Original Investigation

Effect of Postoperative Antibiotic Administration on Postoperative Infection Following Cholecystectomy for Acute Calculous Cholecystitis
A Randomized Clinical Trial

Jean Marc Regimbeau, MD, PhD; David Fuks, MD, PhD; Karine Pautrat, MD; Francois Mauvais, MD; Vincent Haccart, MD; Simon Msika, MD, PhD; Muriel Mathonnet, MD, PhD; Michel Scotté, MD, PhD; Jean Christophe Paquet, MD; Corinne Vons, MD, PhD; Igor Sielezneff, MD, PhD; Bertrand Millat, MD, PhD; Laurence Chiche, MD, PhD; Hervé Dupont, MD, PhD; Pierre Duhaut, MD, PhD; Cyril Cossé, PhD; Momar Diouf, PhD; Marc Pocard, MD, PhD; for the FRENCH Study Group

IMPORTANCE Ninety percent of cases of acute calculous cholecystitis are of mild (grade I) or moderate (grade II) severity. Although the preoperative and intraoperative antibiotic management of acute calculous cholecystitis has been standardized, few data exist on the utility of postoperative antibiotic treatment.

OBJECTIVE To determine the effect of postoperative amoxicillin plus clavulanic acid on infection rates after cholecystectomy.

DESIGN, SETTING, AND PATIENTS A total of 414 patients treated at 17 medical centers for grade I or II acute calculous cholecystitis and who received 2 g of amoxicillin plus clavulanic acid 3 times a day while in the hospital before and once at the time of surgery were randomized after surgery to an open-label, noninferiority, randomized clinical trial between May 2010 and August 2012.

INTERVENTIONS After surgery, no antibiotics or continue with the preoperative antibiotic regimen 3 times daily for 5 days.

MAIN OUTCOMES AND MEASURES The proportion of postoperative surgical site or distant infections recorded before or at the 4-week follow-up visit.

RESULTS An imputed intention-to-treat analysis of 414 patients showed that the postoperative infection rates were 17% (35 of 207) in the nontreatment group and 15% (31 of 207) in the antibiotic group (absolute difference, 1.93%; 95% CI, −8.98% to 5.12%). In the per-protocol analysis, which involved 338 patients, the corresponding rates were both 13% (absolute difference, 0.3%; 95% CI, −5.0% to 6.3%). Based on a noninferiority margin of 11%, the lack of postoperative antibiotic treatment was not associated with worse outcomes than antibiotic treatment. Bile cultures showed that 60.9% were pathogen free. Both groups had similar Clavien complication severity outcomes: 195 patients (94.2%) in the nontreatment group had a score of 0 to I and 2 patients (0.97%) had a score of III to V, and 182 patients (87.8%) in the antibiotic group had a score of 0 to I and 4 patients (1.93%) had a score of III to V.

CONCLUSIONS AND RELEVANCE Among patients with mild or moderate calculous cholecystitis who received preoperative and intraoperative antibiotics, lack of postoperative treatment with amoxicillin plus clavulanic acid did not result in a greater incidence of postoperative infections.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01015417

JAMA. 2014;312(2):145-154. doi:10.1001/jama.2014.7586

Editorial page 135

Related article page 137

Supplemental content at jama.com

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: FRENCH Study Group members are listed at the end of the article.

Corresponding Author: Jean Marc Regimbeau, MD, PhD, Department of Digestive and Oncological Surgery, CHU Nord Amiens and University of Picardie, Place Victor Pauchet, F-80054 Amiens cedex 01, France (regimbeau.jean-marc@chu-amiens.fr).

Acute calculous cholecystitis is the third most frequent cause of emergency admissions to surgical wards.[1] In the United States, approximately 750 000 cholecystectomies are performed each year and about 20% of these operations are due to acute calculous cholecystitis.[2] In France, approximately 37 500 cholecystectomies for acute calculous cholecystitis were performed in 2010.[3]

The initial treatment of acute calculous cholecystitis involves hospital admission, cessation of oral nutrition, intravenous administration of fluids, antibiotic treatment, and cholecystectomy.[4] Many patients receive postoperative antibiotics with the intent to reduce subsequent infections. Part of the rationale for this includes the finding that bacteria in gallbladder bile is cultured in 40% to 60% of cases.[5-7] Controversy exists about the presence of bacterial contamination of the gallbladder[7,8] and postoperative complications including surgical site infections.[9] There is a dearth of controlled studies demonstrating a benefit for postoperative antibiotic treatment after cholecystectomy for acute calculous cholecystitis. The objective of this study was to determine the utility of postoperative antibiotic treatment of patients with mild or moderate acute calculous cholecystitis. We hypothesized that antibiotic treatment after cholecystectomy would not affect outcomes.

Methods

Patient Inclusion and Exclusion Criteria

Patients aged 18 years or older were selected in the emergency department and were eligible for the trial if they had mild (grade I) or moderate (grade II) acute calculous cholecystitis (as defined by the Tokyo consensus meeting[10]). *Acute calculous cholecystitis* was defined as the presence of local inflammation (according to the Murphy sign or right upper quadrant mass, pain, or tenderness) and systemic inflammation (temperature >38°C, elevated C-reactive protein [CRP] levels [>5 mg/L] or an elevated white blood cell count >10 000/μL) and characteristic imaging findings (gallstone or biliary debris with a gallbladder wall thicker than 4 mm (in the absence of chronic liver disease or ascites or right heart failure), enlarged gallbladder (long-axis diameter >8 cm and short-axis diameter >4 cm), pericholecystic fluid collection, or linear high-density areas in the pericholecystic fat tissue.[10-12] *Severe acute calculous cholecystitis* (grade III) was defined as being accompanied by dysfunctions in any one of the following organs or systems: cardiovascular dysfunction (hypotension requiring treatment with dopamine >5 μg/kg per min, or any dose of dobutamine), neurological dysfunction (decreased level of consciousness), respiratory dysfunction (Pa_{O_2}:F_{IO_2} ratio <300), renal dysfunction (oliguria, creatinine >2.0 mg/dL [to convert to μmol/L, multiply by 88.4]), hepatic dysfunction (3 > prothrombin time:international normalized ratio > 2) or hematologic dysfunction (platelet count <100 000/μL). *Moderate acute calculous cholecystitis* (grade II) is accompanied by any of the following conditions: white blood cell count greater than 18 000/μL, a palpable tender mass in the right upper abdominal quadrant, duration of complaints for more than 72 hours or marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, or emphysematous cholecystitis). Cases not meeting the criteria for severe or moderate acute calculous cholecystitis are classified as *mild* (grade I).

Patients were also included if they had received 2 g of amoxicillin plus clavulanic acid 3 times a day before surgery (the number of days of treatment depended on the time between admission and surgery) and received the regimen once during surgery.

The study was approved by the regional investigational review board (CPP Nord Ouest II) and the French drug administration. All the patients gave written, informed consent.

Patients were excluded if they had acalculous cholecystitis or grade III severe acute calculous cholecystitis (with an indication of percutaneous transhepatic biliary drainage or required emergency cholecystectomy for septic shock); had complaints lasting for more than 5 days; had common bile duct stones discovered at the time of surgery; had cholangitis; had biliary peritonitis, defined as a collection of bile in the peritoneal cavity (because it was judged unethical to withhold postoperative antibiotic treatment in the latter patients, even though this situation is part of grade II acute calculous cholecystitis); had acute pancreatitis; had cirrhosis; had suspected biliary cancer; had a β-lactam allergy; were pregnant or breastfeeding; could not understand the study information; or were unable to sign the consent form.

All eligible patients who were not included in the study were registered. The reasons for not participating in the study were recorded (**Figure**). To facilitate enrollment at the other investigating centers, the reasons for noninclusion were only recorded at Amiens University Medical Center.

Intervention

Antibiotic Treatment

Once diagnosed, all selected patients received the amoxicillin regimen before and on injection of general anesthesia at the time of surgery. Patients randomized to the nontreatment group received no antibiotics after surgery. Those randomized to the treatment group received the same antibiotic regimen 3 times daily for 5 days. Patients who were not yet eating received 2 flasks of 1 g/200 mg intravenously and those who could eat received 2 pills of 1 g each. Patients discharged within 5 days of surgery completed oral antibiotic treatment at home.

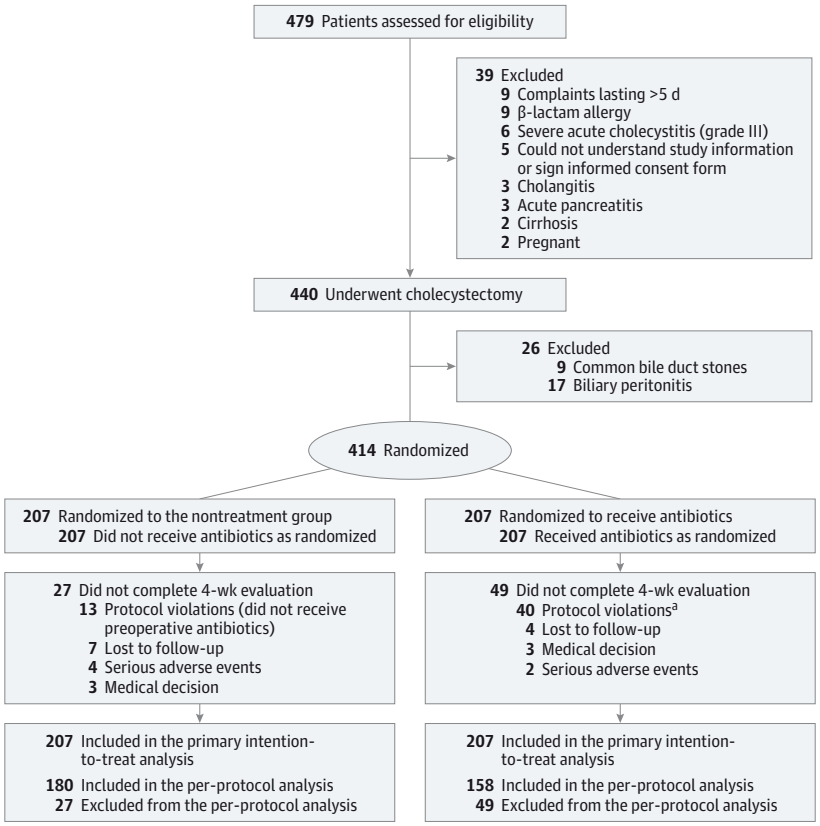
Surgical Procedure

The surgical approach (laparoscopic or open cholecystectomy), intraoperative cholangiography, and abdominal drainage were performed according to each surgeon's preferences and standard practice. Surgeons were instructed to obtain bile cultures and to randomize patients after the cholecystectomy was completed.

Randomization

After cholecystectomy, study participants were randomly assigned using a computer-generated randomization code. To ensure balance between each group, random block sizes of 4 and

Figure. Flow of Patients in FRENCH Study



Data on eligibility (screening and exclusion) were available for the coordinating center but not for the 16 other centers. Each center recruited an average of 24 patients (range, 1–110).

[a] Among the protocol violations were that patients did not receive preoperative or postoperative study antibiotics; had grade III acute calculous cholecysitis, biliary peritonitis, American Association of Anesthesiology classification IV, and complaints lasting more than 5 days; or used postoperative ofloxacin.

10 were generated. The randomization procedure was stratified by site, in a 1:1 ratio.

Efficacy Criteria

Primary Outcome

The primary outcome was the proportion of patients who developed a postoperative infection either at the surgical site or at distant site within 4 weeks. The diagnosis of a postoperative infection was based on clinical, biochemical, or morphological features and was confirmed (if possible) by bacteriological data. A successful outcome was defined as the absence of surgical-site infection.

Postoperative infections were defined as superficial or deep incisional infections or organ-space infections, in accordance with Centers for Disease Control and Prevention's (CDC's) guidelines on the prevention of surgical site infections.[13] Superficial incisional surgical site infections had to meet the following criteria: (1) occurrence within 30 days of the surgical procedure, and (2) involvement of only skin or subcutaneous tissue around the incision but with at least 1 of the following: purulent drainage from the superficial incision; organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision; 1 or more of the following signs or symptoms: pain or tenderness, localized swelling, redness or heat, and opening of the superficial incision by the surgeon unless the culture of the incision tested negative for infection; diagnosis of a superficial incisional surgical site infection by the surgeon or attending physician.[13] Organ-space infections were diagnosed in each case by CT scan. Distant infections included pulmonary (presence of a clinical or biological inflammatory syndrome and localized long contagion) and urinary (presence of clinical symptoms and biological inflammatory syndrome associated with a positive urinary cytology) infections, bacteremia (presence of ≥1 positive hemoccult to the same pathogen), and lymphangitis.[13] On hospital discharge, the patients' primary care physicians were contacted and informed of the patients' inclusion in the trial. The presence or absence of a postoperative infection was systematically checked by study investigators at the 4-week follow-up visit. Patients who neither attended the follow-up visit nor responded to a reminder first made to their home telephone and then to their primary physician were considered lost to follow-up. If a postoperative infection was noticed before week 4, we recorded the associated data at the time of occurrence.

We performed subanalyses that compared patients by grade I vs II acute calculous cholecystitis, by a short vs long course of antibiotic therapy, and by intravenous vs oral antibiotic therapy.

To check the validity of our evaluation of the primary outcome, 2 independent blinded surgeons who were not involved in the study reviewed 40 sets (10%) of the medical records.

Secondary Outcomes

Postoperative morbidity and mortality were assessed according to Clavien classification grades: grade I represents any deviation from the normal course after surgery with no need for pharmacological, surgical, endoscopic, or radiological interventions; grade II, complications requiring pharmacological treatment; grade III, complications requiring surgical, endoscopic, or radiological intervention; grade IV, life-threatening complications requiring intermediate or intensive care unit management; grade V, death. Clavien grades III and IV correspond to serious postoperative complications,[14] adverse events, and microbiological parameters. The postoperative infections (nature, risk factors, and predictive score) were reported. The readmission rate was also recorded. The length of stay in days (as the median value and as a survival curve) is presented in the eAppendix in the Supplement. We performed an analysis of patients with postoperative complications and of those with resistance to amoxicillin plus clavulanic acid in terms of postoperative course.

Clinical Assessment

Each patient's clinical and biochemical status was monitored during hospitalization. Four weeks after surgery, patients were screened in an outpatient clinic for postoperative infections. Patients were discharged from the hospital when free of pain, fever, and any digestive symptoms.

Infection was suspected if a patient's body temperature was higher than 38.5°C at least 2 days after surgery; additional examinations (ultrasound, computed tomographic imaging, urine microscopy and culture, chest imaging, or blood culture) and a biliary fluid antibiogram, an examination of the specimen's sensitivity to various pathogens, were then performed. If infection was confirmed and the test results were available, antibiotic treatment was modified for those in the antibiotic group or initiated for those in the nontreatment group, with amoxicillin plus clavulanic acid if possible.

Safety Assessment and Adverse Events

Adverse events were recorded by the investigators during hospitalization or at the 4-week out-patient follow-up visit.

Statistical Analysis

We hypothesized that the absence of postoperative antibiotic treatment would not be inferior to receiving antibiotics after surgery for development of infections (including surgical site and distant infections) 4 weeks after cholecystectomy. Our calculation of the sample size was based on published data[15-22] and an expected postoperative infection rate in the antibiotic group of 18.5%. We assumed a noninferiority margin of 11%. To choose this margin, we defined half of the rate of postoperative infection in the literature. The US Food and Drug Administration recommends about 10% for antiinfective trials. The clinical relevance of this margin is based on the Altemeier classification (a noncontaminated surgery Altemeier grade 2) of cholecystectomies for which the expected postoperative infection rate is between 10% and 20% without antibiotics. With a 1-sided α risk of 2.5% and a β risk of 20%, application of the equation developed by Piantadosi[24] yielded a sample size of 196 patients per group. Taking into account an expected dropout or missing data rate of 5%, the final sample size was 414 patients. Noninferiority would be established if the upper limit of the 2-sided 95% confidence interval of the difference of proportion of infections between the 2 groups was lower than the noninferiority margin. Qualitative variables were expressed as the number (percentage), and mean values were compared in a χ^2 test or Fisher exact test. Quantitative variables were expressed as the mean (standard deviation) or the median (range) and were compared in a *t* test, a Wilcoxon test, or a Mann-Whitney *U* test, as appropriate. The chosen significance threshold for statistical comparisons was $P < .05$ in a 1-sided test.

To evaluate the association between the occurrence of postoperative infection and the length of stay, we used a time-varying Cox model with a log-rank test. Age, diabetes, clinical biochemistry parameters (including aspartate aminotransferase, alanine aminotransferase, and γ-glutamyltransferase) and clinical signs (Murphy sign) were used as predictor variables with a backward selection procedure. We performed the intention-to-treat analysis with multiple imputation for patients not analyzed for the primary end point, including patients lost to follow-up. We used a multiple imputation technique with 5 replications, yielding a median value of −0.83% (95% CI, −7.40% to 5.75%). Age and other comorbidities were the strongest predictors of missing data and were used in the imputation model. We also performed a per-protocol analysis, which notably excluded patients in the antibiotic group who had been switched from amoxicillin plus clavulanic acid to another antibiotic.

To check the extent of agreement between the investigators' assessment and the blind review of the study's primary outcome, a Cohen κ statistic was calculated.

All statistical analysis was performed with SAS software version 9.2 (SAS Institute Inc).

Results

Between May 2010 and August 2012, 414 patients with acute calculous cholecystitis were recruited at 17 investigating centers into an open-label, parallel-group, randomized, multicenter, clinical, noninferiority study.

Study Population

The 414 patients, mean age of 55 years (range, 18-94), were included in the study during the 27-month period between May 2010 and August 2012 (Figure). One hundred three of 207 patients (49.8%) in the nontreatment group and 97 of 207 patients (46.9%) in the antibiotic group had grade I acute calculous cholecystitis .

Four hundred fourteen patients were included in the intention-to-treat and 338 in the per-protocol analyses. The 2 treatment groups were generally well-balanced in terms of their baseline demographic (**Table 1**) and clinical characteristics and (**Table 2**).

Table 1. Characteristics of the Study Population Before and After Surgery[a]

Variable	No. (%) of Patients			
	Intention-to-Treat Analysis		Per-Protocol Analysis	
	Nontreatment (n = 207)	Antibiotic (n = 207)	Nontreatment (n = 180)	Antibiotic (n = 158)
Men	104 (50)	100 (48)	86 (48)	80 (51)
Age, mean (range), y	56 (20-94)	55 (18-93)	56 (22-94)	56 (18-93)
First episode of acute calculous cholecystitis	152 (73)	152 (74)	130 (72)	121 (76)
Duration of preoperative antibiotic treatment, mean (range), d	2 (0-12)	2 (0-14)	2 (0-4)	2 (0-5)
Murphy sign	163 (79)	146 (71)	142 (79)	112 (71)
Right upper quadrant				
Mass	21 (10)	17 (8)	17 (9)	17 (11)
Tenderness	138 (67)	137 (66)	118 (66)	105 (66)
Temperature, mean (SD), °C	37.33 (0.79)	37.20 (0.81)	37.33 (0.80)	37.21 (0.83)
Diabetes mellitus	26 (13)	35 (27)	22 (12)	28 (18)
Progressing cancer	7 (3)	7 (3)	6 (3)	5 (3)
Chronic kidney disease	2 (1)	3 (1)	2 (1)	1 (1)
Angina pectoris	11 (5)	14 (7)	11 (6)	8 (5)
Peripheral vascular disease	5 (2)	3 (1)	5 (3)	0 (0)
Smoker	69 (33)	78 (38)	59 (33)	55 (35)
Other surgery in the previous 2 wk	2 (1)	3 (1)	1 (1)	1 (1)
Surgical approach				
Laparoscopy	176 (85)	179 (86.5)	154 (85.6)	139 (87.9)
Conversion	20 (9.7)	14 (6.8)	18 (10)	9 (5.7)
Laparotomy	11 (5.3)	14 (6.8)	8 (4.4)	10 (6.3)
Complete cholecystectomy	201 (97.1)	200 (96.6)	175 (97.2)	154 (97.5)
Peroperative cholangiography	147 (71)	141 (68.1)	131 (72.8)	107 (67.7)
Calculus in the main biliary duct	1 (1)	5 (3)	1 (1)	4 (3.3)
Peroperative gallbladder perforation	86 (42)	78 (38)	76 (42.2)	59 (37.6)
Abdominal drainage in the right upper quadrant	120 (58)	116 (56)	99 (55)	94 (59.5)
Duration of surgery, mean (SD), min	102.8 (40.9)	109.2 (48.2)	100.8 (39.2)	108 (45.6)

[a] The number of patients with missing data were 4 or fewer of 414 for temperature, angina pectoris, peripheral vascular disease, hemoglobin, platelets, C-reactive protein, alanine aminotransferase, aspartate aminotransferase, potassium, and sodium; between 5 and 12 of 414 for alkaline phosphatase, γ-glutamyltransferase, total and indirect bilirubin, creatinine, urea, and total serum protein; and between 15 and 22 for amylase, lipase and glycemia.

Patient Enrolment and Protocol Feasibility

As mentioned above, protocol feasibility was only assessed at the Amiens University Medical Center. Of the 175 patients admitted to Amiens University Medical Center, 65 were not included in the study (feasibility, 63% [110 of 175]): 6 had grade III severe acute calculous cholecystitis, 9 had complaints lasting for more than 5 days, 9 had common bile duct stones discovered at the time of surgery, 3 had cholangitis, 17 had biliary peritonitis, 3 had acute pancreatitis, 2 had cirrhosis, 9 had β-lactam allergy, 2 were pregnant, and 5 were unable to understand the study information or give written, informed consent.

Primary Outcome

Outcomes in the Overall Study Population

The study's primary end point was present when the patient displayed 1 of the criteria defining a postoperative infection. In the study population as a whole, 66 patients developed a postoperative infection: 35 in the nontreatment group; 31 in the antibiotic group. Twenty patients in the nontreatment group had 1, 9 had 2, and 6 had 3 postoperative infections. Twenty-four patients in the antibiotic group had 1, 2 had 2, and 5 had 3 postoperative infections.

In the imputed intention-to-treat analysis, the postoperative infection rates were 17% (35 of 207) in the nontreatment group and 15% (31 of 207) in the antibiotic group (absolute difference, 1.93%; 95% CI, −8.98% to 5.12%; P = .007).

In the per-protocol analysis, the postoperative infection rates were 13% (23 of 180) in the nontreatment group and 13% (21 of 158) in the antibiotic group (absolute difference, 0.3%; 95% CI, −5.0% to 6.3%; P = .001).

Outcomes According to the Severity of Acute Calculous Cholecystitis

The postoperative infection rates in intention-to-treat analysis for patients with grade I acute calculous cholecystitis were 15% (15 of 103) in the nontreatment group and 13% (13 of 97) in the antibiotic group (absolute difference, 1.16%; 95% CI,

Table 2. Characteristics of the Study Population Laboratory Values Before and After Surgery[a]

Variable	Intention-to-Treat Analysis		Per-Protocol Analysis	
	Nontreatment (n = 207)	Antibiotic (n = 207)	Nontreatment (n = 180)	Antibiotic (n = 158)
Leukocytes, mean (SD), /μL	13 114 (5007)	13 441 (5546)	12 868 (5014)	13 562 (5026)
Hemoglobin, mean (SD), g/dL	14.00 (1.65)	13.97 (1.65)	13.98 (1.62)	14.06 (1.61)
Platelets, mean (SD), $\times 10^3$/μL	26 0261 (74 910)	26 0391 (76 427)	25 8879 (77 051)	26 2741 (77 075)
C-reactive protein, median (range), mg/L	96 (3-210)	96 (3-265)	94 (3-210)	93 (3-265)
ALAT, median (range), U/L	45 (6-581)	67 (6-550)	46 (6-581)	68 (6-550)
ASAT, median (range), U/L	45 (10-726)	62 (6-803)	47 (13-726)	65 (6-803)
Alkaline phosphatase, mean (SD), U/L	92.39 (64.5)	94.19 (55.6)	90.23 (62)	94.01 (50)
γGT, median (range), U/L	85 (10-896)	131 (3-959)	86 (10-896)	133 (3-959)
Bilirubin, mean (SD), mg/dL				
Total	285 (201.8)	289 (244.6)	287.3 (203.5)	289 (220.6)
Indirect	171 (17-753)	171 (34-1505)	171 (51.3-753)	171 (34-1505)
Creatinine, mean (SD), mg/dL	0.88 (0.28)	0.89 (0.30)	0.89 (0.27)	0.88 (0.29)
Urea, mean (SD), mg/dL	15.7 (7.8)	15.9 (9.6)	15.9 (7.3)	15.8 (10.3)
Amylase, median (range), U/L	1 (0.08-2.03)	0.77 (0.18-1.98)	0.78 (0.08-1.58)	0.77 (0.18-1.43)
Lipase, median (range), U/L	0.72 (0.10-4.47)	0.85 (0.10-4.53)	0.73 (0.10-4.47)	0.85 (0.10-4.45)
Potassium, mean (SD), mEq/L	3.94 (0.46)	3.93 (0.46)	3.94 (0.45)	3.95 (0.47)
Total serum protein, mean (SD), g/dL	73.46 (6.75)	73.01 (9.06)	73.64 (6.78)	73.67 (8.33)
Glucose, mean (SD), mg/dL	130.6 (45.9)	134.2 (57.1)	131.2 (47.56)	134.4 (54.9)
Sodium, mean (SD), mEq/L	137.4 (3.03)	137.4 (3.24)	137.5 (3.02)	137.2 (3.37)

Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; γGT, γ-glutamyltransferase.

SI conversion factors: to convert amylase from UL to μkat/L, multiply by 0.01667; bilirubin from mg/dL to μmol/L, multiply by 17.104; creatinine from mg/dL to μmol/L, multiply by 88.4; glucose from mg/dL, multiply by 0.0555; lipase from U/L to μkat/L, multiply by 0.01667; urea from mg/dL to mmol/L, multiply by 0.357.

[a] The number of patients with missing data were 4 or less for temperature, angina pectoris, peripheral vascular disease, hemoglobin, platelets, C reactive protein, ALALT, ASAT, potassium, and sodium; between 5 and 12 patients had missing values for alkaline phosphatase, γGT, total and indirect bilirubin, creatinine, urea, and total serum protein; and between 15 and 22 for amylase, lipase, and glycemia.

−8.45% to 10.77%; P = .03). For the per-protocol analysis, the postoperative infection rates were 12% (12 of 100) in the nontreatment group and 11% (10 of 94) in the antibiotic group (absolute difference, 1.36%; 95% CI; −7.55% to 10.27%; P = .02).

For patients with grade II acute calculous cholecystitis, the postoperative infection rates in the imputed intention-to-treat analysis were 19% (20 of 104) in the nontreatment group and 16% (18 of 110) in the antibiotic group (absolute difference, 2.78%; 95% CI, −7.39% to 13.12%; P = .04). For the per-protocol analysis, the postoperative infection rates were 17% (17 of 101) in the nontreatment group and 16% (17 of 109) in the antibiotic group (absolute difference, 1.24%; 95% CI, −8.75% to 11.22%; P = .03).

Outcomes According to the Duration of Preoperative Antibiotic Therapy

For patients who received a short course (<24 hours) of preoperative antibiotic therapy, the postoperative infection rates in the imputed intention-to-treat analysis were 15% (29 of 191) in the nontreatment group and 15% (29 of 198) in the antibiotic group (absolute difference, 0.54%; 95% CI, −6.55% to 7.62%; P = .03). In the per-protocol analysis, the postoperative infection rates were 13% (24 of 186) in the nontreatment group and 13% (25 of 194) in the antibiotic group (absolute difference, 9.02%; 95% CI; −6.72% to 6.76%; P = .001).

For patients who received a long course (>24 hours) of preoperative antibiotic therapy, the postoperative infection rates in the imputed intention-to-treat analysis were 38% (6 of 16) in the nontreatment group and 22% (2 of 9) in the antibiotic group (absolute difference, 15.3%; 95% CI −20.78% to 51.34%; P = .59). In the per-protocol analysis, the postoperative infection rates were 33% (5 of 15) in the nontreatment group and 22% (2 of 9) in the antibiotic group (absolute difference, 11.1%; 95% CI, 11.1%; −25.04% to 47.26%; P = .50.

Outcomes According to the Administration Route for Postoperative Antibiotic Therapy

Forty-seven of the 207 patients (23%) in the antibiotic group received solely intravenous administrations of antibiotic. For the imputed intention-to-treat analysis, the postoperative infection rates were 23% (11 of 47) in the intravenous group and 13% (20 of 160) in the oral group (absolute difference, 10.9%; 95% CI, −2.24% to 24.05%; P = .49). For the per-protocol analysis, the postoperative infection rates were 22% (10 of 46) in the intravenous group and 11% (17 of 157) in the oral group (absolute difference, 10.9%; 95% CI, −1.96% to 23.78%; P = .49).

Blind Review

Two independent surgeons who were not involved in the study and were blinded to the randomization reviewed 40 sets of

Table 3. Postoperative Outcomes Including Postoperative Infections and Noninfectious Postoperative Outcomes

Type of Event	Intention-to-treat Analysis, No. (%)			Per-Protocol Analysis, No. (%)		
	Nontreatment (n = 207)	Antibiotic (n = 207)	Absolute Difference (95% CI), %	Nontreatment (n = 180)	Antibiotic (n = 158)	Absolute Difference (95% CI), %
No. of postoperative infections	35	31	23		21	
Incisional infection						
Superficial	8 (3.9)	12 (5.8)	−1.9 (−6.06 to 2.19)	7 (3.9)	9 (5.7)	−1.81 (−6.39 to 2.78)
Deep	3 (1.5)	1 (0.5)	0.97 (−0.92 to 2.85)	3 (1.7)	1 (0.7)	1.03 (−1.21 to 3.28)
Organ space infection	11 (5)	8 (4)	1.45 (−2.58 to 5.48)	10 (6)	2 (1)	4.29 (−0.52 to 8.06)
Temperature ≥38.5°C 2 d after surgery	12 (5.8)	9 (4.4)	1.45 (−2.78 to 5.67)	12 (6.7)	7 (4.4)	2.24 (−2.62 to 7.09)
Pneumopathy	6 (2.9)	2 (0.9)	1.93 (−0.71 to 4.58)	6 (3.3)	0	3.33 (0.71 to 5.96)
Infection						
Catheter	0	2 (0.9)	−0.97 (−2.30 to 0.37)	0	0	
Urinary tract	4 (1.9)	2 (0.9)	0.97 (−1.33 to 3.27)	3 (1.7)	1 (0.7)	1.03 (−1.21 to 3.28)
Septic shock	1 (0.48)	2 (0.9)	−0.42 (−1.88 to 1.88)	1 (0.6)	1 (0.7)	−0.08 (−1.72 to 1.57)
Postoperative noninfectious outcomes						
Postoperative hemorrhage	3 (1.5)	1 (0.5)	0.97 (−0.92 to 2.85)	2 (1.1)	0	1.11 (−0.42 to 2.64)
Pulmonary embolism	3 (1.5)	2 (0.9)	0.48 (−1.62 to 2.59)	2 (1.1)	1 (0.7)	0.08 (−1.72 to 1.57)
Deep venous thrombosis	2 (0.9)	2 (0.9)	0 (−1.88 to 1.88)	2 (1.1)	1 (0.7)	0.48 (−1.49 to 2.45)
Stroke	3 (1.5)	0	1.45 (−0.18 to 3.08)	2 (1.1)	0	1.11 (−0.42 to 2.64)

medical records (20 from each group) and compared them with our assessment of the primary criterion. Cohen κ was calculated to be to 0.98, demonstrating excellent concordance with the unblinded assessment.

Secondary Outcomes

Postoperative Outcomes

Postoperative Complications According to the Clavien-Dindo Classification | Baseline surgical characteristics did not differ significantly by treatment group (Table 1 and Table 2). Postoperative complications did not differ significantly by group (eTable in the Supplement) in any of the intention-to-treat and per-protocol analyses. Five patients had severe complications in the intention-to-treat analysis (P = .12) and 4 in the per-protocol analysis (P = .22). One hundred ninety-five patients (94.2%) in the treatment group had a score of 0 to I and 2 patients (0.97%) had a score of III to V. One hundred eighty-two patients (87.8%) in the antibiotic group had a score of 0 to I and 4 patients (1.93%) had a score of III to V. Mortality was 0.2% (1 of 414): an 84-year-old man (a smoker with a history of chronic cholelithiasis, ischemic stroke, diffuse arthritis, liver steatosis, prostate adenoma, chronic alcohol consumption, and age-related macular degeneration) in the nontreatment group was excluded because he had not disclosed to the medical team that he was under guardianship and could not lawfully give informed consent. He immediately received postoperative antibiotics but died a day after surgery before a second-look laparotomy (indicated for hemodynamic instability, abdominal, pain and abdominal distension) could be attempted. The final diagnosis was an intraabdominal complication or pulmonary embolism.

Readmission Rate | Twelve of the 207 patients (6%) in the nontreatment group and 11 of the 207 patients (5%) in the antibiotic group were readmitted (P = .76). The causes of readmission were small bowel obstruction (n = 1), pulmonary embolism (n = 2), hepatic collection (n = 1), abdominal pain (n = 2), cholelithiasis (n = 3), acute pancreatitis (n = 1), and knee arthritis (n = 2) in the nontreatment group and vertigo (n = 2), fever (n = 2), nephrectomy for incidental kidney cancer (n = 1), adenocarcinoma of gallbladder (n = 1), abdominal pain (n = 4), and pancreatitis (n = 1) in the antibiotic group.

Postoperative Infections | Postoperative infections were recorded for 56 of the 414 patients (14%). Of the 29 patients with infections in the nontreatment group, 21 (72%) received antibiotics after their infections were discovered. Of the 27 patients with infections in the antibiotic group, 12 (44%) required a treatment change from amoxicillin plus clavulanic acid to other antibiotics (**Table 3**). Most of the infections were superficial incisional infections (5% of the entire population). Both groups had similar postoperative infection rates (Kaplan-Meier P log-rank = .86).

Applicability of the Protocol | Overall, 89.8% (186 of 207) of the patients in the nontreatment group did not receive any postoperative antibiotics. Of the 29 patients in the nontreatment group who developed postoperative infections, 21 received postoperative antibiotic treatment once their infections were diagnosed.

Adverse Events | Five patients experienced a serious adverse event: 4 patients (2%) in the nontreatment group (calculus migration, preoperative cardiac arrest, an intraabdominal col-

Table 4. Types of Pathogen and Resistance Status

Pathogen	No. (%)			
	Nontreatment		Antibiotic	
	Isolates Tested for Resistance	Resistant Isolates	Isolates Tested for Resistance	Resistant Isolates
Enterobacteriaceae	62 (69.7)	17 (27.4)	84 (71.8)	28 (33.3)
Other gram-negative bacilli	6 (6.7)	1 (16.7)	11 (9.4)	4 (36.4)
Gram-positive bacilli	19 (21.3)	4 (21.1)	22 (18.8)	3 (13.7)
Other unspecified bacteria	2 (2.2)	0	0	0
Total	89 (100)	22 (24.7)	117 (100)	35 (29.9)

lection and wound hematoma) and 1 (1%) in the antibiotic group (wound hematoma) (P = .86).

Microbiological Aspects | A biliary fluid sample was collected for 384 of the 414 (93%) patients, of whom 234 (60.9%) were pathogen free. A total of 206 different pathogens were isolated (n = 150 patients with isolates) from the study population (89 in the non-antibiotic group and 117 in the antibiotic group). Fifty-seven of these (28%) were resistant to amoxicillin (22 in the nontreatment group and 35 in the antibiotic group). The data are summarized in **Table 4**.

Enterobacteriaceae was the most frequently isolated bacterial family in each group (found in 70% of the positive samples in the nontreatment group and 72% in the antibiotic group). Within this family, *Enterobacter cloacae* were the most frequently isolated species (4 positive samples) in the nontreatment group and *Enterococcus faecium* (2 positive samples) in the antibiotic group. Other gram-positive bacilli constituted the next most frequently isolated group in each group (21% of the positive samples in the nontreatment group and 19% in the antibiotic group).

Postoperative Course of Patients With Postoperative Complications | Postoperative complications, the length of stay, Clavien score, and readmission rate were not significantly related to randomization group.

Postoperative Course of Patients With Pathogens Resistant to Amoxicillin Plus Clavulanic Acid | Patients with pathogens resistant to amoxicillin plus clavulanic acid had essentially the same mean length of stay, Clavien score, and readmission rate as did patients with pathogens sensitive to amoxicillin plus clavulanic acid.

Discussion

Our results showed that after early laparoscopic cholecystectomy for mild and moderate (grades I and II) acute calculous cholecystitis, the absence of postoperative antibiotic treatment was not associated with a higher incidence of postoperative infections or noninfectious complications. The two groups of patients had the same length of stay and readmission rates. The postoperative course did not appear to depend on the study group assignment or the presence or absence of pathogens that were resistant to amoxicillin plus clavulanic acid.

Overall, 85.5% of the patients were free of postoperative complications and the mortality rate was 0.2%.

The mean length of stay was 5 days, which is within the range (4.1-7.6 days) found by Gurusamy et al[4] in a meta-analysis of similar patient populations.

At present, the guidelines published by the Infectious Diseases Society of America[20,24,] the World Society of Emergency Surgery,[25] and the Tokyo consensus meeting[10] all recommend treatment with amoxicillin plus clavulanic acid or sulbactam after cholecystectomy for noncomplicated acute calculous cholecystitis. In the present series, we did not observe a benefit of postoperative antibiotic treatment on infections for patients with grade I or II acute calculous cholecystitis.

In the present study, surgical quality indicators (such as the surgical approach, 85% of which was laparoscopy, the conversion rate (<10%), the use of intraoperative cholangiography (70%), mean operative time (100 min), mean length of stay (5 days), and overall mortality (0.2%) were consistent with outcomes observed in other studies of patients with acute calculous cholecystitis.[4] The same was true for the distribution of bacteriae isolates and the proportion of resistant pathogens found in bile culture.[12]

At present, there is trend toward shorter antibiotic treatments after surgery for uncomplicated appendicitis[30] or anorectal abscess.[23] Recent studies of postoperative antibiotic treatment in acute calculous cholecystitis have compared a variety of antibiotic regimens.[12] Only one study[27] prospectively compared 2 postoperative antibiotic regimens on 203 patients with acute calculous cholecystitis with the "intention to shorten the duration of postoperative antibiotic treatment." Importantly, the latter study was performed before the introduction of the Tokyo criteria, which provides guidelines for calculous cholecystitis management. All the patients received 2 g of cefamandole preoperatively. After surgery, patients were randomized to receive either a short (12-hour) or long (7-day) course of antibiotics. Lau et al[27] found that the longer course of treatment was not associated with a significantly lower surgical site infection rate.

In everyday practice, no consensus statements with strong recommendations on the duration of antibiotic treatment before and after surgery exist from the Infectious Disease Society of America. For example, 87% of surgeons in a retrospective series routinely continued antibiotic treatment beyond 24 hours.[28]

The percentage of included patients among the prescreened patients with acute calculous cholecystitis at the coordinating center was 63%. The relatively low enrollment was due to our choice of the antibiotic (penicillin, with no alternative in the study protocol, such as ciprofloxacin plus metronidazole[12]), the prevalence of penicillin allergy, and the decision to exclude patients with biliary peritonitis (even though this situation is part of grade II acute calculous cholecystitis). However, the applicability of this strategy was high because 89.8% of the patients in the nontreatment group did not receive postoperative antibiotics.

Our study has several limitations. First, the absence of placebo as a comparator and the absence of blind assessment may have decreased the reliability of our evaluation of the primary outcome and the groups' comparability. However, the primary end point was an objective, clinically robust criterion with an internationally accepted definition. To reduce this possible bias, a blind review of 10% of the patients' medical records was performed by 2 independent surgeons not involved in the study. The Cohen κ of 0.98 demonstrates an excellent correlation between the blinded re-reviews and our original classification, suggesting that observer bias for wound infections did not influence our results. The selection of noninferiority margin of 11% and the associated wide confidence intervals could have masked a possible difference in postoperative infections between the 2 groups.

Second, the course of antibiotic therapy was somewhat nonstandardized in the treatment group: 76.3% of these patients were discharged with a prescription for oral antibiotics (for a mean duration of 1 day), which may have caused us to underestimate the true duration of antibiotic administration. Third, the lack of specificity in terms of the patients' visits to primary care physicians could be a study weakness. However, this accounted for less than 5% of the patients not seen by the investigators at the follow-up visit at 4 weeks. Fourth, the high proportion of protocol violations could introduce a bias, especially because most of these were linked to a failure to take amoxicillin plus clavulanic acid before or during surgery or to nonadherence with an inclusion criterion. Fifth, the lack of data on the reasons for noninclusion in all participating centers prevents us from generalizing our conclusions. However, we made a conscious decision to not monitor nonparticipants to facilitate enrollment in participating centers. Overall, only 10% of the reasons for noninclusion were subjective. Last, the choice of antibiotics could be questioned but was prompted by international guidelines and those issued by the French Society of Anesthesia and Intensive Care.

It is well known that continuation of antibiotic treatment increases costs and promotes the selection of multiresistant bacteria.[19,26] In 2010, 37 499 cholecystectomies for acute calculous cholecystitis were performed in France,[3] and 90% of these were for grades I and II acute calculous cholecystitis. Supposing that these patients did not really need postoperative antibiotics (which are generally prescribed for 5 days), we estimate that many days of antibiotic treatment could be avoided each year. Reduction of the use of unnecessary antibiotics is important given that there is an increasing antibiotic resistance and a higher incidence of antibiotic complications such as *Clostridium difficile* infection. Our study demonstrates that postoperative antibiotics following acute calculous cholecystitis are not necessary.

Conclusions

Among patients with mild or moderate calculous cholecystitis who received antibiotics before and during surgery, lack of postoperative treatment with amoxicillin plus clavulanic acid did not result in a greater incidence of infections.

ARTICLE INFORMATION

Author Affiliations: Division of Digestive Surgery, Amiens University Medical Center, Amiens, France (Regimbeau, Fuks, Cossé); Jules Verne University of Picardie, Unit EA4294, Amiens, France (Regimbeau); Clinical Research Center, Amiens University Medical Center, Amiens, France (Regimbeau); Division of Digestive Disease, Paris Lariboisière Hospital, Paris, France (Pautrat, Pocard); Division of Digestive Surgery, Beauvais Hospital, Beauvais, France (Mauvais); Division of Digestive Surgery, Montreuil-sur-Mer Hospital, Montreuil-sur-Mer, France (Haccart); Division of Digestive Surgery, Louis Mourier University Hospital, Colombes, France (Msika); Division of Digestive Surgery, Limoges University Hospital, Limoges (Mathonnet); Division of Digestive Surgery, Rouen University Hospital, Rouen, France (Scotté); Division of Digestive Surgery, Longjumeau Hospital, Longjumeau, France (Paquet); Division of Digestive Surgery, Jean Verdier University Hospital, Bondy, France (Vons); Division of Digestive Surgery, Marseille University Hospital La Timone, Marseille, France (Sielezneff); Division of Digestive Surgery, Montpellier University Hospital, Montpellier, France (Millat); Division of Digestive Surgery, Caen University Hospital, Caen, France (Chiche); Division of Anesthesia and Intensive Care, Amiens University Medical Center, Amiens, France (Dupont); Division of Internal Medicine and Systemic Diseases, Amiens University Medical Center, Amiens, France (Duhaut); Division of Clinical Research and Innovation, Amiens University Medical Center, Amiens, France (Diouf).

Author Contributions: Dr Regimbeau had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Regimbeau, Msika, Scotté, Vons, Sielezneff, Millat, Duhaut, Diouf.
Acquisition, analysis, or interpretation of data: Regimbeau, Fuks, Pautrat, Mauvals, Haccart, Mathonnet, Scotté, Paquet, Millat, Chiche, Dupont, Duhaut, Cossé, Diouf, Pocard.
Analysis and Interpretation of data: Regimbeau, Coss, Diouf.
Drafting of the manuscript: Regimbeau, Cossé, Pocard.
Critical revision of the manuscript for important intellectual content: Regimbeau, Fuks, Pautrat, Mauvals, Haccart, Msika, Mathonnet, Scotté, Paquet, Vons, Sielezneff, Millat, Chiche, Dupont, Duhaut, Cossé, Diouf, Pocard.
Statistical analysis: Duhaut, Cossé, Diouf.
Obtained funding: Regimbeau, Fuks.
Administrative, technical, or material support: Regimbeau, Pautrat, Msika, Mathonnet, Scotté, Chiche, Pocard.
Study supervision: Regimbeau, Scotté, Vons, Sielezneff, Dupont.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Funding/Support: This study was funded by the French Ministry of Health's Programme Hospitalier de Recherche Clinique 2009 program. This study was supported with cooperative agreements from the National Clinical Research Protocol.

Role of the Sponsors: The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

FRENCH Study Group Members: *Amiens University Medical Center:* (Jean-Marc Regimbeau, MD, PhD, David Fuks, MD, PhD). *Paris Lariboisière Hospital:* (Marc Pocard, MD, PhD, Karine Pautrat, MD). *Montreuil-sur-Mer Hospital:* (Vincent Haccart, MD).

Louis Mourier Hospital: (Simon Msika, MD, PhD). *Jean-Verdier Hospital:* (Corinne Vons, MD, PhD). *Montpellier University Medical Center:* (Bertrand Millat, MD, PhD). *Clermont-Ferrand Estaing hospital:* (Karem Slim MD, PhD). *Paris Tenon Hospital:* (Francois Lacaine, MD, PhD). *Claude Huriez Lille University hospital:* (Christophe Mariette MD, PhD).

Coordinating Center: *Clinical Research Center, Amiens University Medical Center, Amiens, France:* Jean-Marc Regimbeau, MD, PhD.

Data and Safety Monitoring Board: Jean-Marc Regimbeau, MD, PhD, David Fuks, MD, PhD, Cyril Cosse, PhD, Sophie Liabeuf, PhD, Momar Diouf, PhD, Elodie Deruche, Sebastien Selve, Delphine Lignier.

Additional Contributions: We thank Jean-Pierre Arnaud, MD, PhD, Angers University Hospital, Division of Digestive Surgery; Catherine Arvieux, MD, PhD, Grenoble University Hospital, Division of Digestive Surgery; Denis Collet, MD, PhD, Pessac University Hospital, Division of Digestive Surgery; François Lacaine, MD, PhD, Paris Tenon University Hospital, Division of Digestive Surgery; Karem Slim, MD, PhD, Clermont-Ferrand University Hospital, Division of Digestive Surgery; Sophie Liabeuf, PharmD, Amiens University Medical Center, Division of Clinical Research Center; Jean Luc Schmit, MD, PhD, Amiens University Medical Center, Division of Infectious Disease, for which they received no compensation.

REFERENCES

1. Payen JL, Muscari F, Vibert E, Ernst O, Pelletier G. Biliary lithiasis [in French]. *Presse Med*. 2011;40(6):567-580.

2. Centers for Disease Control and Prevention, National Center for Health Statistics, Division of Health Care Statistics, Hospital Care Statistics Branch. http://www.cdc.gov/nchs/data/tables/2002/02hus095.pdf. Accessed February 24, 2003.

3. Haute Autorité de Santé. Note de problématique pertinence cholecystectomie. http://www.has-sante.fr/portail/upload/docs/application/pdf/2013-03/points-cle_solution_-_problematique_cholecystectomie.pdf

4. Gurusamy K, Samraj K, Gluud C, Wilson E, Davidson BR. Meta-analysis of randomized controlled trials on the safety and effectiveness of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. *Br J Surg*. 2010;97(2):141-150.

5. Kanafani ZA, Khalifé N, Kanj SS, Araj GF, Khalifeh M, Sharara AI. Antibiotic use in acute cholecystitis: practice patterns in the absence of evidence-based guidelines. *J Infect*. 2005;51(2):128-134.

6. Thompson JE Jr, Bennion RS, Doty JE, Muller EL, Pitt HA. Predictive factors for bactibilia in acute cholecystitis. *Arch Surg*. 1990;125(2):261-264.

7. Bjorvatn B. Cholecystitis—etiology and treatment—microbiological aspects. *Scand J Gastroenterol Suppl*. 1984;90:65-70.

8. Claesson B, Holmlund D, Mätzsch T. Biliary microflora in acute cholecystitis and the clinical implications. *Acta Chir Scand*. 1984;150(3):229-237.

9. Mazeh H, Mizrahi I, Dior U, et al. Role of antibiotic therapy in mild acute calculus cholecystitis: a prospective randomized controlled trial. *World J Surg*. 2012;36(8):1750-1759.

10. Hirota M, Takada T, Kawarada Y, et al. Diagnostic criteria and severity assessment of acute cholecystitis: Tokyo Guidelines. *J Hepatobiliary Pancreat Surg*. 2007;14(1):78-82.

11. Fuks D, Mouly C, Robert B, Hajji H, Yzet T, Regimbeau JM. Acute cholecystitis: preoperative CT can help the surgeon consider conversion from laparoscopic to open cholecystectomy. *Radiology*. 2012;263(1):128-138.

12. Fuks D, Cossé C, Regimbeau JM. Antibiotic therapy in acute calculous cholecystitis. *J Visc Surg*. 2013;150(1):3-8.

13. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. *Am J Infect Control*. 1992;20(5):271-274.

14. 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(2):205-213.

15. Kune GA, Burdon JG. Are antibiotics necessary in acute cholecystitis? *Med J Aust*. 1975;2(16):627-630.

16. Meijer WS. Antibiotic prophylaxis in biliary tract surgery--current practice in The Netherlands. *Neth J Surg*. 1990;42(4):96-100.

17. Havig O, Hertzberg J. Effect of ampicillin, chloramphenicol, and penicillin-streptomycin in acute cholecystitis. *Scand J Gastroenterol*. 1973;8(1):55-58.

18. Groezinger KH. Prophylactic use of mezlocillin in acute cholecystitis. *Chemioterapia*. 1987;6(2)(suppl):590.

19. Yoshida M, Takada T, Kawarada Y, et al. Antimicrobial therapy for acute cholecystitis: Tokyo Guidelines. *J Hepatobiliary Pancreat Surg*. 2007;14(1):83-90.

20. Weigand K, Köninger J, Encke J, Büchler MW, Stremmel W, Gutt CN. Acute cholecystitis—early laparoscopic surgery vs antibiotic therapy and delayed elective cholecystectomy: ACDC-study. *Trials*. 2007;8:29.

21. Rodríguez-Sanjuán JC1, Casella G, Antolín F, et al. How long is antibiotic therapy necessary after urgent cholecystectomy for acute cholecystitis? *J Gastrointest Surg*. 2013;17(11):1947-1952.

22. Jaafar G1, Persson G, Svennblad B, Sandblom G. Outcomes of antibiotic prophylaxis in acute cholecystectomy in a population-based gallstone surgery registry. *Br J Surg*. 2014;101(2):69-73.

23. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Surg Infect (Larchmt)*. 2010;11(1):79-109.

24. Piantadosi S. *Clinical Trials: A Methodological Prespective*. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2005:290.

25. Solomkin JS, Mazuski JE, Baron EJ, et al. Infectious Diseases Society of America. Guidelines for the selection of antiinfective agents for complicated intra-abdominal infections. *Clin Infect Dis*. 2003;37:997-1005.

26. Sözener U, Gedik E, Kessaf Aslar A, et al. Does adjuvant antibiotic treatment after drainage of anorectal abscess prevent development of anal fistulas? a randomized, placebo-controlled, double-blind, multicenter study. *Dis Colon Rectum*. 2011;54(8):923-929.

27. Lau WY, Yuen WK, Chu KW, Chong KK, Li AK. Systemic antibiotic regimens for acute cholecystitis treated by early cholecystectomy. *Aust N Z J Surg*. 1990;60(7):539-543.

28. Kapoor VK, Sikora SS, Bal S. Current practice in biliary surgery: the Indian scenario. *Indian J Gastroenterol*. 1994;13(2):49-51.

29. Sartelli M, Viale P, Koike K, et al. WSES consensus conference: Guidelines for first-line management of intra-abdominal infections. *World J Emerg Surg*. 2011;6:2.

30. Vons C, Barry C, Maitre S, et al. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. *Lancet*. 2011;377(9777):1573-1579.