectively.

Demographic characteristics

Characteristics of the study population are summarized in Table 1. No significant differences were found between the 2 groups. Serious comorbidities were rare in both groups. There were no differences regarding clinical presentation and ultrasound results. Characteristics of the laboratory parameters in the study population are detailed in Table 2. No significant differences were

Table 1
Baseline characteristics.

	Intention-to-treat			Per protocol		
Variable	Placebo $n=105$	Antibiotic $n=96$	*P* value	Placebo $n=104$	Antibiotic $n=91$	*P* value
Male sex, *n* (%)	48 (45.7)	52 (54.2)	.23	47 (45.2)	50 (54.9)	.17
Age, mean (SD)	49.9 (14.3)	49.9 (14.7)	.98	49.7 (14.5)	49.9 (14.6)	.91
BMI, mean (SD), kg/m^2	28.2 (4.3)	28.6 (5.2)	.51	28.2 (4.3)	28.6 (5.1)	.57
Coexisting conditions, *n* (%)						
Hypertension	43 (40.9)	34 (35.4)	.42	42 (40.4)	32 (35.2)	.45
Diabetes mellitus	9 (8.6)	8 (8.3)	.95	9 (8.6)	7 (7.7)	.80
Chronic obstructive pulmonary disease	3 (2.9)	1 (1.0)	.62	3 (2.9)	–	.10
Smoking	12 (11.4)	11 (11.5)	.99	12 (11.5)	10 (10.9)	.90
Coronary heart disease	2 (1.9)	1 (1.0)	.61	2 (1.9)	1 (1.1)	.64
Oncological history	1 (0.9)	3 (3.1)	.35	1 (0.9)	3 (3.3)	.34
Previous intraabdominal surgery, *n* (%)	24 (22.9)	24 (25)	.72	24 (23.0)	22 (24.2)	.86
ASA I–II	22 (20.9)	27 (28.1)	.08	22 (21.2)	27 (29.7)	.08
III	74 (70.5)	67 (69.8)		73 (70.2)	62 (68.1)	
IV	9 (8.6)	2 (2.1)		9 (8.6)	2 (2.2)	
Clinical presentation, *n* (%)						
Fever	7 (6.7)	16 (16.7)	.03	7 (6.7)	16 (17.6)	.02
Chills	4 (3.8)	6 (6.3)	.52	4 (3.9)	6 (6.6)	.39
Vomits	38 (36.2)	30 (31.3)	.46	37 (35.6)	28 (30.8)	.48
Abdominal pain	105 (100)	96 (100)	–	104 (100)	91 (100)	–
Murphy sign	81 (77.1)	86 (89.6)	.02	81 (77.9)	82 (90)	.02
Ultrasound characteristics						
Stone size, mean (SD), mm	10.5 (10.3)	10.6 (11.1)	.94	10.6 (10.3)	10.8 (11.2)	.88
Pericholecystic oedema	31 (29.5)	25 (26.0)	.58	31 (29.8)	25 (27.5)	.72
Length ≥80 mm	30 (28.6)	27 (28.1)	.94	30 (28.9)	25 (27.5)	.83
Gallbladder wall ≥4 mm	66 (62.9)	72 (75)	.06	65 (62.5)	68 (74.7)	.07
Mild cholecystitis, *n* (%)	90 (85.7)	83 (86.5)	.88	89 (85.6)	78 (85.7)	.98
Moderate Cholecystitis, *n* (%)	15 (14.29)	13 (13.54)		15 (14.42)	13 (14.29)	
Preoperative antibiotic treatment, mean (SD), d	1.6 (1.3)	1.6 (1.2)	.95	1.5 (1.3)	1.5 (1.1)	.88
Surgery characteristics						
Length, mean (SD), min	90 (28.5)	91.4 (26.2)	.38	90.7 (28.7)	94.0 (26.7)	.33
Intraoperative complication	23 (20.0)	18 (18.8)	.96	20 (19.2)	17 (18.7)	.92
Accidental gallbladder perforation*	20 (19.0)	16 (16.7)	.66	20 (19.2)	16 (17.6)	.77
Vascular lesion	–	–		–	–	
Intestinal lesion	1 (0.9)	1 (1.0)	.95	–	–	
Bile duct injury	–	–		–	–	

BMI, body mass index; *SD*, standard deviation; *ASA*, American Society of Anesthesiologists.
* Intraoperative accidental gallbladder perforation during laparoscopic cholecystectomy.

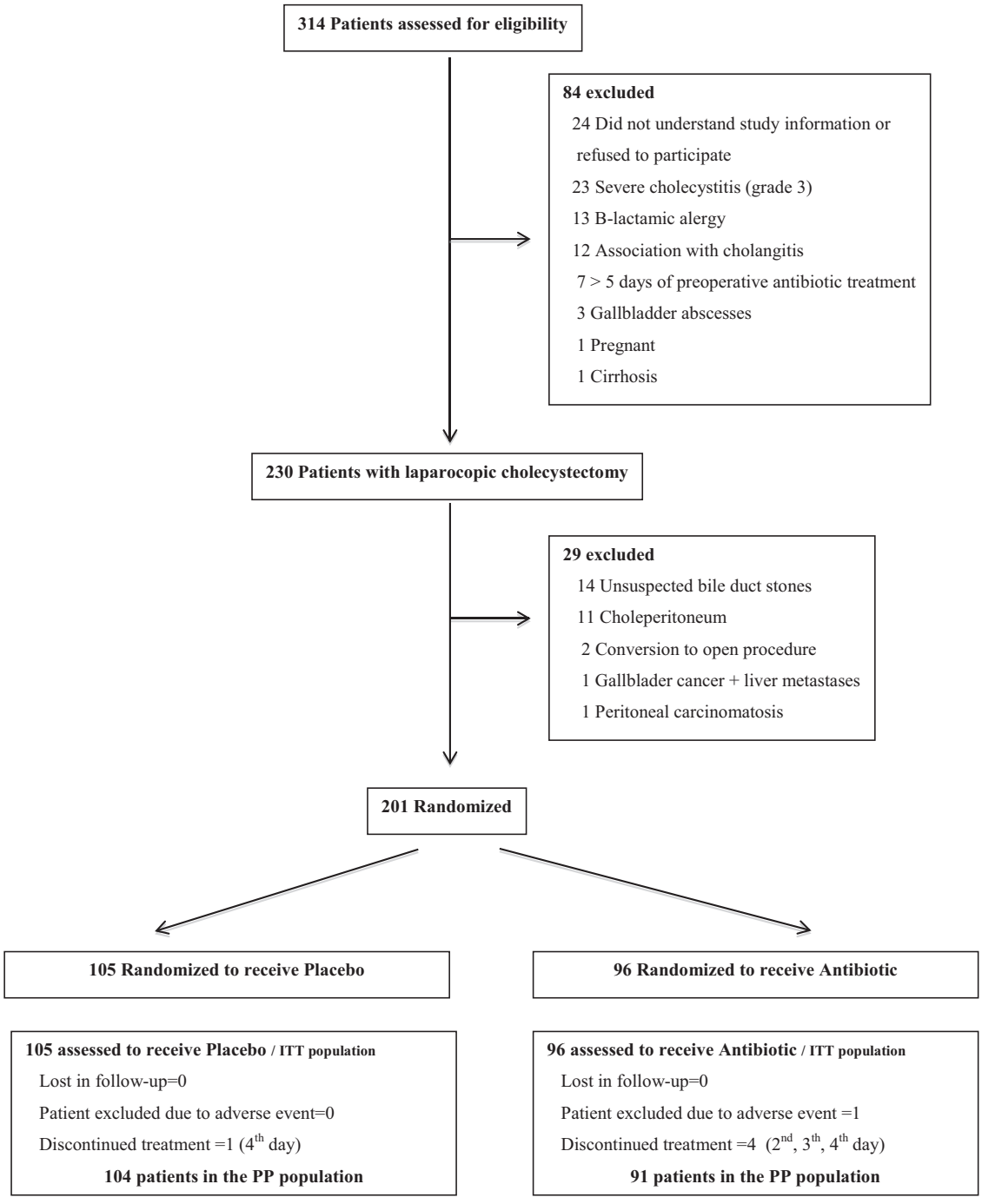

Fig. Flow of study participants in the CHART trial.

found between the 2 groups. All patients in the series received preoperative antibiotic treatment until the time of surgery. The mean duration of the surgeries was 90 minutes. Intraoperative cholangiography was performed in 100% of the patients, without bile duct injuries.

Primary endpoint

Infectious complications are listed in Table 3. In the PP analysis, 6 of 104 patients (5.8%) in the PG and 6 of 91 patients (6.6%) in the AG developed postoperative infectious complications (absolute difference 0.82%; 95% CI, −5.96 to 7.61; $P = .81$). Although no difference was found between the 2 groups, the upper limit of the 95% CI included the 5% noninferiority margin that was set in the protocol design. In the ITT analysis, 6 of 105 patients (5.7%) in the PG and 6 of 96 patients (6.2%) in the AG developed postoperative infectious complications, a risk difference of 0.53% (95% CI, −6.03 to 7.10; $P = .87$).

Secondary endpoint

In the PP analysis, 10 patients (9.6%) from the PG had complications, as did 10 patients (10%) in the AG, with an absolute difference of 1.37% (95% CI, −7.19 to 9.94; $P = .75$). In the ITT analysis, 10 patients (9.5%) from the PG had complications, whereas 11 patients (11.5%) experienced complications in the AG, with an ab-

Table 2
Baseline laboratory characteristics.

Variable	Intention-to-treat			Per protocol		
	Placebo $n=105$	Antibiotic $n=96$	P value	Placebo $n=104$	Antibiotic $n=91$	P value
Hematocrit, mean % (SD)	40.4 (3.9)	40.6 (4.5)	.75	40.5 (3.9)	40.5 (4.5)	.98
Leukocytes, mean (SD), μL	11,841 (3,335)	11,566 (3,330)	.56	11,822 (3,345)	11,562 (3,368.9)	.59
Platelets, mean (SD), ×103/μL	230,773 (59,287)	252,729 (60,577)	.01	230,552 (59,531)	250,382 (60,241)	.02
Prothrombin time, mean (SD), %	82.9 (14.6)	84.2 (13.0)	.50	82.6 (14.4)	83.9 (13.2)	.52
Uremia, mean (SD), mg/dL	31 (12.6)	30.2 (11.6)	.50	31.2 (12.6)	30.6 (11.6)	.73
Creatinine, mean (SD), mg/dL	0.9 (1.0)	0.9 (1.0)	.76	0.9 (1.0)	0.9 (1.0)	.76
Bilirubin, mean (SD), mg/dL						
Total	1.0 (0.9)	0.9 (0.8)	.54	1.0 (0.9)	0.9 (0.8)	.61
Direct	0.7 (0.3)	0.7 (0.5)	.69	0.7 (0.6)	0.7 (0.5)	.80
Alkaline phosphatase, mean (SD), U/L	85.7 (55.2)	95.8 (70.5)	.26	86.3 (55.2)	97.7 (71.5)	.21
Amylase, mean (SD), U/L	43.4 (20.4)	50.2 (52.5)	.22	43.3 (20.4)	50.2 (53.9)	.23

SD, standard deviation.

solute difference of −1.93% (95% CI, −6.55 to 10.42; $P=.65$). Most of the complications were mild (grade I and II), with no difference between the 2 groups ($P=1$; Table 3).

One patient in the AG had a severe complication (IIIb). This patient required a second-look laparoscopy within 24 hours of LC due to an inadvertent small bowel injury, which was resolved with an intestinal resection and primary anastomosis. The patient recovered without complications in the distant postoperative period. Throughout the series, 3 patients had to be readmitted. One patient in the PG was hospitalized on the seventh postoperative day with pneumonia and received appropriate antibiotic treatment. Another patient from the AG had a laparoscopic appendectomy for acute appendicitis on the 27th postoperative day. The third patient was previously mentioned (inadvertent small bowel injury). The overall median hospital stay was 3 days, with no difference between the groups compared ($P=.3$).

Sample size simulation

In the first scenario, the CI included zero in all cases. The mean risk difference for the 1,000 simulations was 0.00250 = 0.25% (infection risk AG to infection risk PG). The missing cases were completed with simulated numbers with an event probability of 3%, having a CI for the risk difference including the noninferiority limit of 5%. Considering an event incidence of 3% and reaching the predefined sample size, 52.5% of the samples include the noninferiority limit.

In the second scenario, the CI included zero in all cases. The mean risk difference for the 1,000 simulations was 0.00749 = 0.75% (infection risk AG to infection risk PG). Completing the missing cases with simulated probability event numbers of 0.0576 (6/104) in the PG and 0.0659 (6/91) in the AG, 738 of 1,000 samples had a CI for the risk difference that included the noninferiority limit of 5%. Considering that the observed incidences were maintained until the end of the recruitment when reaching the predetermined sample size, 73.8% of the samples included the noninferiority limit. With the observed frequencies, a sample size of 682 patients (341 patients per arm) would have been required to demonstrate noninferiority.

Discussion

In this prospective, randomized trial with blinded patients and evaluators, we compared the use of extended antibiotic therapy versus placebo after LC for mild and moderate ACC. The analysis showed that the absence of extended antibiotics treatment was not associated with an increased risk of infectious complications and other types of morbidity. Moreover, both groups had similar results regarding hospital stay, reinterventions, and hospital readmissions.

LC is the gold standard treatment for mild and moderate forms of ACC, with around 120,000 cholecystectomies performed each year in the United States.[2,7] Even though there is consensus to establish preoperative antimicrobial therapy on suspicion of infection, few studies have assessed the role of antibiotic therapy after LC in ACC. In addition, present guidelines propose to administer antibiotics during the postoperative course with a variable time period.[8] Regarding the type of antibiotic treatment, it has been suggested that a β-lactam/inhibitor of β-lactamase combination

Table 3
Postoperative results.

Variable	Intention-to-treat				Per protocol			
	Placebo $n=105$	Antibiotic $n=96$	P value	Absolute difference (95% CI), %	Placebo $n=104$	Antibiotic $n=91$	P value	Absolute difference (95% CI), %
Morbidity, *n* (%)	10 (9.5)	11 (11.5)	.65	−1.93 (−6.55 to 10.42)	10 (9.6)	10 (10)	.75	1.37 (−7.19 to 9.94)
Mortality, *n* (%)	–	–	–	–	–	–		
Infectious complications, *n* (%)	6 (5.7)	6 (6.2)	.87	0.53 (−6.03 to 7.10)	6 (5.8)	6 (6.6)	.81	0.82 (−5.96 to 7.61)
Wound infection, *n* (%)	5 (4.8)	5 (5.2)	.88	0.44 (−5.58 to 6.47)	5 (4.8)	5 (5.5)	.83	0.68 (−5.54 to 6.91)
Abdominal fluid collection, *n* (%)	1 (0.9)	–	1	−0.95 (−2.81 to 0.90)	1 (0.9)	–	1	−0.96 (−2.83 to 0.91)
Urinary infection, *n* (%)	–	1 (1)	1	1.04 (−0.98 to 3.07)	–	1 (1)	1	1.09 (−1.04 to 3.2)
Pneumonia, *n* (%)	1 (0.9)	–	1	−0.95 (−2.81 to 0.05)	1 (0.9)	–	1	−0.96 (−2.8 to 0.91)
Wound hematoma	4 (3.8)	3 (3)	.8	−0.68 (−5.73 to 4.36)	4 (3.8)	3 (3.3)	.84	−0.54 (−5.75 to 4.65)
Mild complications: I and II, *n* (%)	9 (8.6)	9 (9.3)	.48		9 (8.6)	9 (9.9)	1	
Severe complication ≥IIIa, *n* (%)	–	2 (2)			–	1 (1.0)		
Readmission	1 (0.9)	2 (2.0)	.60	1.1 (−2.27 to 4.53)	1 (0.9)	1 (1.1)	.99	0.13 (−2.70 to 2.98)
Medication adverse event	3 (2.9)	4 (4.1)	.61	1.30 (−3.80 to 6.42)	2 (1.9)	1 (1.1)	.64	−0.82 (−4.22 to 2.57)
Duration of hospital stay, median (IQR), d	3 (2)	3 (1)	.33		3 (2)	3 (1)	.36	

monoscheme would be adequate in patients with mild and moderate ACC without intraoperative complications such as bile peritonitis, cholangitis, gallbladder perforation, or abscesses.[8-11] Based on these recommendations, we decided to use an AMC scheme for the group of patients who received postoperative antibiotics treatment, extending it for a period of 5 days. Despite this, we did not observe a reduction in the incidence of postoperative infectious complications. These findings yield similar results to recently published studies.[21-24] Delivering adequate preoperative antibiotic treatment to a patient with ACC and then removing the septic focus through a cholecystectomy seems to be a sufficient therapeutic strategy to definitively resolve this disease. This change in treatment paradigm leads to a more rational use of antibiotics, reducing bacterial resistance and the incidence of pseudomembranous colitis by *Clostridium difficile*.[25] Moreover, although the incidence of adverse events caused by medication in the group of patients receiving antibiotics was low, it is well described in the literature.[26]

Laparoscopic cholecystectomy for ACC is a low to medium complexity surgical procedure, with lower morbidity, mortality, and hospital stay rates compared to the open approach.[27] Several studies have found that early LC in patients with mild and moderate ACC is a safe and effective surgical strategy.[28-31] Following this therapeutic approach, all the patients in this series were operated within the first 5 days of admission. Early cholecystectomy has been shown to reduce morbidity, hospital stay, and costs with respect to late cholecystectomy (7–45 days) for ACC.[28] The surgical quality standards in this series are equal to or higher than those reported in the literature for the treatment of this pathology.[30,31] In all cases, an intraoperative cholangiography could be performed, without bile duct injuries. The mean duration of the surgeries was 90 minutes, with a 3-day hospital stay, without mortality, and with a very low reoperation and readmission rate.

The overall morbidity reported in the literature ranges from 15% to 30%, and surgical site infection is the most frequent complication.[32] In our study, this incidence was around 5% and was higher than those reported in the literature. A recent meta-analysis reported an incidence of wound infection of 2.7% for early cholecystectomy and 4.1% for late cholecystectomy in acute cholecystitis.[31] This fact could be explained by the strict follow-up of the patients in the present study. In spite of this, the use of antibiotics did not reduce the incidence of surgical site infections, as other studies have shown.[21,22] In a recent study, Regimbeau et al[21] analyzed a total of 414 patients treated with 2 g of AMC in the postoperative period of cholecystectomies due to acute cholecystitis, without a decrease in the incidence of infectious complications. Although the study was randomized and included 17 medical centers in France, its main limitations were that there was no comparison with a placebo or a strictly blinded analysis of the results. In addition, the course of antibiotic therapy was nonstandardized, with a variable number of treatment days. There were also problems in the postoperative follow-up of patients, with a high proportion of protocol violations. On the other hand, both patients operated with conventional surgery (15%) and laparoscopic surgery (with a conversion rate of 10%) were included in the same analysis. These situations could generate doubts in the interpretation of results. Loozen et al[22] randomized 156 patients to receive a single preoperative dose of cefazolin (2,000 mg) versus antibiotic prophylaxis for 3 days after cholecystectomy (intravenous Cefuroxima 750 mg plus metronidazole 500 mg 3 times daily). The main conclusion was that standard single-dose antibiotic prophylaxis did not lead to an increase in postoperative infectious complications. However, to demonstrate the noninferiority of this treatment, a sample size of almost 600 patients would have been necessary. Given the low rate of infection in LC it would be questionable if such a study were necessary. From a methodologic point of view, our study solves many of the problems previously discussed. First, our antibiotic treatment with AMC was compared with a placebo, and both the patient and the investigators were blinded until the end of the study. The duration of the antibiotic treatment was set for 5 consecutive days for both branches, with a high adherence to the protocol. At the same time, patients were strictly scheduled for clinical controls at 7 and 30 postoperative days, with a complete follow-up of all patients recruited.

The main limitation of this trial is that although we found no differences between the results of the primary and secondary endpoints raised for the study, the noninferiority of the placebo compared with antibiotics for development of infectious complications could not be proven because the noninferiority margin of 5% lay within the 95% confidence interval. Therefore, our study was finally underpowered to demonstrate noninferiority, which would have required a sample size of 682 patients. Wound infection was the most frequent complication of the present series, with the same distribution in both arms of treatment. The clinical relevance of this type of complication for a LC would be debatable because it is an infection in a small wound, which had no impact on the postoperative evolution of the patients. On the other hand, we estimated the probabilities of including the noninferiority limits in the confidence intervals of the risk difference, which ranged between 52.5% and 73.8%. The first scenario is reasonably optimistic for its effect on the standard errors of the difference, while the second scenario is more conservative in the same sense and probably looks more realistic. Finally, other studies used a noninferiority margin of 11%, and the associated wide confidence intervals could have masked a possible difference in postoperative infections between the compared groups.[21] Since the noninferiority margin is arbitrarily set, if we had applied a larger margin for our study (eg, $\geq$7), based on our results we would have concluded noninferiority in our final analysis.

In conclusion, although this trial failed to show noninferiority of postoperative placebo compared to antibiotic treatment after LC for mild and moderate acute cholecystitis within a noninferiority margin of 5%, the use of antibiotics in the postoperative period does not seem justified because it was not associated with an increased risk of infectious complications and other types of morbidity in the present study. Moreover, both groups compared had similar results regarding hospital stay.

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