Optimal treatment of acute cholecystitis

Charlotte Susan Loozen

OPTIMAL TREATMENT OF ACUTE CHOLECYSTITIS

Thesis, Utrecht University, The Netherlands

Printed by Ipskamp printing

ISBN 978-94-028-0704-2

The studies described in Chapter 2, Chapter 3 and Chapter 9 were financially supported by the St. Antonius Research Foundation (St. Antonius Onderzoeksfonds)

Publication of this thesis was financially supported by maatschap heelkunde van het St. Antonius Ziekenhuis, raad van bestuur van het St. Antonius Ziekenhuis, Nederlandse Vereniging voor Endoscopische Chirurgie and Chipsoft B.V.

Optimal treatment of acute cholecystitis

Optimale behandeling van cholecystitis acuta
(met een samenvatting in het Nederlands)

PROEFSCHIFT

ter verkrijging van de graad van doctor
aan de Universiteit Utrecht
op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen
op dinsdag 5 september 2017
des middags te 4.15 uur

door

Charlotte Susan Loozen
geboren op 3 februari 1988
te Haarlem

PROMOTOR:

Prof. dr. M.R. Vriens

COPROMOTOREN:

Dr. D. Boerma

Dr. H. C. van Santvoort

Aan mijn lieve moedertje
(en ‘n beetje aan papa)

CONTENTS

CHAPTER 1

General introduction and thesis outline

INTRODUCTION

Acute cholecystitis is a common indication for hospital admission and an increasing burden on the Western health care system. More than 90% of cases of acute cholecystitis are associated with cholelithiasis; a condition that afflicts at least 10% of the people in Western countries.[1] The prevalence of gallstones increases with age; in patients aged ≥ 60 the prevalence rate ranges from 20% to 30%[2,3] and increases to 80% in institutionalized individuals aged ≥ 90.[4]

The key element in the pathogenesis of acute calculous cholecystitis seems to be an obstruction of the cystic duct in the presence of bile supersaturated with cholesterol.[4] Brief impaction may cause pain only, whereas prolonged impaction can result in inflammation. With inflammation, the gallbladder becomes enlarged and tense, and wall thickening and an exudate of pericholecystic fluid may develop.[5] While in most cases the inflammation initially is sterile, secondary infection occurs in approximately 30-50% of the patients,[6] most commonly caused by E. coli and K. pneumoniae. Bacterial superinfection with gas-forming organisms may lead to gas in the wall or lumen of the gallbladder (emphysematous cholecystitis). The wall of the gallbladder may undergo necrosis and gangrene (gangrenous cholecystitis). Without appropriate treatment, the gallbladder may perforate, leading to the development of an abscess or generalized peritonitis.[5]

Acute cholecystitis usually starts with an attack of biliary colic, often in a patient who had previous attacks. The pain persists and localizes in the right upper quadrant. Besides a positive Murphy's sign and tenderness in the right upper quadrant, also fever and elevation in the white blood cell count are classically described.[7] According to the international guidelines for the management of acute cholecystitis, the "Tokyo guidelines", acute cholecystitis is clinically suspected if at least one local sign of inflammation (Murphy's sign or pain, tenderness or mass in the right upper quadrant) and one sign of systematic inflammation (fever, leucocytosis, elevated C-reactive protein level) is present.[8] Only if confirmed by imaging, the diagnosis is definitive. Several imaging modalities can be used. Ultrasonography is usually favoured as the first test because it is relatively inexpensive and widely available, it involves no radiation exposure and has high sensitivity and specificity (81% and 83%, respectively).[9] Typical diagnostic findings include thickening of the gallbladder wall, presence of pericholecystic fluids and a sonographic Murphy's sign. Scintigraphy and CT-tomography are usually reserved for

patients in whom the diagnosis after ultrasonography is unclear or in patients suspected of complications.[10]

The severity of acute cholecystitis varies widely among patients. According to the Tokyo Guidelines, the severity is divided in three grades based on the degree of local and systemic inflammation and the presence of organ dysfunction.[8] Mild (grade I) acute cholecystitis is defined as acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder. Moderate (grade II) acute cholecystitis is defined as acute cholecystitis associated with any of the following conditions: elevated white blood cell count (>18.000/mm3), palpable tender mass in the right upper abdominal quadrant, duration of complaints > 72 hours, or marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis). Severe (grade III) acute cholecystitis is defined as acute cholecystitis associated with organ dysfunction. The definition and grading as proposed by the Tokyo Guidelines are adapted in the Dutch Guidelines for the treatment of gallstone related disease.[11]

Laparoscopic cholecystectomy is the gold standard treatment of acute cholecystitis. This procedure can be performed either at the time of the initial attack (early cholecystectomy) or several weeks after the initial attack has subsided (delayed cholecystectomy). In the latter case, during the acute phase patients are treated with intravenous fluids and analgesics, and, if necessary, percutaneous drainage for complete resolution of inflammation. In randomized controlled trials comparing early cholecystectomy with a delayed procedure, early treatment has been associated with lower complication rates, shorter overall hospitalization and reduced costs.[12] In addition, more than 10% of the patients awaiting delayed cholecystectomy sho5wed persistent or recurrent symptoms requiring intervention, which also favours early cholecystectomy.

Laparoscopic compared to open cholecystectomy is associated with reduced morbidity and mortality and shorter hospitalization, and therefore is the technique of choice for most patients with acute cholecystitis.[12] The conversion rate from laparoscopic to open cholecystectomy for acute cholecystitis is approximately 15%.[13] Predictors for conversion include a white blood cell count of more than 18.000 cells per millimeter at time of presentation, a more than 96 hours duration of symptoms and an age over 60 years.[14-18]

An alternative treatment for acute cholecystitis is percutaneous drainage, a technique that consists of placement of a percutaneous catheter in the gallbladder lumen under imaging

guidance. This procedure is minimally invasive, resolves local and systemic inflammation and avoids the risk of surgery. It is often used as treatment for severe acute cholecystitis and in patients unfit for surgery in whom conservative treatment by itself fails. Percutaneous drainage has a high technical success rate and a low complication rate, and usually results in resolution of acute cholecystitis.[19] Yet, the gallbladder being left in situ may lead to recurrent symptoms in up to 22% of patients.[20-21] According to a meta-analysis of 1751 patients who underwent percutaneous drainage for acute cholecystitis, more than 40% of the patients eventually came to surgery. Emergency surgery due to therapeutic failure, recurring cholecystitis or procedural complications was performed in 5% of patients whereas elective cholecystectomy, either sub-acute or delayed, was performed in 38% of patients.

THESIS OUTLINE

The studies presented in this thesis focus on two main issues: treatment strategies for acute calculous cholecystitis (Part I), and the management of acute calculous cholecystitis in high-risk patients in particular (Part II). The last chapter focuses on the surgical treatment of common bile duct stones (Part III).

PART I: Treatment strategies for acute calculous cholecystitis

Whether or not antibiotic prophylaxis has any additional value in preventing infectious complications in patients with acute cholecystitis is a much debated subject in the surgical community. Many patients undergoing emergency cholecystectomy receive postoperative antibiotic prophylaxis intended to reduce infectious complications. The positive effect of extending antibiotics beyond a single preoperative dose, however, has never been proven. **Chapter 2** presents the PEANUTS trial; a randomized controlled, multicenter trial to assess the effect of extended antibiotic prophylaxis on infectious complications in patients with mild acute cholecystitis undergoing cholecystectomy.

Also the use of preoperative antibiotic prophylaxis in patients undergoing surgery for acute cholecystitis is disputable. **Chapter 3** presents the protocol of the PEANUTS II-trial; a randomized controlled, multicenter trial to assess the effect of preoperative antibiotic prophylaxis in patients undergoing emergency cholecystectomy for mild and moderate acute calculous cholecystitis.

In medical practice, the tendency to remove an inflamed gallbladder is deeply rooted. The decision to perform surgery, however, should be well-considered since cholecystectomy can result in serious morbidity. For some patients the surgical risk-benefit profile may favour conservative treatment. **Chapter 4** provides a literature review on the short and long-term outcome of conservative treatment of patients with acute calculous cholecystitis.

The severity of acute cholecystitis and its clinical manifestation vary widely among patients. According to the international guidelines of gallstone disease, the severity is divided in three grades based on the degree of local and systemic inflammation and the presence of organ dysfunction. For each grade a different treatment strategy is proposed. Percutaneous catheter drainage is advised in patients with severe acute cholecystitis. Delayed cholecystectomy should be performed in patients with moderate acute cholecystitis whereas early cholecystectomy should be performed in patients with mild acute cholecystitis. In recent years, however, several randomized controlled trials demonstrated a clear benefit in performing early rather than delayed cholecystectomy. **Chapter 5** presents a large retrospective observational cohort study on the outcome of emergency cholecystectomy for mild and moderate acute cholecystitis. Based on the findings an adaptation of the Tokyo guidelines is proposed.

Chapter 6 provides an overview of the recent advances in the management of acute cholecystitis. Various aspects of the treatment are discussed, such as the optimal timing of surgery, the indication for percutaneous drainage, the feasibility of nonoperative management and the role of antibiotics.

PART II: Management of high-risk patients with acute calculous cholecystitis

The optimal treatment of elderly patients with acute cholecystitis remains controversial. In view of the aging population, addressing this controversy becomes a matter of increasing urgency. In the era of advanced surgical techniques and improved perioperative care, the willingness to perform emergency operations in elderly patients continues to increase. **Chapter 7** presents a retrospective study on the safety and feasibility of emergency cholecystectomy in elderly patients with acute cholecystitis. **Chapter 8** provides a comprehensive literature review on the clinical outcome of early cholecystectomy in the elderly population.

In elderly patients with significant comorbidities or seriously ill patients, increased risk of perioperative morbidity and mortality due to reduced physiologic reserve is of concern. Percutaneous drainage is considered an alternative treatment option. **Chapter 9** presents the CHOCOLATE-trial: a randomized controlled, multicenter trial to determine whether percutaneous drainage or laparoscopic cholecystectomy is best suited for high risk patients with acute calculous cholecystitis.

PART III: Surgical treatment of common bile duct stones

Over the past century, the management of common bile duct stones has evolved considerably, and endoscopic as well as surgical options are currently available. **Chapter 10** describes the surgical techniques, and its complications, that are currently available, focusing on the laparoscopic approach.

Chapter 11 provides a summary of the results of this thesis and a general discussion.

REFERENCES

1 Schirmer BD, Winters KL, Edlich R. Cholelithiasis and cholecystitis. J Long Term Eff Med 2005;15(3).

2 Lirussi F, Nassuato G, Passera D, Toso S, Zalunardo B, Monica F, et al. Gallstone disease in an elderly population: the Silea study. Eur J Gastroenterol Hepatol 1999;11 (5):485-492.

3 Festi D, Dormi A, Capodicasa S, Staniscia T, Attili AF, Loria P, et al. Incidence of gallstone disease in Italy: results from a multicenter, population-based Italian study (the MICOL project). World J Gastroenterol 2008;14(34):5282-5289.

4 Ratner J, Lisbona A, Rosenbloom M, Palayew M, Szabolcsi S, Tupaz T. The prevalence of gallstone disease in very old institutionalized persons. JAMA 1991;265 (7):902-903.

5 Strasberg SM. Acute calculous cholecystitis. N Engl J Med 2008;358(26):2804-2811.

6 Gomi H, Solomkin JS, Takada T, Strasberg SM, Pitt HA, Yoshida M, et al. TG13 antimicrobial therapy for acute cholangitis and cholecystitis. Journal of hepato-biliary-pancreatic sciences 2013;20(1):60-70.

7 Gruber PJ, Silverman RA, Gottesfeld S, Flaster E. Presence of fever and leukocytosis in acute cholecystitis. Ann Emerg Med 1996;28(3):273-277.

8 Yokoe M, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Gomi H, et al. TG13 diagnostic criteria and severity grading of acute cholecystitis (with videos). Journal of hepato-biliary-pancreatic sciences 2013;20(1):35-46.

9 Kiewiet JJ, Leeuwenburgh MM, Bipat S, Bossuyt PM, Stoker J, Boermeester MA. A systematic review and meta-analysis of diagnostic performance of imaging in acute cholecystitis. Radiology 2012;264(3):708-720.

10 Bennett GL, Rusinek H, Lisi V, Israel GM, Krinsky GA, Slywotzky CM, et al. CT findings in acute gangrenous cholecystitis. Am J Roentgenol 2002;178(2):275-281.

11 Nederlandse Vereniging voor Heelkunde (NVvH). Richtlijn galsteenlijden. 2016; Available at: http://heelkunde.nl/sites/heelkunde.nl/files/Richtlijn_Galsteenlijden_09032016.pdf.

12 Coccolini F, Catena F, Pisano M, Gheza F, Fagiuoli S, Di Saverio S, et al. Open versus laparoscopic cholecystectomy in acute cholecystitis. Systematic review and meta-analysis. International Journal of Surgery 2015;18:196-204.

13 Cao AM, Eslick GD, Cox MR. Early cholecystectomy is superior to delayed cholecystectomy for acute cholecystitis: a meta-analysis. Journal of Gastrointestinal Surgery 2015;19(5):848-857.

14 Brodsky A, Matter I, Sabo E, Cohen A, Abrahamson J, Eldar S. Laparoscopic cholecystectomy for acute cholecystitis: can the need for conversion and the probability of complications be predicted? Surg Endosc 2000;14(8):755-760.

15 Halachmi S, DiCastro N, Matter I, Cohen A, Sabo E, Mogilner JG, et al. Laparoscopic cholecystectomy for acute

cholecystitis: how do fever and leucocytosis relate to conversion and complications? European Journal of Surgery 2000;166(2):136-140.

16 Hadad SM, Vaidya JS, Baker L, Koh HC, Heron TP, Thompson AM. Delay from symptom onset increases the conversion rate in laparoscopic cholecystectomy for acute cholecystitis. World J Surg 2007 ;31(6):1300-1303.

17 Lim K, Ibrahim S, Tan N, Lim S, Tay K. Risk factors for conversion to open surgery in patients with acute cholecystitis undergoing interval laparoscopic cholecystectomy. annals-academy of medicine Singapore 2007;36(8):631.

18 Lo C, Fan S, Liu C, Lai EC, Wong J. Early decision for conversion of laparoscopic to open cholecystectomy for treatment of acute cholecystitis. The American journal of surgery 1997;173(6):513-517.

19 Winbladh A, Gullstrand P, Svanvik J, Sandström P. Systematic review of cholecystostomy as a treatment option in acute cholecystitis. HPB 2009;11(3):183-193.

20 Jang WS, Lim JU, Joo KR, Cha JM, Shin HP, Joo SH. Outcome of conservative percutaneous cholecystostomy in high-risk patients with acute cholecystitis and risk factors leading to surgery. Surg Endosc 2015;29(8):2359-2364.

21 Sanjay P, Mittapalli D, Marioud A, White RD, Ram R, Alijani A. Clinical outcomes of a percutaneous cholecystostomy for acute cholecystitis: a multicentre analysis. HPB 2013;15(7):511-516.

PART I

Treatment strategies for acute cholecystitis

CHAPTER 2

Randomized clinical trial of extended versus single-dose perioperative antibiotic prophylaxis for acute calculous cholecystitis

British Journal of Surgery, 2017

C. S. Loozen
K. Kortram
V. N. N. Kornmann
B. van Ramshorst
B. Vlaminckx
C. A. J. Knibbe
J. C. Kelder
S. C. Donkervoort
G. A. P. Nieuwenhuijzen
J. E. H. Ponten
N. A. W. van Geloven
P. van Duijvendijk
W. J. W. Bos
M. G. H. Besselink
D. J. Gouma
H. C. van Santvoort
D. Boerma

ABSTRACT

Introduction

Many patients who have surgery for acute cholecystitis receive postoperative antibiotic prophylaxis, with the intent to reduce infectious complications. There is, however, no evidence that extending antibiotics beyond a single perioperative dose is advantageous. This study aimed to determine the effect of extended antibiotic prophylaxis on infectious complications in patients with mild acute cholecystitis undergoing cholecystectomy.

Methods

For this randomized controlled non-inferiority trial, adult patients with mild acute calculous cholecystitis undergoing cholecystectomy at six major teaching hospitals in the Netherlands, between April 2012 and September 2014, were assessed for eligibility. Patients were randomized to either a single preoperative dose of cefazoline (2000 mg), or antibiotic prophylaxis for 3 days after surgery (intravenous cefuroxime 750 mg + metronidazole 500 mg, three times daily), in addition to the single dose. The primary endpoint was rate of infectious complications within 30 days after operation.

Results

In the intention-to-treat analysis, three of 77 patients (4%) in the extended antibiotic group and three of 73 (4%) in the standard prophylaxis group developed postoperative infectious complications (absolute difference 0.2%, 95% c.i.– 8.2 to 8.9). Based on a margin of 5%, non-inferiority of standard prophylaxis compared with extended prophylaxis was not proven. Median length of hospital stay was 3 days in the extended antibiotic group and 1 day in the standard prophylaxis group.

Conclusion

Standard single-dose antibiotic prophylaxis did not lead to an increase in postoperative infectious complications in patients with mild acute cholecystitis undergoing cholecystectomy. Although non-inferiority of standard prophylaxis compared with extended prophylaxis cannot be proven, extended antibiotic prophylaxis seems clinically irrelevant considering the low infection rate. Registration number: NTR3089.

INTRODUCTION

Acute calculous cholecystitis is a frequent cause of emergency admission to surgical wards. Approximately 120 000 cholecystectomies are performed for acute cholecystitis in North America each year.[1] Emergency cholecystectomy is considered a low-risk procedure, although the complication rate ranges from 15% for early cholecystectomy to 30% for delayed cholecystectomy.[2] The most common complication is a surgical-site infection which occurs in approximately 10% of patients who have surgery for mild to moderate cholecystitis.[3]

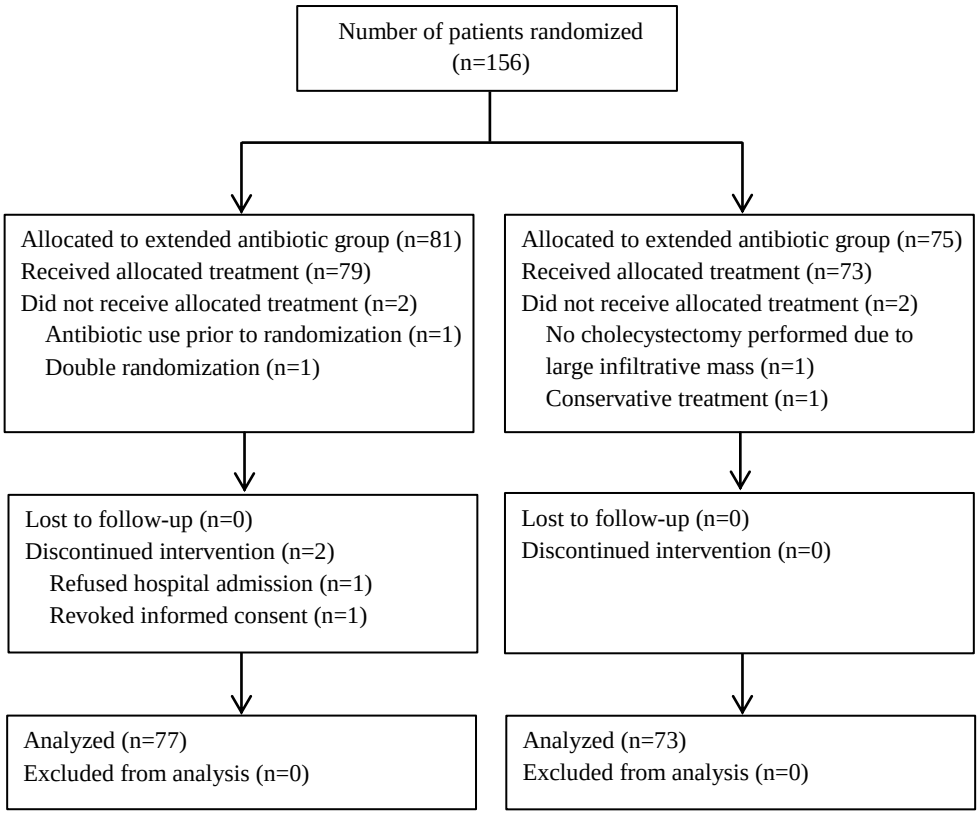
In current practice, many patients with acute cholecystitis receive perioperative antibiotic prophylaxis, often continued for several postoperative days to reduce infectious complications. Guidelines recommend antimicrobial therapy in different doses and durations, varying from 24 h to 7 days, depending on the severity of cholecystitis.[4-6] These guidelines are, however, based on low-quality evidence.[5] There is a lack of randomized trials demonstrating any beneficial effect of extended postoperative antibiotic treatment after cholecystectomy for acute cholecystitis. Thus the use of perioperative antibiotics is variable among physicians, hospitals and countries. Disadvantages of extended postoperative antibiotic prophylaxis include prolongation of hospital stay with increased medical costs, and potentially increased bacterial resistance.

The aim of the present study was to determine the effect of extended postoperative antibiotic prophylaxis on postoperative infectious complications in patients undergoing emergency cholecystectomy for mild acute calculous cholecystitis. The hypothesis was that the absence of extended antibiotic treatment after cholecystectomy would not lead to an increase in infectious complications.

METHODS

This randomized controlled, open, parallel-group, non-inferiority trial was designed following the CONSORT guidelines (http://www.consort-statement.org/). The study protocol was approved by the institutional review board on 4 April 2012. Secondary approval of the protocol was obtained from all local ethics committees of the participating hospitals. Patients were recruited at six major teaching hospitals in the Netherlands between April 2012 and October 2014. The trial was registered in the Dutch Trial Register (www.trialregister.nl) with identification number NTR3089.

Figure 2.1 CONSORT diagram for the trial



Study participants and eligibility criteria

Adult patients suffering from mild acute calculous cholecystitis, with an Acute Physiology And Chronic Health Evaluation (APACHE) II score of 6 or lower, were considered eligible for the trial.[7] Acute cholecystitis was defined according to the Tokyo guidelines.[8] Specific eligibility criteria are shown in Table 2.1. Written informed consent was obtained from all included patients before randomization.

Randomization

Randomization was performed by the study coordinator or primary investigator using an online generator (ALEA 2.2; Academic Medical Centre, Amsterdam, the Netherlands,

https://nl.tenalea.net/amc/ALEA/). Permuted-block randomization with varying block sizes was used. The sequence of the different blocks was predetermined by an independent programmer and concealed from all investigators. The blocks were generated separately within the different study sites, stratified by hospital. Neither the patients nor the investigators were blinded to treatment allocation. Laparoscopic cholecystectomy had to be performed within 24 hours after randomization.

Procedures and intervention

All patients presenting with suspected acute calculous cholecystitis at the emergency department underwent standard evaluation, including laboratory measurements and abdominal ultrasound imaging. Once included, patients received a single prophylactic dose of antibiotics 15–30 min before surgery (cefazoline 2000mg intravenously).

Laparoscopic cholecystectomy was performed by the four-trocar technique, with transection of the cystic duct and artery after reaching the critical view of safety as described by Strasberg.[1] Patients randomized to the extended antibiotic group were admitted for 3 days after surgery to receive intravenous cefuroxime 750 mg and metronidazole 500 mg three times daily. Patients randomized to the standard prophylaxis group received no antibiotic treatment after surgery, and were discharged home according to clinical condition.

Data collection

Baseline characteristics (sex, age, BMI, co-morbidity, APACHE II score, laboratory findings, duration of symptoms) were documented on admission. Operative details (duration of surgery, difficulty, intraoperative events) and clinical data (vital signs, laboratory data, complications) were collected by local physicians using case report forms. The study coordinator verified all forms in accordance with on-site source data. Discrepancies were resolved through consensus by two investigators not involved in patient care. Follow-up took place at the outpatient clinic 1 month after discharge.

Outcomes

The primary endpoint of the trial was a composite of all infectious complications within 30 days after cholecystectomy. Definitions are provided in Table 2.2. The secondary

Table 2.1 Inclusion and exclusion criteria for randomized trial of extended or single-dose antibiotic prophylaxis for acute cholecystectomy

Inclusion criteria	Exclusion criteria
Acute calculous cholecystitis, defined according to Tokyo guidelines[8] *:	Aged 18 < years
A. Local signs of inflammation:	Antibiotics before diagnosis of cholecystitis
Murphy's sign	Known allergy to cefuroxime/ metronidazole
RUQ mass/pain/tenderness	Pregnancy
B. Systemic signs of inflammation:	Indication for ERCP on admission
Fever	Abnormal liver test results with suspicion of acute cholangitis †
Raised CRP level	
Raised WBC count	
C. Imaging findings of acute cholecystitis	
Laparoscopic cholecystectomy	
APACHE II score between 1 and 6	
Written informed consent	

* A definite diagnosis was based on the presence of one item from A and one from B. † Alkaline phosphatase, γ-glutamyl transferase, aspartate aminotransferase and alanine aminotransferase.

RUQ denotes right upper quadrant, CRP C-reactive protein, WBC white blood cell, APACHE Acute Physiology And Chronic Health Evaluation and ERCP endoscopic retrograde cholangio-pancreatography.

endpoints included all individual components of the primary endpoint, all other complications and total duration of hospital stay. Complications were assessed according to Clavien–Dindo classification grades.[9]

A data safety monitoring committee of three independent clinicians assessed all serious adverse events after inclusion after every 30 patients in an unblinded fashion.

Statistical analysis

Owing to a lack of published data, the sample size calculation was derived from data from a retrospective cohort of 279 patients who underwent laparoscopic cholecystectomy for acute cholecystitis in St Antonius Hospital between 2002 and 2010 (unpublished data). An overall infectious complication rate of 12% was found, which was used as the reference. Patients who had prolonged antibiotic treatment had a complication rate of

Table 2.2 Definitions of infectious complications

Complication	Definition
Wound infection	Erythema of incision(s), pus and/or turbid fluid
Intra-abdominal abscess	Fever and/or raised CRP level/WBC count and intra-abdominal fluid collection on CT or ultrasound imaging
Pneumonia	Coughing or dyspnoea, radiography with infiltrative abnormalities, 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 a positive urine culture

CRP denotes C-reactive protein and WBC white blood cell.

17% versus 7% in patients not receiving prolonged antibiotic treatment. Although higher infectious complication rates were encountered in patients who had extended antibiotic treatment, this finding seemed to be (partly) due to selection bias. The difference between the lowest encountered rate (7%) and the overall infectious complication rate (12%) was 5%, which was defined as the acceptable difference (non-inferiority margin). The hypothesis of this study was that a single dose of antibiotic prophylaxis (standard prophylaxis) would not be inferior to extended prophylaxis for development of infectious complications within 4 weeks after cholecystectomy. To demonstrate non-inferiority, a total of 156 patients (78 in each group) had to be randomized, for which infection rates of 7% in the single-dose group and 14% in the extended group were assumed, with 80% power and a one-sided 5% α level.

Patients were analysed according to the intention-to-treat approach. Dichotomous data and counts are presented as frequencies. Continuous data are presented as median (range). The χ^2 test or Fisher's exact test was used for analysis of nominal data, and the Mann–Whitney U test for continuous data. Non-inferiority was determined by computing the 95% confidence interval (c.i.) for the difference in incidence of the primary endpoint. Two-tailed $P < 0.050$ was considered statistically significant. Statistical analysis was done using SPSS® version 21 (IBM, Armonk, New York, USA).

RESULTS

Between April 2012 and October 2014, a total of 156 patients were randomized, 81 in the extended antibiotic group and 75 in the standard prophylaxis group (Figure 2.1). Because treatment of acute cholecystitis was often performed in an acute setting outside regular working hours, data on patients who were eligible, but not recruited, were incomplete. In the initiating hospital, however, this information was well documented: 223 patients were assessed for eligibility during the study interval, 134 of whom were eligible for inclusion. Eighty patients (59.7%) were included in the trial whereas 54 (40.3%) were not asked or declined participation. The characteristics of the latter patients were similar to those of included patients (data not shown).

Six patients were excluded after randomization: one patient revoked informed consent, one refused hospital admission, one used antibiotics before randomization, two did not undergo a cholecystectomy and one patient was double randomized. A total of 150 patients remained for data analysis: 77 in the extended antibiotic group and 73 in the standard prophylaxis group.

Adherence to study protocol

Laparoscopic cholecystectomy was performed within 24 h after randomization in all patients. In the extended antibiotic group, the study protocol was adhered to accurately in 66 of 77 patients (86%); four patients did not receive extended postoperative antibiotic prophylaxis, three received antibiotics for 1 day, and four patients received antibiotics for 2 days. In the standard prophylaxis group, the protocol was adhered to accurately in 71 of 73 patients (97%); in two patients the surgeon felt that extended antibiotic treatment was indicated because a necrotic gallbladder was encountered during surgery.

Baseline characteristics

There were no differences in baseline characteristics between the two groups (Table 2.3). Four (2.7%) of the 150 laparoscopic procedures were converted to open cholecystectomy: one (1%) in the extended antibiotic group because of adhesions and three (4%) in the standard prophylaxis group owing to lack of exposure. Gallbladder empyema was encountered in 17 patients (11.3%): ten (13%) in the extended antibiotic group and seven (10%) in the standard prophylaxis group. No change in treatment strategy was made in

these patients. Bile spillage occurred in 38 patients (49%) in the extended antibiotic group and 39 (53%) in the standard prophylaxis group, and stone loss occurred in 15 (19%) and eight (11%) respectively.

Although obtaining bile during cholecystectomy for bacterial cultures was part of the treatment protocol, bile swabs were obtained in only 51 patients; 20 cultures (39%) were positive: 15 of 32 in the extended antibiotic group and five of 19 in the standard prophylaxis group (P = 0.146). *Escherichia coli* was isolated most frequently, followed by *Klebsiella pneunomoniae*. None of the observed differences reached statistical significance.

Primary outcome

In the intention-to-treat analysis, three of 77 patients (3.9%) in the extended antibiotic group and three of 73 (4%) in the standard prophylaxis group developed postoperative infectious complications (absolute difference 0.2%, 95% c.i. – 8.2 to 8.9) (Table 2.4). Based on this result, non-inferiority of single-dose postoperative antibiotic prophylaxis compared with extended prophylaxis for development of infectious complications cannot be proven, because the non-inferiority margin of 5% lies within the confidence interval. In per-protocol analysis, the postoperative infectious complication rate was 4% (3 of 75) in both groups.

Secondary outcomes

The rate of infectious and non-infectious complications combined, was 12 of 77 (16%) in the extended antibiotic group and 8 of 73 (11%) in the standard prophylaxis group (P = 0.405) (Table 2.4). All but two complications were Clavien–Dindo grade II or lower, and resolved either spontaneously or with non-invasive therapy. The remaining two complications were graded Clavien–Dindo IIIB, and included cystic duct leakage requiring endoscopic retrograde cholangiopancreatography (ERCP) on the fourth postoperative day, and choledocholithiasis requiring ERCP and readmission.

Empyema was present in ten patients (13%) in the extended antibiotic group, none of whom developed an infectious complication, and seven (10%) in the standard prophylaxis group, of whom one developed a urinary tract infection.

The median duration of hospital stay was 3 (range 1–4) days in the extended antibiotic

Table 2.3 Baseline characteristics and operative details

Variables	Extended antibiotic (n = 77)	Standard prophylaxis (n = 73)
Age (years) *	52 (23–89)	54 (24–82)
Sex ratio (M : F)	32 : 45	38 : 35
APACHE II score on admission *	3 (1–6)	4 (1–6)
Temperature on admission (°C) *	37.2 (35.9–39.6)	37.2 (36–39)
CRP on admission (mg/l) *	44 (1–424)	68 (1–345)
WBC count on admission (µl) *	12.8 (4.6–19.9)	12.9 (1.5–26.4)
Duration of symptoms (days) *	2 (1–7)	3 (1–7)
Duration of operation (min) *	70 (25–160)	60 (25–153)
Difficulty of cholecystectomy * †	7 (2–10)	7 (1–10)

* Values are median (range). † Scored on a visual analogue scale from 1 to 10.

APACHE denotes Acute Physiology And Chronic Health Evaluation, CRP C-reactive protein and WBC white blood cell.

group and 1 (1–5) days in the standard prophylaxis group (P < 0.001) (Table 2.4). There were no deaths in either of the groups.

DISCUSSION

The absence of extended antibiotic treatment did not lead to an increase in postoperative infectious complications in patients with mild acute cholecystitis undergoing cholecystectomy. The infectious complication rate was 4% in both groups. Although non-inferiority of standard single-dose prophylaxis compared with extended prophylaxis cannot be proven, extended antibiotic prophylaxis seems clinically irrelevant considering the low overall infection rate.

According to the Tokyo guidelines [5] and the guidelines published by the Surgical Infection Society and the Infectious Diseases Society of America,[6] the selection and duration of antibiotic prophylaxis should be guided by the severity of cholecystitis and whether or not the source of infection is well controlled. In mild cases, postoperative treatment with cephalosporins is recommended, which can be discontinued within 24

Table 2.4 Primary and secondary outcome measures

	Extended antibiotic (n = 77)	**Standard prophylaxis (n = 73)**	**P-value**
Primary outcome			
Infectious complications (total)	3 (4)	3 (4)	
Wound infection	2	1	
Urinary tract infection	1	2	
Secondary outcomes			
Complications (total †)	12 (16)	8 (11)	0.405 ‡
Diarrhoea	2	1	
Fever	0	2	
Nausea	2	0	
Heart failure	1	0	
Chest pain	1	0	
Bile leakage	1	0	
Biliary pancreatitis	0	1	
Choledocholithiasis	1	0	
Rectal bleeding	0	1	
Pain	1	0	
Duration of hospital stay (days) *	3 (1-4)	1 (1-5)	<0.001 §

Values in parentheses are percentages unless indicated otherwise; * values are median (range). † Overall complications (including infectious complications). ‡ χ^2 test; § Mann–Whitney U test.

hours after surgery.[5-6] Antibiotic treatment for 4–7 days is recommended if perforation, surgical emphysema or gallbladder necrosis is encountered during surgery, or in patients with moderate or severe acute cholecystitis. These guidelines, however, are based on low-quality evidence (which might contribute to the low adherence to these guidelines). Among clinicians, there is no consensus regarding the duration of perioperative antibiotics, and as a result the use of antibiotics is mainly dependent on the patient's clinical condition, perioperative findings and, most of all, the surgeon's preference.

The effectiveness of prophylactic antibiotics in elective cholecystectomy has been studied in several randomized trials,[10-14] clearly demonstrating no reduction in the risk of

surgical-site infections in low-risk patients. According to recent studies,[3,15] the use of antibiotic prophylaxis is disputable even in urgent cholecystectomy. Regimbeau and colleagues [3] conducted a large randomized trial demonstrating no beneficial effect of postoperative treatment with amoxicillin plus clavulanic acid on the infectious complication rate in patients with mild and moderate acute cholecystitis undergoing emergency cholecystectomy. Also in 2014, Jafaar and co-workers [15] found no significant benefit of antibiotic prophylaxis on postoperative infectious complications in patients undergoing acute cholecystectomy, in a large retrospective nationwide study in Sweden. The present study corroborates these findings in low-risk patients with acute calculous cholecystitis.

Similarly, the use of antibiotics is disputable even in the conservative management of acute cholecystitis. A recent systematic review [16] demonstrated that there is little evidence on this subject, and the available evidence is of poor quality and has a high risk of bias. The review identified only one small study [17] that compared antibiotic treatment with a conservative strategy without antibiotics, showing that antibiotics did not improve the outcome of acute calculous cholecystitis.

The rationale for perioperative antibiotics is based on the results of either bile or gallbladder cultures from patients with acute cholecystitis. Positive cultures are reported in minority of the patients, ranging from 29 to 54%.[5,18-24] In the present study, intraoperative bile cultures were obtained in 51 patients, of which 39% were positive. *E coli* was most frequently found, followed by *K. pneunomoniae*, which is in accordance with the results in previous studies.[5, 18-25] Cefuroxime is effective against these bacteria. Owing to the small number of bile cultures obtained, correlation between positive bile culture and infectious complications could not be performed. Nevertheless, none of the 20 patients with a positive bile culture developed an infection. Studies comparing postoperative outcome according to the presence or absence of bacteria have shown a significantly higher incidence of infectious and non-infectious postoperative complications in the group with bacteria in the bile.[26-27]

The hypothesis of the present study was that a single dose of antibiotic prophylaxis would not be inferior to extended prophylaxis. The sample size calculations were based on an expected infectious complication rate of 12%, according to findings in a retrospective cohort. The present study included only patients with mild acute cholecystitis and reported a postoperative infectious complication rate of only 4%, much lower than

expected. Consequently, non-inferiority could not be proven. In retrospect, a sample size of almost 600 patients would be needed to demonstrate non-inferiority. Considering the very low infection rate, it is questionable whether such a study is still necessary.

Extended intravenous antibiotic prophylaxis leads to prolongation of hospital stay. As acute cholecystectomy is a frequently performed operation, increasing the duration of hospital stay will have a large impact on healthcare costs. Oral antibiotics might be an alternative in order to shorten hospital stay; however, because intravenous antibiotics did not reduce infectious complications, this will most likely also be the case for oral antibiotics. In addition, bacterial resistance is a serious and growing issue in contemporary medicine. Thus, reducing needless use of antibiotics is of upmost importance.

Acknowledgements

This study was funded by the St Antonius Research Foundation. The sponsor had no role in the study design, execution, data analysis or publication. The first author, statistician and last author had full access to all data. The last author had final responsibility for the decision to submit for publication.

REFERENCES

1 Strasberg SM. Clinical practice. Acute calculous cholecystitis. N Engl J Med 2008 Jun 26;358(26):2804-2811.

2 Cao AM, Eslick GD, Cox MR. Early Cholecystectomy Is Superior to Delayed Cholecystectomy for Acute Cholecystitis: a Meta-analysis. J Gastrointest Surg 2015 May;19(5):848-857.

3 Regimbeau JM, Fuks D, Pautrat K, Mauvais F, Haccart V, Msika S, et al. Effect of postoperative antibiotic administration on postoperative infection following cholecystectomy for acute calculous cholecystitis: a randomized clinical trial. JAMA 2014 Jul;312(2):145-154.

4 NVvH. The Dutch guidelines for gallstone disease. 2007; Available at: http://www.heelkunde.nl/uploads/_6/re/_6reZZkgrYUAuCG6uvcN-A/richtlijn_galsteen.pdf. Accessed 12/22/2015.

5 Gomi H, Solomkin JS, Takada T, Strasberg SM, Pitt HA, Yoshida M, et al. TG13 antimicrobial therapy for acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci 2013 Jan;20(1):60-70.

6 Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, 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 Feb;11(1):79-109.

7 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985 Oct;13(10):818-829.

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

9 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 Aug;240(2):205-213.

10 Yan RC, Shen SQ, Chen ZB, Lin FS, Riley J. The role of prophylactic antibiotics in laparoscopic cholecystectomy in preventing postoperative infection: a meta-analysis. J Laparoendosc Adv Surg Tech A 2011 May;21(4):301-306.

11 Sharma N, Garg PK, Hadke NS, Choudhary D. Role of prophylactic antibiotics in laparoscopic cholecystectomy and risk factors for surgical site infection: a randomized controlled trial. Surg Infect (Larchmt) 2010 Aug;11(4): 367-370.

12 Choudhary A, Bechtold ML, Puli SR, Othman MO, Roy PK. Role of prophylactic antibiotics in laparoscopic cholecystectomy: a meta-analysis. J Gastrointest Surg 2008 Nov;12(11):1847-53; discussion 1853.

13 Chang WT, Lee KT, Chuang SC, Wang SN, Kuo KK, Chen JS, et al. The impact of prophylactic antibiotics on postoperative infection complication in elective laparoscopic cholecystectomy: a prospective randomized study. Am J Surg 2006 Jun;191(6):721-725.

14 Koc M, Zulfikaroglu B, Kece C, Ozalp N. A prospective randomized study of prophylactic antibiotics in elective laparo-

scopic cholecystectomy. Surg Endosc 2003 Nov;17(11):1716-1718.

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

16 van Dijk A, de Reuver P, Tasma T, van Dieren S, Hugh T, Boermeester M. Systematic review of antibiotic treatment for acute calculous cholecystitis. Br J Surg 2016;103(7):797-811.

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

18 Csendes A, Burdiles P, Maluenda F, Diaz JC, Csendes P, Mitru N. Simultaneous bacteriologic assessment of bile from gallbladder and common bile duct in control subjects and patients with gallstones and common duct stones. Arch Surg 1996 Apr;131(4):389-394.

19 Maluenda F, Csendes A, Burdiles P, Diaz J. Bacteriological study of choledochal bile in patients with common bile duct stones, with or without acute suppurative cholangitis. Hepatogastroenterology 1989 Jun;36(3):132-135.

20 Chang WT, Lee KT, Wang SR, Chuang SC, Kuo KK, Chen JS, et al. Bacteriology and antimicrobial susceptibility in biliary tract disease: an audit of 10-years' experience. Kaohsiung J Med Sci 2002 May;18(5):221-228.

21 Csendes A, Mitru N, Maluenda F, Diaz JC, Burdiles P, Csendes P, et al. Counts of bacteria and pyocites of choledochal bile in controls and in patients with gallstones or common bile duct stones with or without acute cholangitis. Hepatogastroenterology 1996 Jul-Aug;43(10):800-806.

22 Csendes A, Becerra M, Burdiles P, Demian I, Bancalari K, Csendes P. Bacteriological studies of bile from the gallbladder in patients with carcinoma of the gallbladder, cholelithiasis, common bile duct stones and no gallstones disease. Eur J Surg 1994 Jun-Jul;160(6-7):363-367.

23 Csendes A, Fernandez M, Uribe P. Bacteriology of the gallbladder bile in normal subjects. Am J Surg 1975 Jun; 129(6):629-631.

24 Kune GA, Schutz E. Bacteria in the billary tract. A study of their frequency and type. Med J Aust 1974 Feb 23;1(8):255-258.

25 Lee CC, Chang IJ, Lai YC, Chen SY, Chen SC. Epidemiology and prognostic determinants of patients with bacteremic cholecystitis or cholangitis. Am J Gastroenterol 2007 Mar;102(3):563-569.

26 Galili O, Eldar S,Jr, Matter I, Madi H, Brodsky A, Galis I, et al. The effect of bactibilia on the course and outcome of laparoscopic cholecystectomy. Eur J Clin Microbiol Infect Dis 2008 Sep;27(9):797-803.

27 Asai K, Watanabe M, Kusachi S, Tanaka H, Matsukiyo H, Osawa A, et al. Bacteriological analysis of bile in acute cholecystitis according to the Tokyo guidelines. J Hepatobiliary Pancreat Sci 2012 Jul;19(4):476-486.

CHAPTER 3

The use of perioperative antibiotic prophylaxis in the treatment of acute cholecystitis (PEANUTS II trial): study protocol for a randomized controlled trial

Accepted for publication in Trials (minor revisions)

C. S. Loozen
H. C. van Santvoort
N. A. W. van Geloven
G. A. P. Nieuwenhuijzen
P. R. de Reuver
M. G. H. Besselink
B. Vlaminckx
J. C. Kelder
C. A. J. Knibbe
D. Boerma

ABSTRACT

Background

The additional value of perioperative antibiotic prophylaxis in preventing infectious complications after emergency cholecystectomy for acute cholecystitis is a much debated subject in the surgical community. Evidence based guidelines are lacking and consequently the use of antibiotic prophylaxis varies greatly among surgeons and hospitals. Recently, high level evidence became available demonstrating that *postoperative* antibiotic prophylaxis in patients with acute cholecystitis does not reduce the risk of infectious complications. Preoperative antibiotic prophylaxis in relation to the risk of infectious complications, however, has never been studied.

Methods

The PEANUTS II trial is a randomized controlled, multicenter, open-label, non-inferiority trial aiming to determine the utility of preoperative antibiotic prophylaxis in patients undergoing emergency cholecystectomy for acute calculous cholecystitis. Patients with mild or moderate acute cholecystitis, as defined according the Tokyo Guidelines, will be randomly assigned to a single preoperative dose antibiotic prophylaxis (2000 milligrams of first generation cephalosporin, IV) or no antibiotic prophylaxis before emergency cholecystectomy. The primary endpoint is a composite endpoint consisting of all postoperative infectious complications occurring during the first 30 days after surgery. Secondary endpoints include all the individual components of the primary endpoint, all other complications, duration of hospital stay and total costs. The hypothesis is that the absence of antibiotic prophylaxis is non-inferior to the presence of antibiotic prophylaxis. A non-inferiority margin of 10% is assumed. With a 1-sided risk of 2.5% and a power of 80%, a total of 454 will have to be included. Analysis will be performed according to the intention-to-treat approach.

Discussion

The PEANUTS II trial will provide evidence based advice concerning the utility of antibiotic prophylaxis in patients undergoing emergency cholecystectomy for acute calculous cholecystitis.

Trial registration

The study protocol (number: NL53084.100.15) has been approved by the Medical Ethical Committee (MEC-U) of the St Antonius Hospital, Nieuwegein, the Netherlands, on November 24th 2015. The study protocol was retrospectively registered (after enrollment of the first participant) at www.trialregister.nl (NTR registration number: 5802) on June 4th 2016.

BACKGROUND

Acute calculous cholecystitis is a frequently encountered disease in surgical practice which generally mandates emergency cholecystectomy. Although this is considered to be a low-risk procedure, the complication rate is not negligible. The most common complication is a postoperative infection, either at the surgical or the distant site, occurring in approximately 17% of patients.[1] As such, many patients receive antibiotic prophylaxis before cholecystectomy, often to be continued for several postoperative days, in order to reduce postoperative infectious complications.

The Working Party on Antibiotic Policy in the Netherlands (Stichting Werkgroep Antibioticabeleid) issued guidelines for perioperative antibiotic prophylaxis in Dutch hospitals.[2] According to these guidelines, perioperative antibiotic prophylaxis is recommended for surgical procedures with a moderate or high risk of postoperative infections, including biliary surgery. Prophylaxis given within two hours before incision appears to be most effective.[2] Recommended is single-dose prophylaxis, not only because it has proven to be as effective as multiple-dose prophylaxis, but also for reasons of cost-effectiveness and prevention of bacterial resistance. The Surgical Infection Society and the Infectious Diseases Society of America as well as the Tokyo Guidelines also recommend antimicrobial prophylaxis for patients undergoing cholecystectomy for acute cholecystitis.[3,4] These recommendations, however, are based on low quality evidence and therefore the actual effect of perioperative antibiotic prophylaxis remains unclear. Consequently, the use of antibiotic prophylaxis in the treatment of acute cholecystitis is highly variable among surgeons and hospitals.

In patients undergoing *elective* cholecystectomy for uncomplicated cholelithiasis, high level evidence is available demonstrating that prophylactic antibiotics do not reduce the incidence of postoperative infections.[5-9] For this indication, the use of perioperative antibiotic prophylaxis is discouraged. According to a recent randomized controlled trial, also in *emergency* cholecystectomy the continuation of antibiotic prophylaxis after surgery is disputable.[1] This study demonstrated that postoperative antibiotic prophylaxis (in addition to a single prophylactic dose prior to surgery) in patients with mild and moderate acute cholecystitis did not reduce the risk of infectious complications. Antibiotic prophylaxis after cholecystectomy for acute cholecystitis may therefore be omitted. The remaining question is whether a single preoperative dose of antibiotic prophylaxis is beneficial in patient undergoing emergency cholecystectomy for acute

cholecystitis. This has never been studied.

If this study demonstrates that omitting antibiotic prophylaxis does not increase the postoperative infection rate, the use of antibiotics for this indication can be dropped as a whole. If so, the role of antibiotic prophylaxis in surgery of the entire upper gastrointestinal tract will become questionable. A decrease of antibiotic use, on such a scale, may result in a large reduction of needless medical activities, costs and bacterial resistance. The latter is a growing issue in contemporary medicine and has emerged as one of the eminent public health concerns nowadays.[10]

The PEANUTS II trial is designed to assess whether preoperative antibiotic prophylaxis is indicated in patients undergoing emergency cholecystectomy for acute calculous cholecystitis, to prevent postoperative infectious complications. The hypothesis is that the absence of antibiotic prophylaxis does not lead to an increase in infectious complications.

METHODS

Design

The PEANUTS II trial is a randomized controlled, multicenter, open-label, non-inferiority trial. Patients will be randomly allocated to receive either no antibiotics or a single dose of antibiotic prophylaxis before emergency cholecystectomy (Figure 3.1).

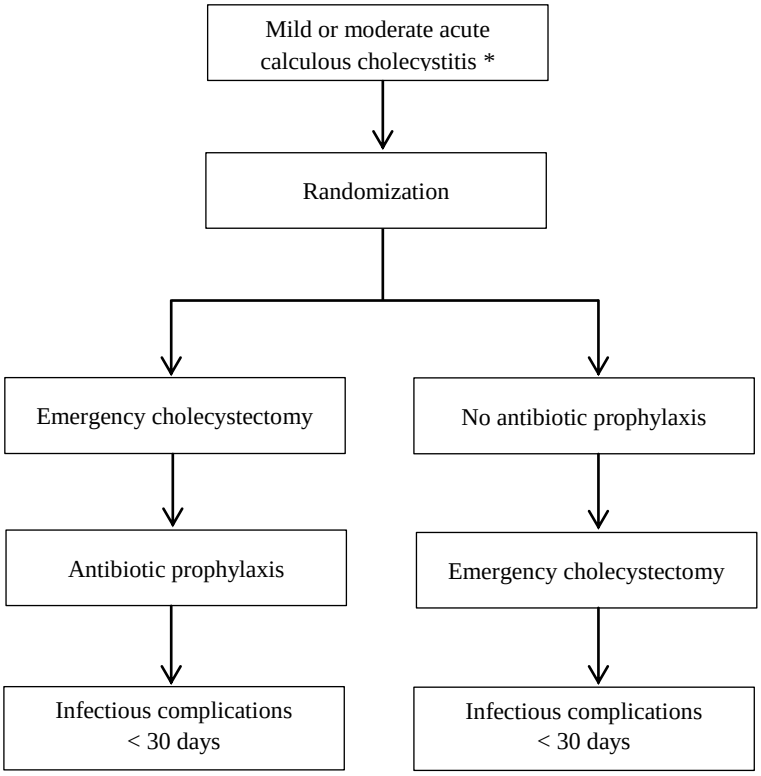
Study population

All patients presenting with acute calculous cholecystitis to one of the participating hospitals will be assessed for eligibility. Patients are eligible if diagnosed with mild or moderate acute calculous cholecystitis as defined according the Tokyo Guidelines[11] (Table 3.1). The in- and exclusion criteria are presented in Table 3.2.

Primary and secondary endpoints

The primary endpoint is a composite endpoint consisting of all postoperative infectious complications occurring during the first 30 days after surgery. Table 3.3 provides an overview of the definitions. Secondary endpoints include all the individual components of the primary endpoint and, in addition, all other complications, the total postoperative duration of hospital stay and the total costs.

Figure 3.1 CONSORT diagram for the trial



* According to the severity assessment criteria of the Tokyo Guidelines[11]

Randomization

Patients will be randomly assigned to the treatment group (antibiotic prophylaxis) or the non-treatment group (no antibiotic prophylaxis) as shown in the flowchart (figure 3.1). Randomization is performed using an online randomization module (ALEA2.2 Academic Medical Centre Amsterdam, the Netherlands https://nl.tenalea.net/amc/ALEA) and stratified according to center. Computer generated permuted block randomization with varying block sizes is used, with a maximum block size of six patients. The sequence of the different blocks is predetermined by an independent programmer and concealed to all investigators.

Table 3.1 Diagnostic criterion for acute cholecystitis according to Tokyo Guidelines[11]

Severity grade	Criteria
Mild	Does not meet the criteria of 'Severe' of 'Moderate' acute cholecystitis. Can also be defined as acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder.
Moderate	Associated with any one of the following conditions: 1. Elevated white blood cell count (>18.000/mm^3). 2. Palpable tender mass in the right upper abdominal quadrant. 3. Duration of complaints > 72 h. 4. Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)
Severe	Associated with dysfunction of any of the following organs/systems: 1. Cardiovascular dysfunction (Hypotension requiring treatment with dopamine > 5µg/kg per min, or any dose of norepinephrine). 2. Neurological dysfunction (Decreased level of consciousness). 3. Respiratory dysfunction (PaO2/FiO2 ratio < 300). 4. Renal dysfunction (Oliguria, creatinine > 2.0mg/dl). 5. Hepatic dysfunction (PT-INR > 1.5). 6. Haematological dysfunction (Platelet count < 100.000/mm^3)

Treatment protocol

Preoperative management

To confirm the diagnosis, all patients presenting with suspected acute calculous cholecystitis will undergo standard laboratory work-up and ultrasound examination of theabdomen, or contrast enhanced CT-scan in case ultrasound is inconclusive. When patients are eligible for inclusion and informed consent is obtained, randomization will take place. Patients in the treatment group will receive 2000 milligrams of first generation cephalosporin, administered intravenously, 15-30 minutes before surgery. Patients in the non-treatment group will not receive any antibiotic prophylaxis. Cholecystectomy should be performed within 24 hours after randomization. Figure 3.1 demonstrates the study outline for included patients.

Surgical management

Cholecystectomy will be performed laparoscopically by the four trocar technique according to the guidelines of the Dutch Society of Surgery, which includes the critical

Table 3.2 In- and exclusion criteria

Inclusion criteria	Exclusion criteria
Acute calculous cholecystitis, defined according to Tokyo guidelines[8] *:	Aged 18 < years
	Acalculous cholecystitis
A. Local signs of inflammation:	Acute calculous cholecystitis, graded as severe according to Tokyo Guidelines[11] †
Murphy's sign	
RUQ mass/pain/tenderness	Antibiotics before diagnosis of cholecystitis
B. Systemic signs of inflammation:	Known allergy to Cefazoline
Fever	Pregnancy
Raised CRP level	Indication for ERCP on admission
Raised WBC count	
C. Imaging findings of acute cholecystitis	
Patient will undergo cholecystectomy	

* A definite diagnosis is based on the presence of one item from A and one from B. † The diagnostic criteria for mild, moderate and severe acute cholecystitis are shown in Table 3.1.

RUQ denotes Right upper quadrant, CRP C-reactive protein, WBC White blood cell, ERCP Endoscopic retrograde pancreaticocholangiography.

view of safety technique.[12] The surgical procedure will be performed by, or under the supervision of, an experienced laparoscopic surgeon.

Postoperative management

Patients will be discharged based on their clinical condition and at the decision of the treating physician. If patients in either group develop infectious complications, antibiotic therapy is started. All events will be recorded.

Data collection & follow-up

Each patient will receive an anonymous study number which will be used for the study-record-forms and the database. On admission, baseline characteristics including age, sex, body mass index, comorbidity, American Society of Anesthesiologists (ASA) score, clinical data (i.e. temperature on admission, white blood cell count (WBC), C-reactive protein (CRP) and duration of symptoms) will be collected and documented by the admitting physician or (local) study coordinator (Figure 3.2). Data regarding the surgical

Table 3.3 Definitions of various infectious complications

Complication	Definition
Superficial incisional	Localised signs such as redness, pain, heat or swelling at the site of the incision or by the drainage of pus
Deep incisional	Presence of pus or an abscess, fever with tenderness of the wound, or a separation of the edges of the incision exposing the deeper tissues
Organ or space infection	Fever and/or elevated CRP/WBC and intra-abdominal fluid collection on CT-imaging or ultrasound
Pneumonia	Coughing or dyspnoea, radiography with infiltrative abnormalities, elevated infection parameters in combination with positive sputum culture
Urinary tract infection	Dysuria, elevated white blood cells and/or presence of nitrate in urine sediment in combination with a positive urine culture
Bacteraemia	Presence of ≥1 positive hemoccult to the same pathogen

CRP denotes C-reactive protein, WBC white blood cell, CT computed tomography.

procedure including conversion, bile culture, empyema, bile spill and the severity of the cholecystitis will be documented by the performing surgeon immediately after the procedure. At the day of discharge, a case record form will be completed with information on the occurrence of infectious complications and, if so, the way the infection was objectified and treated. One week after discharge the patients will be called by phone by the study coordinator and one month after discharge the patient will be seen in the outpatient clinic by a surgeon who will complete a questionnaire on the patient's clinical condition and the development of infectious complications. Every three months, all entered data will be checked for completion by the study coordinator and missing data will be collected from the participating centers.

Safety

A Data Safety Monitoring Board (DSMB) consisting of three independent members have been appointed to assess patient safety. The first meeting will take place after 20 included

patients, and subsequently once per 50 included patients. The DSMB has unblinded access to all data.

Adverse events

An adverse event is defined as an undesirable experience occurring to a subject during the study, whether or not considered related to the intervention. Participating physicians will report all adverse events to the study coordinator immediately on occurrence. The study coordinator will list all adverse events and will present these to the DSMB for every 30 randomized patients. All adverse events will be reported to the Dutch Central Committee on Research involving Human Subjects using the online module [http://www.toetsingonline.nl].

Ethics

The PEANUTS II trial is conducted in accordance with the declaration of Helsinki and the Dutch law regarding research involving human subjects (Wet Medisch Wetenschappelijk Onderzoek met Mensen). The study protocol (number: NL53084.100.15, version 1.0) has been approved by the Medical Ethical Committee (MEC-U) of the St Antonius Hospital, Nieuwegein, the Netherlands, on November 24th 2015. Secondary approval has been obtained from the executive boards of all participating centers. The study protocol was retrospectively registered (after enrollment of the first participant) at www.trialregister.nl (NTR registration number: 5802) on June 4th 2016. Written informed consent will be obtained from each participant before any trial-related procedures are carried out.

The present manuscript is written according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement for reporting a clinical trial protocol.[13] The SPIRIT checklist is provided as an additional file.

Statistical considerations

Sample size calculation

A recently published randomized controlled trial showed a postoperative infectious complication rate of 17% in patients with mild and moderate acute calculous cholecystitis undergoing laparoscopic cholecystectomy.[1] This percentage has been used as the

Figure 3.2 Content for schedule of enrolment, interventions and assessments according to the SPIRIT statement[13]

	Study period				
	Enrolment	**Allocation**	**Postoperative follow-up**		**Close-out**
Timepoint	Preoperative	0	1wk	1mo	1mo
Enrolment					
Eligibility screen	x				
Informed consent	x				
Allocation		x			
Interventions					
Antibiotic prophylaxis		x			
No antibiotic prophylaxis		x			
Assessments					
Age	x				
Sex	x				
BMI	x				
Comorbidity	x				
ASA score	x				
Clinical data	x				
Surgical data		x			
Infectious complications			x	x	x
Other complications			x	x	x
Duration of hospital stay			x	x	x
Total medical costs				x	x

ASA denotes American Society of Anesthesiologists and BMI Body Mass Index.

reference number for the sample size calculations of the PEANUTS II trial. A non-inferiority margin of 10% is assumed. This figure is based on recommendations from the US Food and Drug Administration who recommend 10% for anti-infective trials. With a 1-sided risk of 2.5% and a power of 80%, a total of 454 will have to be included in the trial.

Descriptive statistics

Dichotomous data and counts will be presented in frequencies. Continuous data will be presented in means with standard deviation, or, in case of skewed distribution, in median value with interquartile range.

Analyses

After the last patient has completed follow-up, raw data will be presented to an adjudication committee to determine whether the endpoints meet the protocol-specified criteria. Each member of the adjudication committee is blinded to the treatment allocation and will assess the potential endpoints individually. Disagreement will be resolved in a plenary consensus meeting. After reaching consensus on each individual endpoint for each patient, final analysis will be performed by an unblinded independent statistician. This analysis will be performed according to the intention-to-treat approach which means that all randomized patients are included in their initially assigned study arm, regardless of adherence to the protocol.

For nominal data the Chi-Square test or the Fisher's exact test will be used; for continuous data the independent sample t-test or Mann-Whitney test. Non-inferiority will be demonstrated if the upper limit of the 2-sided 95% confidence interval of the difference of the proportion of the primary endpoint between the two groups is lower than the non-inferiority margin. The effect will be measured by the absolute risk difference and the precision will be quantified by means of the 95% confidence interval. The formal statistical hypothesis regarding non-inferiority will be tested by the Westlake-Schuirmann test, with the non-inferiority margin set at 10% and an one tailed p-value < 0.025 considered statistically significant. For all other tests, a two-tailed p-value < 0.050 is considered statistically significant. In general, for the primary endpoint, we do not expect data to be missing, and if so, missing data will not be imputed.

Premature termination of the study

The DSMB will perform a formal interim-analysis for superiority with respect to the primary endpoint when 50% (n=227) of the total number of patients have been randomised and have completed the 1 months follow-up. The Peto approach will be followed, which includes that the study will only be stopped for benefit or harm in case

of a p-value <0.001.[14] Knowing that this is the first randomized trial on this subject and realizing that future treatment policy will be based on it, this trial will not be stopped for futility.

Feasibility

Recruitment commenced in March 2016 and is anticipated to run until March 2019. At present, patients are being recruited at six major teaching hospitals in the Netherlands. Every six month the inclusion rate will be assessed. If accrual is too slow, additional centers will be invited to participate.

DISCUSSION

Whether or not antibiotic prophylaxis has any additional value in preventing infectious complications after emergency cholecystectomy is a much debated subject in the surgical community. Evidence based guidelines are lacking and, as a result, the use of antibiotic prophylaxis varies greatly among surgeons and hospitals. Recently, high level evidence became available demonstrating that *postoperative* antibiotic prophylaxis (in addition to a single preoperative dose) does not reduce the risk of infectious complications.[1] *Preoperative* antibiotic prophylaxis in relation to the risk of infectious complications, however, has never been studied. We therefore designed the PEANUTS II trial, aiming to determine the utility of preoperative antibiotic prophylaxis in patients undergoing emergency cholecystectomy for acute calculous cholecystitis.

The PEANUTS II trial has a non-inferiority design. The hypothesis is that the absence of antibiotic prophylaxis will not lead to an increase of postoperative infectious complications. In the non-treatment group, either an increase of the infectious complication rate or no effect will be seen. Because it is very improbable that the absence of antibiotic prophylaxis will lead to a decrease of infectious complications, and thus deviation is possible in only one direction, a non-inferiority design is best suited to answer to this primary question.

The best design for a therapeutic trial is a placebo-controlled, double-blind trial but since treatment of acute cholecystitis is often performed in an acute setting outside regular working hours, such a design is difficult to organize. Therefore, an open comparative design was chosen. We believe that blinding and placebo are not of absolute importance

because the primary outcome of the study is an objective criterion with a clearly defined (internationally accepted) definition. In addition, all potential endpoints will individually be assessed by the members of the adjudication committee who are blinded to the treatment allocation. Only after reaching consensus on each individual endpoint for each patient, final analysis will be performed by an unblinded independent statistician.

Patients with grade III (severe acute cholecystitis) are septic and require antibiotic treatment in addition to appropriate organ support.[11,15] This is the rationale for exclusively including patients with grade I (mild) and grade II (moderate) acute cholecystitis.

If this study demonstrates that omitting antibiotic prophylaxis does not increase the postoperative infection rate in patients with acute cholecystitis, the role of antibiotic prophylaxis in surgery of the entire upper gastrointestinal tract will become questionable. A decrease in the use of antibiotics may result in a large reduction of bacterial resistance, the latter being an increasingly serious threat to global public health.[10]

Trial status

Recruitment commenced in March 2016 and is anticipated to run until March 2019. At the time of writing (January 20th 2017), 80 patients had been randomised and six hospitals were participating in the trial. The study results will be communicated via publication.

List of abbreviations

AE Adverse Event
ASA American Society of Anesthesiologists
CRP C-Reactive Protein
CT Computed Tomography
DSMB Data Safety Monitoring Board
ERCP Endoscopic Retrograde Pancreaticocholangiography
RUQ Right Upper Quadrant
WBC White Blood Cell

Declarations

Acknowledgements

The DSMB is composed of three members: B.M. de Jong, E. Tromp and D.J. Gouma. The DSMB reviews the progress and safety of study procedures and is independent of the sponsor.

Ethics approval and consent to participate

The study protocol (number: NL53084.100.15, version 1.0) has been approved by the Medical Ethical Committee (MEC-U) of the St Antonius Hospital Nieuwegein, The Netherlands, on November 24th 2015 (ethical approval reference number: V.50514/R15.051/mp/cl). Secondary approval has been obtained from the executive boards of all participating centers. Prior to randomization written informed consent will be obtained from each participant.

Consent for publication

Not applicable

Availability of data and material

Not applicable

Competing interests

The authors declare that they have no competing interests.

Funding

The study is funded by the St. Antonius Research Foundation (St. Antonius Onderzoeksfonds). The funding agency was not involved in development of the study design or preparation of this manuscript, nor will they be involved with subsequent data collection and analysis. The funding agency has no ultimate authority over any of these activities.

REFERENCES

1 Regimbeau JM, Fuks D, Pautrat K, Mauvais F, Haccart V, Msika S, et al. Effect of postoperative antibiotic administration on postoperative infection following cholecystectomy for acute calculous cholecystitis: a randomized clinical trial. JAMA 2014;312(2):145-154.

2 Van Kasteren M, Gyssens I, Kullberg B, Bruining H, Stobberingh E, Goris R. Optimaliseren van het antibioticabeleid in Nederland. V. SWAB-richtlijnen voor perioperatieve antibiotische profylaxe. Ned Tijdschr Geneeskd 2000;144(43) :2049-2055.

3 Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, 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. Surgical infections 2010;11(1):79-109.

4 Gomi H, Solomkin JS, Takada T, Strasberg SM, Pitt HA, Yoshida M, et al. TG13 antimicrobial therapy for acute cholangitis and cholecystitis. Journal of hepato-biliary-pancreatic sciences 2013;20 (1):60-70.

5 Yan R, Shen S, Chen Z, Lin F, Riley J. The role of prophylactic antibiotics in laparoscopic cholecystectomy in preventing postoperative infection: a meta-analysis. Journal of Laparoendoscopic & Advanced Surgical Techniques 2011;21(4) :301-306.

6 Sharma N, Garg PK, Hadke NS, Choudhary D. Role of prophylactic antibiotics in laparoscopic cholecystectomy and risk factors for surgical site infection: a randomized controlled trial. Surgical infections 2010;11(4):367-370.

7 Choudhary A, Bechtold ML, Puli SR, Othman MO, Roy PK. Role of prophylactic antibiotics in laparoscopic cholecystectomy: a meta-analysis. Journal of Gastrointestinal Surgery 2008;12(11): 1847-1853.

8 Chang W, Lee K, Chuang S, Wang S, Kuo K, Chen J, et al. The impact of prophylactic antibiotics on postoperative infection complication in elective laparoscopic cholecystectomy: a prospective randomized study. The American journal of surgery 2006;191(6): 721-725.

9 Koc M, Zulfikaroglu B, Kece C, Ozalp N. A prospective randomized study of prophylactic antibiotics in elective laparoscopic cholecystectomy. Surgical Endoscopy and Other Interventional Techniques 2003;17(11):1716-1718.

10 World Health Organization. Antimicrobial resistence. 2016; Available at: http://www.who.int/mediacentre/factsheets /fs194/en/.

11 Hirota M, Takada T, Kawarada Y, Nimura Y, Miura F, Hirata K, et al. Diagnostic criteria and severity assessment of acute cholecystitis: Tokyo Guidelines. J Hepato-biliary Pancreat 2007;14(1):78-82.

12 NVvH. The Dutch guidelines for the treatment of gallstone disease. 2016; Available at: http://heelkunde.nl/nieuws/-richtlijn-galsteenlijden-geautoriseerd.

13 Chan A, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining

standard protocol items for clinical trials. Ann Intern Med 2013;158(3):200-207.

14 Ellenberg SS, Fleming TR, DeMets DL. Data monitoring committees in clinical trials: a practical perspective. : John Wiley & Sons; 2003.

15 Miura F, Takada T, Strasberg SM, Solomkin JS, Pitt HA, Gouma DJ, et al. TG13 flowchart for the management of acute cholangitis and cholecystitis. Journal of hepato-biliary-pancreatic sciences 2013; 20(1):47-54.

CHAPTER 4

Conservative treatment of acute cholecystitis: a systematic review and pooled analysis

Surgical endoscopy, 2017

C. S. Loozen
J. E. Oor
B. van Ramshorst
H. C. van Santvoort
D. Boerma

ABSTRACT

Background

In medical practice, the tendency to remove an inflamed gallbladder is deeply rooted. Cholecystectomy, however, is associated with relatively high complication rates and therefore the decision whether or not to perform surgery should be well-considered. For some patients the surgical risk-benefit profile may favour conservative treatment. The objective of this study was to examine the short and long-term outcome of conservative treatment of patients with acute calculous cholecystitis.

Methods

A systematic search of MEDLINE, Embase and Cochrane Library databases was performed. Prospective studies reporting on the success rate of conservative treatment (i.e. non-invasive treatment) of acute cholecystitis during index admission were included, as well as prospective and retrospective studies reporting on the recurrence rate of gallstone-related disease during long term follow-up (i.e. ≥12 months) after initial non-surgical management. Study selection was undertaken independently by two reviewers using pre-defined criteria. The risk of bias was assessed. The pooled success and mortality rate during index admission and the pooled recurrence rate of gallstone-related disease during long-term follow-up were calculated using a random-effects model.

Results

A total of 1841 patients were included in 10 randomized controlled trials and 14 non-randomized studies. Conservative treatment during index admission was successful in 87% of patients with acute calculous cholecystitis, and in 96% of patients with mild disease. In the long term 22% of the patients developed recurrent gallstone-related disease. Pooled analysis showed a success rate of 86% (95% C.I. 0.8-0.9), a mortality rate of 0.5% (95% C.I. 0.001-0.009) and a recurrence rate of 20% (95% C.I. 0.1-0.3).

Discussion

Conservative treatment of acute calculous cholecystitis during index admission seems feasible and safe, especially in patients with mild disease. During long-term follow-up, less than a quarter of the patients appear to develop recurrent gallstone-related disease, although this outcome is based on limited data.

INTRODUCTION

In Western countries, acute calculous cholecystitis is a common disease with a high socioeconomic impact. Cholecystectomy is considered the treatment of choice in patients deemed fit for surgery.[1-4] In surgical practice, cholecystectomy is one of the most frequently performed procedures, mostly performed by laparoscopy nowadays. The rationale for cholecystectomy is based on the old adage that an inflammatory focus should be eliminated immediately from the body to prevent clinical deterioration.

Even though cholecystectomy is the treatment of choice, the benefit of surgery in case of acute calculous cholecystitis has never been properly researched. Prospective, let alone randomized studies demonstrating superiority of surgical over conservative treatment are lacking. Performing cholecystectomy in case of acute cholecystitis prevents further episodes of gallstone-related disease, but the relatively high complication rate associated with both early and delayed cholecystectomy (i.e.15% and 30%, respectively)[5], especially in high risk patients, should not go unnoticed. The decision to perform surgery should therefore be well-considered. Conservative treatment prevents the surgical risk, however, leaving the gallbladder in situ may cause recurrent gallstone-related disease.

To assess whether it is safe (or even safer) to leave the gallbladder in situ in patients with acute calculous cholecystitis, the feasibility and safety of conservative treatment during index admission should be assessed. Subsequently, the recurrence rate of gallstone-related disease during long-term follow-up should be evaluated. It has been demonstrated that delayed cholecystectomy is associated with significant higher complication rates than early cholecystectomy,[5] and therefore conservative treatment is only feasible if a delayed cholecystectomy is not required.

The aim of this study was to assess the available evidence concerning the feasibility of conservative treatment of acute calculous cholecystitis. The question for this review is thus twofold: 1. Is conservative treatment for acute calculous cholecystitis effective and safe during index admission? 2. What is the recurrence rate of gallstone-related disease during long term follow-up?

METHODS

A systematic review was conducted following the guidance of the Centre for Reviews and

Dissemination concerning undertaking reviews in health care and reported in accordance with the PRISMA statement.[6-7]

Literature search

In May 2015, two authors (CL and JO) independently performed a literature search to identify studies reporting on conservative treatment for adults suffering from acute calculous cholecystitis. MEDLINE, Embase and Cochrane Library databases were searched for papers using the keywords: "acute cholecystitis" in combination with "conservative" or "antibiotic" or "anti-bacterial" or "non-invasive" or "non-surgical" or "non-operative" or "observation" or "drain" or "cholecystostomy" or "delayed/interval/planned/elective/late cholecystectomy". The search was limited to articles published in English and Dutch and published after January 1990.

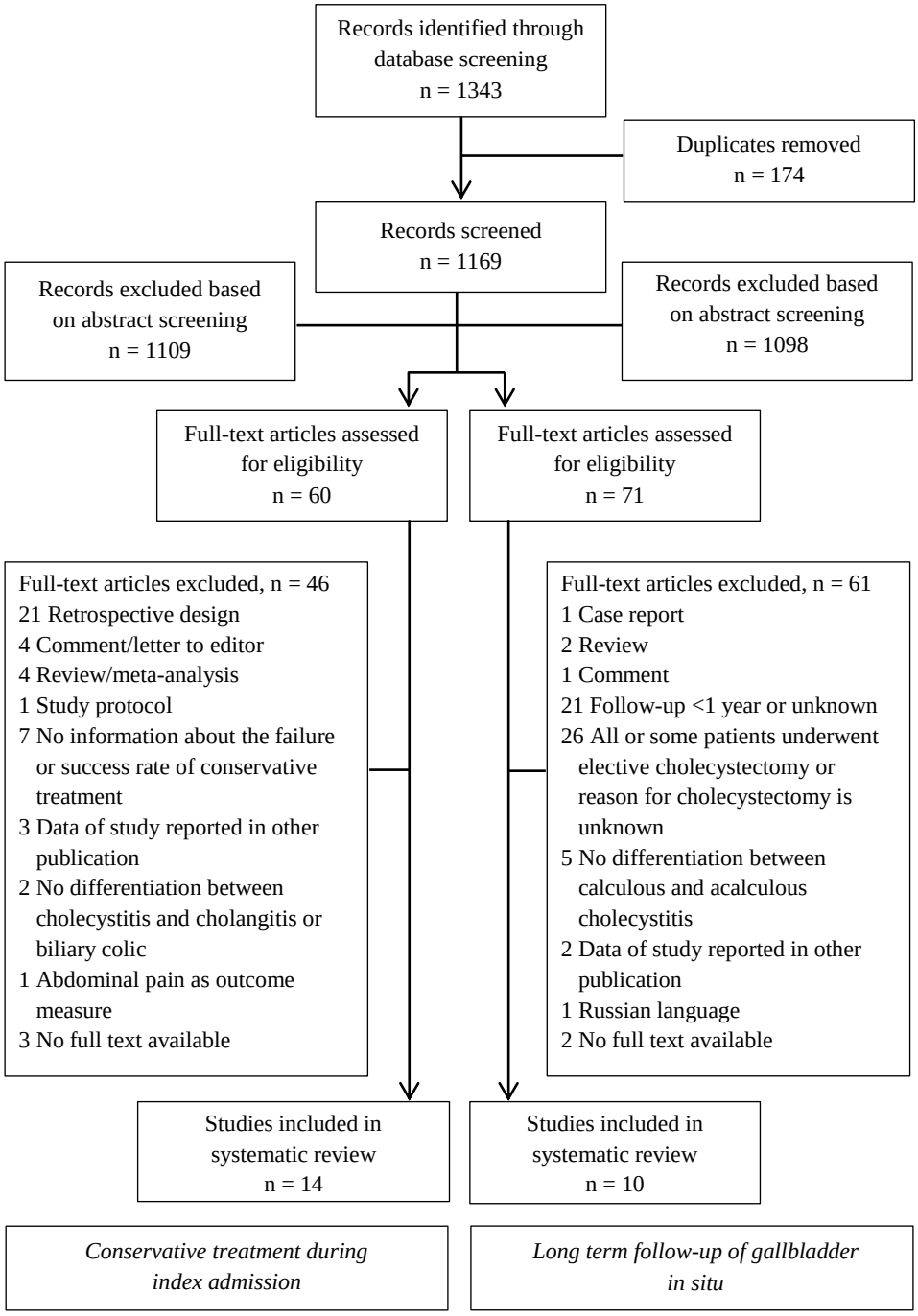
Study selection

All titles and abstracts of publications were independently identified and reviewed for relevance by two authors (CS and JO), with referral to a third author (DB) to resolve queries in case of discordant opinions. Subsequently, full text papers were retrieved and checked. A cross-reference-search of the remaining articles was performed to identify other studies previously missed. In case of unclear methods or results, authors were contacted to seek clarification. If the same data were reported in two or more publications, the most comprehensive paper was selected. Reviews, case-reports, unpublished data as well as articles of which no full text was available were excluded (Figure 4.1).

Conservative treatment during index admission was defined as non-invasive management of acute calculous cholecystitis, i.e. supportive care with or without antibiotics. Uneventful resolution of symptoms without the need for intervention was considered as a successful conservative treatment. To reduce the risk of bias, only prospective studies were included.

To evaluate the long-term success of non-surgical management of acute calculous cholecystitis, the inclusion criteria were adjusted. Only studies with at least 12 months follow-up and explicit information on the recurrence of gallstone-related disease were included. Studies describing patients who initially underwent percutaneous

Figure 4.1 Flowchart of study selection process



cholecystostomy were also eligible, since these patients still have their gallbladder in situ after initial successful non-surgical treatment of acute calculous cholecystitis and may therefore develop recurrent gallstone disease. Due to the limited amount of prospective studies with long term follow-up, retrospective studies were also included.

Data extraction

Data were extracted by two independent authors (CS and JO) with referral to a third author (DB) in case of any disagreements. The characteristics of the included studies are visualized in Table 4.1 and 4.2.

Validity assessment

The methodological quality of the articles was independently assessed by both authors. The MINORS scoring scale was used to assess the risk of bias in non-randomized studies, with a global ideal score of 16 (Table 4.3).[8] The Cochrane Collaboration's tool was used to assess the risk of bias in randomized controlled trials (Table 4.4).[9]

Data analysis

The pooled success and mortality rate of conservative treatment during index admission and the pooled recurrence rate of gallstone-related disease during long-term follow-up were calculated with a random-effects model, using meta-analysis software version 3.1. Statistical heterogeneity among the included studies was determined by using forest plots and by performing a χ^2("chi-squared") heterogeneity test and by calculating the I^2-index. A high I^2-index represents a high suspicion of heterogeneity. All pooled event rates were shown in forest plots despite the level of heterogeneity.

RESULTS

Figure 4.1 shows the article selection according to the PRISMA statement.[6,7] A total of 1343 references were identified from medical journal databases. No new articles were identified by cross-reference-search. After removing duplicates, 1169 potentially relevant studies were screened based on title and abstract, leaving 60 full manuscripts to be assessed for eligibility concerning efficacy of conservative treatment during index

admission, and 71 manuscripts concerning long term outcome of non-surgical treatment of acute calculous cholecystitis. As a result of this assessment, inclusion criteria were met in 14 and 10 studies, respectively. There was total agreement among the authors regarding the inclusion of studies.

Conservative treatment of acute cholecystitis during index admission

Fourteen prospective studies, either randomized[10-17] or non-randomized[18-22], were included. Seven trials[10,12,13,16,17,21,23] were designed to compare emergency cholecystectomy with delayed cholecystectomy. Patients assigned to delayed cholecystectomy were treated conservatively during index admission, followed by elective laparoscopic cholecystectomy several weeks after discharge. Data of these patients were used to assess the success rate of conservative treatment during index admission. Three studies[14,15,22] were designed to compare conservative management with another treatment for acute calculous cholecystitis (e.g. sphincterotomy or cholecystostomy), whereas in the remaining studies [11,18-20] all patients were treated by means of conservative management.

Table 4.1 shows the characteristics of the included studies. A total of 1315 patients with acute calculous cholecystitis were analysed. The severity of cholecystitis was explicitly reported in three studies[10-11-18]; all three concerned patients with mild cholecystitis. One study[14] excluded patients that required urgent surgical or percutaneous management, thus probably severely ill patients. In the remaining studies, the severity of cholecystitis was not mentioned.[12,13,16,17,19-23]

Outcome

A total of 1315 patients, included in 14 studies, were treated conservatively for acute calculous cholecystitis, of whom 1137 (87%) showed an uneventful resolution of symptoms without the need for intervention. Conservative treatment included bowel rest, intravenous administration of broad-spectrum antibiotics and fluids. Table 4.1. shows specific information about the antibiotic treatment, as far as described in detail in the articles. Failure of conservative treatment was determined at the discretion of the attending surgeon based on subjective findings, such as lack of improvement, or objective findings, such as worsening of clinical signs and laboratory results. In case of failure of

Table 4.1 Demographic information and findings of studies concerning short-term follow-up

Reference, year	Study design	N	Age, years	Severity of AC	Antibiotic treatment during index admission (as specified in the article)	Mortality, n (%)	Patients successfully treated conservatively n (%)
Agrawal, 2015	RCT	25	51	Mild	Antibiotic treatment NS (IV)	0	25 (100)
Gutt, 2013	RCT	314	57	NS	Moxifloxacin (400 mg, IV, once daily, ≥ 48 hours)	1 (0.3)	289 (92)
Mazeh, 2012	RCT	84	46	Mild	No antibiotics (n = 42), Augmentin (1g every 8 h, IV) until discharge (n = 42)	0	77 (92)
Rodriguez-Cerrillo, 2011	P	136	59 †	Mild	Ertapenem (IV, ≥ 1 week) (n=25), NA (n=111)	0	134 (99)
Barak, 2009	P	103	60 *	NS	Broad-spectrum antibiotics (usually ampicillin and an aminoglycoside, IV)	0	76 (74)
Paran, 2006	P	224	61 ‡	NS	Ampicillin and gentamicin (IV)	2 (0.9)	116 (74)
Vracko, 2006	P	53	76	NS §	NA	1 (2)	38 (72)
Kolla, 2004	RCT	20	39	NS	Ampicillin, gentamicin and metronidazole (IV)	0	20 (100)
Johansson, 2003	RCT	71	55	NS	Antibiotics treatment NS	0	57 (80)
Serralta, 2003	P	87	60	NS	2nd generation cephalosporin and metronidazole (IV)	0	79 (91)
Vethrus, 2003	RCT	64	55	NS ¶	Antibiotics treatment NS	0	64 (100)
Hatzidakis , 2002	RCT	42	79	NS ‖	Broad spectrum antibiotics NS (IV)	7 (17)	35 (83)
Lai, 1998	RCT	51	56	NS	Ampicillin, cefuroxime and metronidazole (IV)	0	44 (86)
Lo, 1998	RCT	41	61*	NS	Cefuroxime (750 mg every 8 h, IV)	0	33 (81)
Total		1315				11 (0.8)	1137 (87)

Data are expressed as mean unless stated otherwise, * Median. † Mean age of the select group of patients treated at home (n=25), mean age of the entire cohort is not available. ‡ Mean age of patients who underwent percutaneous cholecystostomy due to failure of conservative treatment (n=54), mean age of the entire cohort is not available. § All included patients were elderly patients with high a surgical risk. ¶ Patients who needed urgent surgical or percutaneous treatment were not included. ‖ All included patients were high-risk patients with an APACHE-II score ≥ 12.

AC denotes acute cholecystitis, NS not specified, NA not applicable, EC emergency cholecystectomy, PC percutaneous cholecystostomy, P prospective study, RCT randomized controlled trial and N number of patients.

conservative treatment, either emergency cholecystectomy[13,15-18,21-23] or percutaneous cholecystostomy[11,19,20] was performed.

The mortality rate associated with conservative treatment during index admission was 0.8% (11 of 1315).[10-23] The highest mortality rate (17%) was reported by Hatzidakis et al.[15] This study included 42 high surgical risks patients with an APACHE-II score ≥12 of whom seven died during index admission.

A total 245 patients diagnosed with explicitly mentioned mild cholecystitis were included in three studies.[10,11,18] In this specific group, conservative treatment was successful in 96% (236 of 245). Only nine patients required intervention due to failure of conservative treatment, of whom seven underwent percutaneous cholecystostomy and two cholecystectomy. Mortality in this group was nil. Mean length of hospital was mentioned in only one study and was 4 days.[11]

The pooled success rate of conservative treatment during index admission was 86% (95% CI 0.8-0.9) (Figure 4.2). There was a strong heterogeneity among the included studies (I^2 = 95%). A pooled analysis of only randomized controlled trials showed a success rate of 91% (95% C.I. 0.9-1.0) with an I^2-index of 82% (forest plot not shown). The pooled mortality rate of conservative treatment during index admission was 0.5% (95% C.I. 0.001-0.009) with an I^2-index of 0% (Figure 4.3).

Long-term outcome of non-surgical treatment of acute cholecystitis

To evaluate the long-term outcome of conservative treatment, ten studies were included; two randomized controlled trials,[15,24] three retrospective studies of prospectively collected data[25-27] and five retrospective studies.[28-32] The characteristics of the selected studies are summarized in Table 4.2. A total of 526 patients, who were initially treated conser-

Table 4.2 Demographic information and findings of included studies concerning long term follow-up

Reference, year	Study design	N	Age †	Patient characteristics	Antibiotic treatment during index admission	Initial treatment (%)	Follow-up, months	Patients with new event of gallstone related disease, n (%)
Horn, 2014	R	183	73 *	High-risk: severe comorbidities or symptom duration >5 days	NA	PC	5 yr *	55 (30)
Chang, 2013	R	31	69	High-risk: severe comorbidities	Yes	PC	38 *	3 (10)
Rodriguez-Sanjuan, 2012	RP	19	82	High-risk: severe comorbidities or advanced age	Yes	PC	15	2 (11)
McGilllicuddy, 2012	R	94	80	High-risk: advanced age (>65)	Yes	PC (36), CO (64)	30	3 (3)
Melloul, 2011	RP	9	65 *	High-risk: critically ill due to biliary sepsis	Yes	PC	16 *	4 (44)
Schmidt, 2011	RCT	33	55	No high risk patients ‡	Yes	CO	14 yr	10 (30)
Griniatsos, 2007	RP	21 §	79 *	High-risk: severe comorbidities or advanced age	Yes	PC	18 *	2 (10)
Hatzidakis, 2002	RCT	47	79	High-risk: APACHE-II score ≥ 12	Yes	PC (40), CO (60)	12	4 (9)
Andren-Sandberg, 2001	R	60	73	High-risk: critically ill due to biliary sepsis and advanced age	Yes	PC	18	28 (47)
Hamy, 1996	R	29	83	High-risk: severe comorbidities or advanced age	Yes	PC	33	6 (21)
Total		526						117 (22)

Data are expressed as mean unless stated otherwise, * Median. † In case the mean age of the conservatively treated patients was not provided, the mean age of the entire cohort is shown. ‡ Patients who needed urgent surgical or percutaneous treatment were not included. § One of the included patients was diagnosed with acute acalculous cholecystitis.

AB denotes antibiotic, PC percutaneous cholecystostomy, CO conservative treatment, R retrospective study, RP Retrospective analysis of prospectively collected data, RCT randomized controlled trial, NA not applicable and N number of patients.

vatively for acute calculous cholecystitis, and in whom cholecystectomy was not electively planned, were analysed. Follow-up ranged from 12 months to five years. One randomized controlled trial[24] was specifically designed to examine the long-term efficacy of complete conservative treatment versus immediate surgery in non-high-risk patients with acute calculous cholecystitis.

Outcome

During long term follow-up, 117 of the 526 patients (22%) developed recurrence of cholecystitis. The recurrence rate varied substantially across the included studies and ranged from 3% to 47%. The definition of recurrence of gallstone disease differed between studies. Eight studies[25,27-32] described recurrent gallstone disease only as recurrence of acute calculous cholecystitis, whereas two studies[24,26] included all gallstone-related problems. The randomized controlled trial specifically designed to examine the long-term efficacy of complete conservative treatment, included 33 patients of whom 10 (30%) experienced gallstone-related events during a median follow-up of 14 years.[24]

The time from initial treatment to recurrence varied between the included studies, but the recurrence mainly occurred within two years after initial cholecystitis; three studies[15,26,32] reported a range from 2 to 24 months, one study reported a mean of 14 months[29] and two studies reported a median of 2 months[28] and 15 months[24]. Recurrent diseases were successfully controlled by conservative medical measurements,[26,27,32] cholecystectomy[24,30,31] or percutaneous cholecystostomy.[25,28]

The pooled recurrence rate of gallstone-related disease during long-term follow-up was 19.7% (95% C.I. 0.1-0.3) (Figure 4.4). There was a strong heterogeneity among the included studies (I^2 = 90%). When dividing the studies in two groups based on duration of follow-up, a pooled recurrence rate of 22% (95% C.I. 0.06-0.04) was found for studies with a follow-up of < 2 years (I^2 = 87%) and a recurrence rate of 18% (95% C.I. 0.04-0.3) for studies with a follow-up of > 2 years (I^2 = 93%) (forest plot not shown).

Quality assessment of the included studies

The results of the methodological quality assessment of the included studies are shown in Table 4.3 and 4.4. Ten studies[10-17,23,24] were randomized controlled trials, eight studies[18-22,25-27] collected data according to a protocol established before the commencement of the study, whereas five studies[28-32] did not have such protocol and identified all patients retrospectively. None of the studies had blinded evaluation of the endpoint due to the nature of the intervention and study. Overall, the included studies were of an estimated moderate quality.

DISCUSSION

This systematic review demonstrates that conservative treatment during index admission is successful in 87% of all patients with acute calculous cholecystitis. Especially in mild acute cholecystitis, conservative treatment appears safe and effective: 96% of the patients showed uneventful resolution of symptoms without the need for intervention. After initial non-surgical treatment, 22% of the patients developed recurrent biliary symptoms, mainly within two years after initial cholecystitis. Pooled analysis shows comparable results. According to a randomized controlled trial[24] with a median follow-up of 14 years, the likelihood of recurrent gallstone disease was slightly higher (30%), but this study included only 33 patients.

When comparing surgical with non-surgical treatment, and determining the feasibility of the latter, not just the likelihood of recurrence but also the surgical risk of the patient should be regarded. In patients with advanced age and/or severe comorbidities the risk of recurrence is anyhow reduced, due to a relatively limited survival time.[33] In these patients, non-surgical management can be considered as a definitive treatment. Younger, non-high-risk patients would probably easier withstand conservative treatment compared to their older counterparts, but in the same time, are exposed to an increased risk of recurrence due to their longer life expectancy. In view of prevention of future episodes of gallstone disease, cholecystectomy might be a reasonable choice.[24] Nevertheless, the risk-benefit profile shifts towards non-operative management, considering the fact that a second episode of cholecystitis might never occur, as well as the relatively high complication rate associated with cholecystectomy.[23]

In medical practice, the tendency to remove an inflamed gallbladder is deeply rooted, even though high-quality evidence is lacking. As in case of cholecystitis, in other acute gastro-intestinal inflammations the benefit of surgery over conservative care is not always clearly demonstrated, and therefore, treatment algorithms (in select cases) are slowly shifting towards conservative management. In case of uncomplicated acute diverticulitis, conservative treatment seems feasible and safe[34,35]; so surgery should be reserved for cases with significant complications, unresponsive to medical treatment.[36] Also in acute appendicitis, randomized trials have shown feasibility and safety of initial non-surgical management.[37] A comparable management algorithm for (mild) acute calculous cholecystitis is plausible.[30]

Is it possible to identify patients for whom conservative treatment is most suitable? Concerning the severity of cholecystitis it seems clear that, without any doubt, conservative treatment during index admission is feasible in mild cases. Concerning the long-term outcome of conservatively treated mild cholecystitis no definitive conclusions could be drawn, since all (but one) studies with long term follow-up concerned high-risk patients and none reported on the initial severity of cholecystitis. But given the fact that the overall recurrence rate of biliary symptoms never exceeded one third of the patients a conservative approach during follow-up is justified. From the available data of the included studies is was not possible to identify other factors that might determine the feasibility of conservative treatment.

The success rate of conservative treatment found in this systematic review may have been influenced by several factors. Firstly, studies not reporting on the failure rate of conservative treatment were not included, since it was unclear whether failure had not been mentioned by the authors or did not occur at all. Since the latter is most likely, the success rate of conservative treatment in this review might be underestimated. Secondly, the definition of recurrent gallstone disease differed per study. Some studies described recurrent gallstone-related disease as acute cholecystitis, not reporting whether other complications (e.g. gallstone attack) did not occur or had not been reported. Therefore, the recurrence rate might have been underestimated. Lastly, the duration of follow-up varied substantially between the studies, ranging from one to 14 years. In studies with a relatively short follow-up, a recurrence after follow-up could have been developed, and therefore the recurrence rate might be underestimated. However, the majority of recurrences occur within two years after initial cholecystitis, and the risk of new gallstone-related disease decreases over time. Vethrus et al. showed that more than 70%

Table 4.3 Methodological quality of the included non-randomized studies (MINORS)

	Horn [28]	Chang [29]	Rodriguez – Sanjuan [25]	McGillicuddy [30]	Melloul [26]	Griniatsos [27]	Andren-Sandberg [31]	Hamy [32]	Rodriguez-Cerillo [18]	Barak [19]	Paran [20]	Vracko [22]	Serralta [21]
Methodological items for non-randomized studies													
A clearly stated aim	2	2	2	2	2	2	2	1	2	2	2	2	2
Inclusion of consecutive patients	2	2	2	2	2	2	2	2	2	2	0	2	2
Prospective collection of data	1	1	2	1	1	2	1	1	2	2	2	2	2
Endpoints appropriate to aim of study	2	2	2	2	2	2	2	2	1	2	2	2	2
Unbiased assessment of study endpoint	0	0	0	0	0	0	0	0	0	0	0	0	0
FU period appropriate to aim of study	2	2	2	2	2	2	2	2	2	1	2	2	2
Loss to FU < 5%	2	1	2	1	2	2	2	2	2	2	2	2	2
Prospective calculation of the study size	0	0	0	0	0	0	0	0	0	0	0	0	0
Additional criteria for comparative studies													
An adequate control group	-	-	2	-	2	-	-	-	-	-	-	2	2
Contemporary groups	-	-	2	-	2	-	-	-	-	-	-	2	2
Baseline equivalence of groups	-	-	2	-	2	-	-	-	-	-	-	2	1
Adequate statistical analysis	-	-	1	-	1	-	-	-	-	-	-	1	2
Total	11	10	19	10	18	12	11	10	11	11	10	19	19

The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate), with the global ideal score being 16 for non-comparative studies.[8]

FU denotes follow-up

of the events occurred within 20 months after acute cholecystitis.[14] Similar results regarding the development of complications have been found in patients with symptomatic uncomplicated gallstones.[38]

There was a strong heterogeneity among the included studies, demonstrated by the high I^2-values. Possible explanations include differences in sample size, patients characteristics (e.g. age, comorbidities, duration of symptoms, severity of cholecystitis) and antibiotic regimens (e.g. type of antibiotics and duration of treatment) between the included studies.

Table 4.4 Methodological quality of the included randomized controlled trials (Cochrane collaboration's tool)

	Agrawal [10]	Gutt, [23]	Mazeh [11]	Kolla [12]	Johannsson [13]	Vethrus [14]	Hatzidakis [15]	Lai [16]	Lo [17]	Schmidt [24]
Adequate sequence generation	?	+	+	+	?	+	+	+	+	+
Allocation concealment generation	?	+	+	+	?	+	+	+	-	+
Blinding of participants, personnel and outcome assessors	-	-	-	-	?	?	?	?	?	+
Incomplete outcome data addressed	+	+	+	+	+	+	+	+	+	+
Free of selective outcome reporting	+	+	+	+	+	+	+	+	+	+
Free of other bias	+	+	+	+	+	+	+	+	+	+

Risk of bias of included randomized controlled trials, using the Cochrane collaboration's tool.[9]
+ low risk of bias, - high risk of bias, ? Unknown risk of bias

The pooled mortality rate of 0.5%, on the other hand, was associated with an I^2-index of 0%, enabling us to conclude that during index admission, conservative treatment of acute cholecystitis is indeed associated with a low mortality.

Cancer may be present in a gallbladder complicated with acute cholecystitis. A large retrospective study of 2700 patients with acute calculous cholecystitis managed with cholecystectomy showed that malignant pathologies were found in 2.3% of the patients.[39] Gallbladder cancer was most frequently diagnosed in women and patients with advanced age. In our hospital, 590 patients with acute calculous cholecystitis underwent laparoscopic cholecystectomy between 2002 and 2015; pathological examination of the gallbladder showed malignant pathologies in 2 patients (0.3%). Imaging modalities such as endoscopic ultrasonography, computed tomography and magnetic resonance are useful to diagnose gallbladder cancer.[40,41] With these figures, however, it is debatable whether additional imaging studies to diagnose malignancies should be performed in all conservatively treated patients.

This systematic review implicates that conservative treatment in case of acute cholecystitis is a feasible treatment option. There is, however, insufficient evidence to demonstrate actual superiority of conservative treatment over cholecystectomy for this

indication. Currently, we are designing a prospective randomized controlled trial comparing both treatment options in patients with mild acute calculous cholecystitis.

To determine superiority of one or the other treatment strategy, not only the technical aspects but also the expenditures of both strategies should be evaluated. The costs of emergency cholecystectomy have been subject to many studies, whereas studies focussing on the economic aspects of conservative treatment are lacking. When comparing early with delayed cholecystectomy for acute cholecystitis, total hospital costs are significantly lower for early cholecystectomy.[23,42,43] Since our study, however, shows that only 22% of the patients need to be readmitted for recurrent gallstone-related disease, of whom only some need a surgical re-intervention, the total costs of conservative treatment may be reduced compared to emergency cholecystectomy. A randomized controlled trial and a complementary research using economic and public health approaches including assessment of quality of life, direct and indirect costs are needed.

To the best of our knowledge, this is the first systematic review examining short and long-term outcome of conservative treatment of patients with acute calculous cholecystitis. Based on the best available evidence, conservative treatment of acute calculous cholecystitis during index admission seems feasible and safe, especially in patients with mild disease. During long-term follow-up, about a quarter of the patients seem to develop recurrent gallstone disease, although this is based on limited data.

Acknowledgements

None

REFERENCES

1 Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, 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 Feb;11(1):79-109.

2 The Dutch guidelines for gallstone disease. Available at: http://www.heelkunde.nl/-uploads/_6/re /_6re ZZkgr YUAuCG6uvc-N-A/richtlijn_galsteen.pdf.

3 Yokoe M, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Gomi H, et al. TG13 diagnostic criteria and severity grading of acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci 2013 Jan;20(1):35-46.

4 Mayumi T, Takada T, Kawarada Y, Nimura Y, Yoshida M, Sekimoto M, et al. Results of the Tokyo Consensus Meeting Tokyo Guidelines. J Hepatobiliary Pancreat Surg 2007;14(1):114-121.

5 Cao AM, Eslick GD, Cox MR. Early Cholecystectomy Is Superior to Delayed Cholecystectomy for Acute Cholecystitis: a Meta-analysis. J Gastrointest Surg 2015 May;19(5):848-857.

6 Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009 Oct;62(10):e1-34.

7 Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. Open Med 2009;3(3):e123-30.

8 Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 2003 Sep;73(9):712-716.

9 Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011 Oct 18;343:d5928.

10 Agrawal R, Sood KC, Agarwal B. Evaluation of Early versus Delayed Laparoscopic Cholecystectomy in Acute Cholecystitis. Surg Res Pract 2015:-349801.

11 Mazeh H, Mizrahi I, Dior U, Simanovsky N, Shapiro M, Freund HR, et al. Role of antibiotic therapy in mild acute calculus cholecystitis: a prospective randomized controlled trial. World J Surg 2012 Aug;-36(8):1750-1759.

12 Kolla SB, Aggarwal S, Kumar A, Kumar R, Chumber S, Parshad R, et al. Early versus delayed laparoscopic cholecystectomy for acute cholecystitis: a prospective randomized trial. Surg Endosc 2004 Sep;18(9):1323-1327.

13 Johansson M, Thune A, Blomqvist A, Nelvin L, Lundell L. Management of acute cholecystitis in the laparoscopic era: results of a prospective, randomized clinical trial. J Gastrointest Surg 2003 Jul-Aug;7(5):642-645.

14 Vetrhus M, Soreide O, Nesvik I, Sondenaa K. Acute cholecystitis: delayed surgery or observation. A randomized clinical trial.

Scand J Gastroenterol 2003 Sep;38(9):-985-990.

15 Hatzidakis AA, Prassopoulos P, Petinarakis I, Sanidas E, Chrysos E, Chalkiadakis G, et al. Acute cholecystitis in high-risk patients: percutaneous cholecystostomy vs conservative treatment. Eur Radiol 2002 Jul;12(7):1778-1784.

16 Lai PB, Kwong KH, Leung KL, Kwok SP, Chan AC, Chung SC, et al. Randomized trial of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. Br J Surg 1998 Jun;85(6):764-767.

17 Lo CM, Liu CL, Fan ST, Lai EC, Wong J. Prospective randomized study of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. Ann Surg 1998 Apr;227(4):461-467.

18 Rodriguez-Cerrillo M, Poza-Montoro A, Fernandez-Diaz E, Inurrieta-Romero A, Matesanz-David M. Home treatment of patients with acute cholecystitis. Eur J Intern Med 2012 Jan;23(1):e10-3.

19 Barak O, Elazary R, Appelbaum L, Rivkind A, Almogy G. Conservative treatment for acute cholecystitis: clinical and radiographic predictors of failure. Isr Med Assoc J 2009 Dec;11(12):739-743.

20 Paran H, Zissin R, Rosenberg E, Griton I, Kots E, Gutman M. Prospective evaluation of patients with acute cholecystitis treated with percutaneous cholecystostomy and interval laparoscopic cholecystectomy. Int J Surg 2006;4(2):101-105.

21 Serralta AS, Bueno JL, Planells MR, Rodero DR. Prospective evaluation of emergency versus delayed laparoscopic cholecystectomy for early cholecystitis. Surg Laparosc Endosc Percutan Tech 2003 Apr;13(2):71-75.

22 Vracko J, Markovic S, Wiechel KL. Conservative treatment versus endoscopic sphincterotomy in the initial management of acute cholecystitis in elderly patients at high surgical risk. Endoscopy 2006 Aug; 38(8):773-778.

23 Gutt CN, Encke J, Koninger J, Harnoss JC, Weigand K, Kipfmuller K, et al. Acute cholecystitis: early versus delayed cholecystectomy, a multicenter randomized trial (ACDC study, NCT00447304). Ann Surg 2013 Sep;258(3):385-393.

24 Schmidt M, Sondenaa K, Vetrhus M, Berhane T, Eide GE. Long-term follow-up of a randomized controlled trial of observation versus surgery for acute cholecystitis: non-operative management is an option in some patients. Scand J Gastroenterol 2011 Oct;46(10):1257-1262.

25 Rodriguez-Sanjuan JC, Arruabarrena A, Sanchez-Moreno L, Gonzalez-Sanchez F, Herrera LA, Gomez-Fleitas M. Acute cholecystitis in high surgical risk patients: percutaneous cholecystostomy or emergency cholecystectomy? Am J Surg 2012 Jul;204(1):54-59.

26 Melloul E, Denys A, Demartines N, Calmes JM, Schafer M. Percutaneous drainage versus emergency cholecystectomy for the treatment of acute cholecystitis in critically ill patients: does it matter? World J Surg 2011 Apr;35(4):826-833.

27 Griniatsos J, Petrou A, Pappas P, Revenas K, Karavokyros I, Michail OP, et al. Percutaneous cholecystostomy without interval cholecystectomy as definitive treatment of acute cholecystitis in elderly and critically ill patients. South Med J 2008 Jun;101(6):586-590.

28 Horn T, Christensen SD, Kirkegard J, Larsen LP, Knudsen AR, Mortensen FV. Percutaneous cholecystostomy is an effective treatment option for acute calculous cholecystitis: a 10-year experience. HPB (Oxford) 2015 Apr;17(4):326-331.

29 Chang YR, Ahn YJ, Jang JY, Kang MJ, Kwon W, Jung WH, et al. Percutaneous cholecystostomy for acute cholecystitis in patients with high comorbidity and re-evaluation of treatment efficacy. Surgery 2014 Apr;155(4):615-622.

30 McGillicuddy EA, Schuster KM, Barre K, Suarez L, Hall MR, Kaml GJ, et al. Non-operative management of acute cholecystitis in the elderly. Br J Surg 2012 Sep; 99(9):1254-1261.

31 Andren-Sandberg A, Haugsvedt T, Larssen TB, Sondenaa K. Complications and late outcome following percutaneous drainage of the gallbladder in acute calculous cholecystitis. Dig Surg 2001; 18(5):393-398.

32 Hamy A, Visset J, Likholatnikov D, Lerat F, Gibaud H, Savigny B, et al. Percutaneous cholecystostomy for acute cholecystitis in critically ill patients. Surgery 1997 Apr;121(4):398-401.

33 Li M, Li N, Ji W, Quan Z, Wan X, Wu X, et al. Percutaneous cholecystostomy is a definitive treatment for acute cholecystitis in elderly high-risk patients. Am Surg 2013 May;79(5):524-527.

34 Beckham H, Whitlow CB. The medical and nonoperative treatment of diverticulitis. Clin Colon Rectal Surg 2009 Aug;22(3):156-160.

35 Unlu C, Gunadi PM, Gerhards MF, Boermeester MA, Vrouenraets BC. Outpatient treatment for acute uncomplicated diverticulitis. Eur J Gastroenterol Hepatol 2013 Sep;25(9):1038-1043.

36 Bauer VP. Emergency management of diverticulitis. Clin Colon Rectal Surg 2009 Aug;22(3):161-168.

37 Mason RJ. Surgery for appendicitis: is it necessary? Surg Infect (Larchmt) 2008 Aug;9(4):481-488.

38 Friedman GD, Raviola CA, Fireman B. Prognosis of gallstones with mild or no symptoms: 25 years of follow-up in a health maintenance organization. J Clin Epidemiol 1989;42(2):127-136.

39 Lam CM, Yuen AW, Wai AC, Leung RM, Lee AY, Ng KK, et al. Gallbladder cancer presenting with acute cholecystitis: a population-based study. Surg Endosc 2005 May;19(5):697-701.

40 Oikarinen H. Diagnostic imaging of carcinomas of the gallbladder and the bile ducts. Acta Radiol 2006 May;47(4):345-358.

41 Andren-Sandberg A. Diagnosis and management of gallbladder cancer. N Am J Med Sci 2012 Jul;4(7):293-299.

42 Wilson E, Gurusamy K, Gluud C, Davidson BR. Cost-utility and value-of-information analysis of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. Br J Surg 2010 Feb;97(2):210-219.

43 Johner A, Raymakers A, Wiseman SM. Cost utility of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. Surg Endosc 2013 Jan;27(1):256-262.

CHAPTER 5

Optimal treatment of patients with mild and moderate acute cholecystitis: time for a revision of the Tokyo Guidelines

Surgical Endoscopy, 2017

C. S. Loozen
M. M. Blessing
B. van Ramshorst
H. C. van Santvoort
D. Boerma

ABSTRACT

Introduction

According to the Tokyo Guidelines, severity of acute cholecystitis is divided in three grades based on the degree of inflammation and the presence of organ dysfunction. These guidelines recommend grade I (mild) acute cholecystitis to be treated with early laparoscopic cholecystectomy and grade II (moderate) acute cholecystitis with delayed cholecystectomy. Yet, several studies have shown that, for acute cholecystitis in general, early cholecystectomy is superior to delayed cholecystectomy in terms of complication rate, duration of hospital stay and costs. The aim of this study was to determine the clinical outcomes of emergency cholecystectomy in patients with grade II acute cholecystitis. Based on our findings we propose a revision of the Tokyo Guidelines.

Methods

We performed a retrospective observational cohort study of 589 consecutive patients undergoing emergency cholecystectomy for acute calculous cholecystitis in a large teaching hospital between January 2002 and January 2015. Patients were classified according to the severity assessment criteria of the Tokyo Guidelines. Patients with grade I and grade II acute cholecystitis were compared for perioperative outcomes.

Results

Emergency cholecystectomy was performed in 270 patients with grade I acute cholecystitis and 187 patients with grade II acute cholecystitis. There was no difference in conversion rate (6% vs. 6%, p=0.985) and operating time (60 min [25-255] vs. 70 min [30-255], p=0.421). Also the perioperative complication rate (7% vs. 9%, p=0.517), 30-day mortality (1% vs. 1%, p=0.648) and length of hospital stay (4 days [1-42] vs. 4 days [1-62], p=0.327) were similar between grade I and II acute cholecystitis.

Conclusion

The clinical outcomes of emergency cholecystectomy did not differ between patients with grade I and grade II acute cholecystitis. The findings support a revision of the Tokyo Guidelines with respect to the recommendation of performing emergency cholecystectomy in both grade I and grade II acute cholecystitis.

INTRODUCTION

Acute cholecystitis is a common cause for emergency admission in surgical departments. Annually it affects more than 20 million Americans and leads to direct costs of over US $ 6.3 billion.[1,2] Cholecystectomy is considered the standard treatment in fit, otherwise healthy patients. In the United States about 120.000 cholecystectomies for acute cholecystitis are performed annually.[3]

The severity of acute cholecystitis and its clinical manifestation vary widely among patients. Consequently the optimal treatment strategy may differ for each individual patient. In 2006, the Tokyo Guidelines were published in an attempt to obtain a clear classification and treatment algorithm for acute cholecystitis.[4-7] These guidelines, that were based on studies with variable levels of evidence and expert opinion of leaders in the field, have gained much popularity since their introduction and are of great value in current surgical practice.

According to the Tokyo Guidelines, severity of acute cholecystitis is divided in three grades based on the degree of local and systemic inflammation and the presence of organ dysfunction.[6] For each grade a different treatment strategy is proposed: early laparoscopic cholecystectomy should be performed in patients with grade I (mild) acute cholecystitis, while in patients with grade II (moderate) acute cholecystitis delayed/elective laparoscopic cholecystectomy after initial medical treatment with antimicrobial agent is the first-line treatment. Early laparoscopic cholecystectomy for grade II acute cholecystitis could be indicated if advanced laparoscopic techniques are available. Grade III (severe) acute cholecystitis is accompanied by organ failure and is suggested to be treated by percutaneous drainage.[7] The different treatment strategies for each grade suggests that the clinical outcomes differ for each severity grade, i.e. that increasing severity is associated with increasing perioperative risks.

In recent years, several studies aimed to determine the optimal timing of surgery for acute cholecystitis, showing a clear benefit in performing early rather than delayed cholecystectomy.[8] For acute cholecystitis in general, early cholecystectomy is associated with lower complication rates, shorter hospital stay, lower costs and higher patient satisfaction.

The aim of this study was to compare the clinical outcomes of patients undergoing emergency cholecystectomy for grade I and grade II acute cholecystitis in a large cohort of patients. Based on our findings, an adaptation of the Tokyo guidelines is proposed.

METHODS

Patient selection

A retrospective analysis of a prospectively collected database of consecutive patients who underwent emergency cholecystectomy for acute calculous cholecystitis in a large teaching hospital between January 2002 and January 2015 was performed. In our hospital, emergency cholecystectomy is standard treatment for patients fit for surgery. Before data collection, approval was obtained from the Institutional Review Board of the St. Antonius Hospital in Nieuwegein, The Netherlands.

Patients had been diagnosed with acute cholecystitis according to the Tokyo Guidelines, including all three of the following criteria: [1] local signs of inflammation including Murphy's sign or right upper quadrant pain, [2] systemic signs of inflammation including fever (body temperature > 38.3), elevated C-reactive protein (> 3 mg/dL) and/or elevated white blood cell (WBC) count (higher than the upper limit of normal), [3] imaging findings characteristic of acute cholecystitis (gall bladder wall thickening > 3 mm, gall bladder enlargement >8 cm in long axis or 4 cm in short axis, pericholecystic fluid accumulation, and striated intramural lucency).[6] The severity of acute cholecystitis was graded according to the severity assessment criteria of the Tokyo Guidelines (Table 5.1). Patients with grade III (severe) acute cholecystitis were excluded.

Data collection

Data collected from medical records included age, sex, body mass index (BMI), American Society of Anaesthesiologists (ASA) score and preexistent medical conditions including ischemic heart disease, chronic obstructive pulmonary disease (GOLD-classification I-IV), diabetes mellitus (type I and II), chronic renal failure and previous abdominal surgery. Specific aspects of the surgical procedure were collected from the operation records.

Outcomes

The specific outcomes to be assessed were the need for conversion, operative time, perioperative complications within 30 days (i.e. iatrogenic bowel injuries, bile duct injuries, bleedings requiring transfusion or reintervention, intra-abdominal abscesses,

Table 5.1 Severity assessment of acute cholecystitis according to the Tokyo Guidelines[6]

Complication	Definition
Grade I (Mild)	Does not meet the criteria of grade II or grade III acute cholecystitis. Can also be defined as acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder.
Grade II (Moderate)	Associated with any one of the following conditions: 1. Elevated white blood cell count (>18.000/mm^3). 2. Palpable tender mass in the right upper abdominal quadrant. 3. Duration of complaints > 72 h. 4. Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)
Grade III (Severe)	Associated with dysfunction of any of the following organs/systems: 1. Cardiovascular dysfunction (hypotension requiring treatment with dopamine > 5µg/kg per min, or any dose of norepinephrine). 2. Neurological dysfunction (decreased level of consciousness). 3. Respiratory dysfunction (PaO_2/FiO_2 ratio < 300). 4. Renal dysfunction (oliguria, creatinine > 2.0mg/dl). 5. Hepatic dysfunction (PT-INR > 1.5). 6. Hematological dysfunction (platelet count < 100.000/mm^3)

cystic stump leakages, wound infections, urinary tract infections, pulmonary complications and cardiac complications), mortality within 30 days and length of hospital stay.

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA). The outcome variables were compared between patients with grade I and grade II acute cholecystitis. The chi-square test, or where appropriate the Fisher exact test, was used for an univariable analysis of categorical data. The Mann-Whitney U-test was used to assess continues variables. All tests were two sided, and a p-value of < 0.05 was considered statistically significant. Results are presented as median (range) unless stated otherwise.

RESULTS

Patient characteristics

Between January 2002 and January 2015, a total of 4904 patients underwent laparoscopic cholecystectomy of whom 589 patients (12%) met the criteria for acute calculous cholecystitis. The study population included 270 (46 %) males and 319 (54%) females, with a mean age of 57.1 ± 16.1 years. The majority of patients (86%) had an ASA-classification score of 1 or 2. Thirty percent of the patients had previously undergone abdominal surgery, 12% suffered from diabetes, 9% from ischemic heart disease, 9% from chronic obstructive pulmonary disease and 1% of the patients suffered from chronic renal failure. The median duration of symptoms on presentation was 2 days (range 1-7). The cholecystectomy was primarily performed laparoscopically in 583 patients (99%) and primarily open in 6 patients (1%). The procedure was performed by a surgeon in 285 patients (48%) and by a surgical resident under supervision of a surgeon in 304 patients (52%).

Perioperative outcomes

Laparoscopic cholecystectomy was converted to an open procedure in 44 of 583 patients (8%). The most common reasons for conversion included severe inflammation of the gallbladder, concerns about anatomy and intraperitoneal adhesions. The median duration of surgery was 60 minutes (range 25-255). In 44 patients (8%), one or more complications occurred (52 in total). The most common complications were intra-abdominal abscess (2%), cystic stump leakage (2%), wound infection (2%) and pneumonia (1%) (Table 5.2). Lesion of the common bile duct occurred in 0.5%. Postoperative mortality was 1%. Median postoperative hospital stay was 4 days (1-62).

Perioperative outcomes per severity group

The severity of acute cholecystitis according to the Tokyo Guidelines could be assessed in457 of the 589 patients (78%) whereas in the remaining patients the specific information required for severity assessment, such as duration of symptoms and WBC count on admission, was not available. Of the 457 patients, 270 (59%) suffered from grade I acute cholecystitis and 187 (41%) from grade II acute cholecystitis. Baseline characteristics (other than Tokyo Guidelines criteria) were similar between both groups (Table 5.3).

The perioperative outcomes of emergency cholecystectomy in both severity groups are

Table 5.2 Perioperative complications of emergency cholecystectomy for acute cholecystitis in 44 of the 589 patients

Complication	**N**
Total	52
Intra-abdominal abscess	12
Cystic stump leakage	10
Wound infection	9
Pneumonia	7
Urinary tract infection	4
CBD lesion	3
Bleeding	3
Iatrogenic bowel injury	3
Congestive heart failure	1

CBD denotes common bile duct.

summarized in Table 5.4. None of the outcome variables significantly differed between groups. The conversion rate, operating time, and number and type of perioperative complications were similar between patients with grade I and grade II acute cholecystitis. There was also no difference in mortality and length of hospital stay.

DISCUSSION

This study shows that, in the large cohort of patients with acute calculous cholecystitis, the perioperative outcomes of emergency cholecystectomy did not differ between patients with grade I and grade II acute cholecystitis. Therefore, the question arises whether the differentiation between both grades is clinically relevant. The difference between grade I and grade II acute cholecystitis is based, inter alia, on the duration of symptoms (> 72 hours) and WBC count (>18.000 uL). The rationale underlying these criteria is probably based on expert opinion, since evidence from published studies was not provided for the recommendations in the Tokyo Guidelines.

Based on our findings, the differentiated approach in timing of cholecystectomy for grade and II acute cholecystitis, as proposed by the Tokyo Guidelines, seems not to be justified.

Table 5.3 Baseline characteristics of patients with grade I and grade II acute cholecystitis

Baseline characteristics	**Grade I (n = 270)**	**Grade II (n = 187)**	**P-value**
Men	120 (44)	88 (47)	0.581
Age	56.2 ± 15.5	57.6 ± 15.7	0.369
BMI (kg/m^2)	28.6 ± 5.2	28.3 ± 5.7	0.692
ASA I or II	231 (86)	166 (89)	0.317
Duration of complaints, days	1.0 (1-3)	3.5 (1-7)	<0.001
WBC count (x109/L)	12.5 ± 3.3	16.2 ± 5.9	<0.001

Data are presented as n (%), mean ± SD or median (range).

BMI denotes Body Mass Index, ASA American Society of Anaesthesiologists, WBC White Blood Cell.

The favourable perioperative outcomes in both grade I and II acute cholecystitis is further substantiated by current literature showing a clear benefit in performing early rather than delayed cholecystectomy,[9-10] indicating that emergency cholecystectomy should be considered the standard of care in good-risk patients with both grade I or grade II acute cholecystitis. One might therefore argue to adapt the current Tokyo Guidelines treatment algorithm with a grade I/III severity grading and hence only differentiate between acute cholecystitis with or without organ failure instead.

The Tokyo Guidelines recommend delayed cholecystectomy for patients with grade II acute cholecystitis, "unless laparoscopic expertise is available". Several studies have shown that emergency cholecystectomy for acute cholecystitis is best performed by a laparoscopic surgeon.[11,12] In our opinion the recommendation of the Tokyo Guidelines for both grade I and grade II acute cholecystitis should be re-defined in a way that both grade I and II patients are best treated with emergency cholecystectomy by a laparoscopically skilled surgeon. At this day and age, delayed cholecystectomy should be considered second best and only be recommended when no laparoscopic surgeon is available for index cholecystectomy.

The Tokyo Guidelines were introduced to provide a treatment algorithm for the surgical and non-surgical treatment of acute cholecystitis. Although differentiation between grade I and grade II acute cholecystitis obviously has no value in the choice for surgery, this

Table 5.4 Perioperative outcomes of emergency cholecystectomy in patients with grade I and grade II acute cholecystitis

Perioperative outcome	**Grade I (n = 270)**	**Grade II (n = 187)**	**P-value**
Conversion to open surgery	16 (6)	11 (6)	0.985
Operating time, min	60 (25-240)	70 (30-255)	0.421
Complications < 30 days	20 (7)	17 (9)	0.517
CBD lesion	1 (<1)	1 (1)	
Cystic stump leakage	6 (2)	4 (2)	
Iatrogenic bowel injury	1 (<1)	1 (1)	
Bleeding	0	3 (2)	
Intra-abdominal abscess	5 (2)	4 (2)	
Wound infection	5 (2)	4 (2)	
Pneumonia	2 (1)	2 (1)	
Urinary tract infection	3 (1)	1 (1)	
Congestive heart failure	0	1 (1)	
Mortality < 30 days	3 (1)	1 (1)	0.648
Duration of hospital stay, days	4 (1-42)	4 (1-62)	0.327

Data are presented as n (%) or median (range).
CBD denotes common bile duct.

differentiation might otherwise contribute to decisions on post-operative care such as antibiotic treatment or expected recovery time. Perioperative parameters such as empyema or necrosis of the gallbladder could be used, but these criteria have not been investigated yet. A recent randomized trial demonstrated that continuation of antibiotics after cholecystectomy is not indicated in patients with grade I and grade II acute cholecystitis.[13] Whether perioperative administration of antibiotics is necessary at all is currently under investigation in the randomized PEANUTS II-trial (NTR5802).

Cystic stump leakage is a relatively common complication that occurs in approximately 3% of patients treated with early laparoscopic cholecystectomy for acute cholecystitis.[10] The present study corroborates this finding. Cystic stump leakage occurred in 10 patients (2%), all of whom were successfully treated with endoscopic retrograde cholangiopancreato-

graphy. Since 2013, when the performing surgeons started to use hemoclips to ligate the cystic duct and gallbladder vessels, no more cystic stump leaks were encountered.

Several retrospective studies have been conducted to determine the perioperative outcome of emergency cholecystectomy in patients classified into the three severity grades. Two small retrospective series among patients with all three grades of acute cholecystitis report an increased complication rate and an increase in length of hospital stay along with Tokyo grading.[14,15] However, the number of patients was small in both studies. Kamalapurkar et al. assessed the feasibility of index cholecystectomy in patients with either grade II (n=60) or grade III acute cholecystitis (n=24) and demonstrated that length of hospital stay (5 vs. 12 days, $p < 0.001$), conversion rate (2% vs. 27%, $p = 0.006$) and minor morbidity (8% vs. 33%, $p = 0.029$) was significantly higher in the grade III group, whereas major morbidity did not significantly differ (2% vs. 9%, $p = 0.219$) and no deaths occurred.[16] Based on these results, the authors concluded that emergency cholecystectomy even in the setting of severe acute cholecystitis appears to be technically feasible and safe.

The optimal treatment strategy for patients with grade III (severe) acute cholecystitis, i.e. those patients with organ failure, remains unclear. According to the Tokyo Guidelines percutaneous drainage of the gallbladder together with supportive care and resuscitation is the preferred treatment. Only data from retrospective studies are available to support this widely accepted strategy. Currently a prospective randomized trial is being conducted, in which high-risk or septic patients are being randomized to either percutaneous drainage or emergency cholecystectomy (CHOCOLATE-trial, NTR2666).[17] The results of this trial are expected in 2017.

A limitation of the present study is its retrospective nature which carries the risk of selection bias. Since only patients who underwent emergency cholecystectomy were included, it is theoretically possible that patients with a severe form of grade II acute cholecystitis underwent percutaneous drainage and were therefore not included in the present study, which results in an underestimation of the severity of acute cholecystitis in the surgery group. However, in our hospital all patients with acute cholecystitis standardly undergo emergency cholecystectomy, except those with organ failure. The possibility that grade II patients underwent drainage is unlikely. In addition, the proportion of patients with grade I and grade II acute cholecystitis corresponds with literature.[6]

In conclusion, this study shows that the clinical outcomes of emergency cholecystectomy did not differ between patients with grade I and grade II acute cholecystitis. The findings

support a revision of the Tokyo Guidelines with respect to the recommendation of performing emergency cholecystectomy in both grade I and grade II acute cholecystitis.

Acknowledgements

None

REFERENCES

1. Everhart JE, Khare M, Hill M, Maurer KR. Prevalence and ethnic differences in gallbladder disease in the United States. Gastroenterology 1999 Sep;117(3):632-639.

2 Bethesda, MD: American Gastroenterological Association, 2001. The burden of gastrointestinal diseases. 2001.

3 Strasberg SM. Clinical practice. Acute calculous cholecystitis. N Engl J Med 2008 Jun 26;358(26):2804-2811.

4 Takada T, Kawarada Y, Nimura Y, Yoshida M, Mayumi T, Sekimoto M, et al. Background: Tokyo Guidelines for the management of acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Surg 2007;14(1):1-10.

5 Mayumi T, Takada T, Kawarada Y, Nimura Y, Yoshida M, Sekimoto M, et al. Results of the Tokyo Consensus Meeting Tokyo Guidelines. J Hepatobiliary Pancreat Surg 2007;14(1):114-121.

6 Yokoe M, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Gomi H, et al. TG13 diagnostic criteria and severity grading of acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci 2013 Jan;20(1):35-46.

7 Miura F, Takada T, Strasberg SM, Solomkin JS, Pitt HA, Gouma DJ, et al. TG13 flowchart for the management of acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci 2013 Jan;20(1):47-54.

8 Song G, Bian W, Zeng X, Zhou J, Luo Y, Tian X. Laparoscopic cholecystectomy for acute cholecystitis: early or delayed?: Evidence from a systematic review of discordant meta-analyses. Medicine 2016;95(23):e3835.

9 Cao AM, Eslick GD, Cox MR. Early laparoscopic cholecystectomy is superior to delayed acute cholecystitis: a meta-analysis of case-control studies. Surg Endosc 2016 Mar;30(3):1172-1182.

10 Cao AM, Eslick GD, Cox MR. Early Cholecystectomy Is Superior to Delayed Cholecystectomy for Acute Cholecystitis: a Meta-analysis. J Gastrointest Surg 2015 May;19(5):848-857.

11 Boddy A, Bennett J, Ranka S, Rhodes M. Who should perform laparoscopic cholecystectomy? A 10-year audit. Surg Endosc 2007;21(9):1492-1497.

12 Kortram K, Reinders JSK, van Ramshorst B, Wiezer MJ, Go PM, Boerma D. Laparoscopic cholecystectomy for acute cholecystitis should be performed by a laparoscopic surgeon. Surg Endosc 2010;24(9):2206-2209.

13 Regimbeau JM, Fuks D, Pautrat K, Mauvais F, Haccart V, Msika S, et al. Effect of postoperative antibiotic administration on postoperative infection following cholecystectomy for acute calculous cholecystitis: a randomized clinical trial. JAMA 2014;312(2):145-154.

14 Cheng WC, Chiu YC, Chuang CH, Chen CY. Assessing clinical outcomes of patients with acute calculous cholecystitis in addition to the Tokyo grading: a retrospective study. Kaohsiung J Med Sci 2014 Sep;30(9):459-465.

15 Lee SW, Yang SS, Chang CS, Yeh HJ. Impact of the Tokyo guidelines on the management of patients with acute

calculous cholecystitis. J Gastroenterol Hepatol 2009 Dec;24(12):1857-1861.

16 Kamalapurkar D, Pang TC, Siriwardhane M, Hollands M, Johnston E, Pleass H, et al. Index cholecystectomy in grade II and III acute calculous cholecystitis is feasible and safe. ANZ J Surg 2015 Nov;85 (11):854-859.

17 Kortram K, van Ramshorst B, Bollen TL, Besselink MG, Gouma DJ, Karsten T, et al. Acute cholecystitis in high risk surgical patients: percutaneous cholecystostomy versus laparoscopic cholecystectomy (CHOCOLATE trial): study protocol for a randomized controlled trial. Trials 2012 Jan 12;13:7-6215-13-7.

CHAPTER 6

Stand van zaken: behandeling van cholecystitis acuta

Accepted for publication in Nederlands Tijdschrift Voor Geneeskunde
(minor revisions)

C. S. Loozen
D. Boerma
H. C. van Santvoort

SAMENVATTING

In dit artikel bespreken wij de huidige stand van zaken met betrekking tot de behandeling van cholecystitis acuta. Verschillende aspecten zullen aan bod komen zoals de timing en benadering van een cholecystectomie, de voor- en nadelen van percutane galblaasdrainage en conservatieve behandeling en het nut van antibiotische profylaxe.

Een vroege cholecystectomie geniet de voorkeur boven een uitgestelde cholecystectomie omdat deze behandeling geassocieerd is met minder wondinfecties, een kortere opnameduur, lagere kosten en hogere patiënttevredenheid.

Radiologische percutane galblaasdrainage is succesvol in de acute fase van cholecystitis maar lijkt gepaard te gaan met een hoog risico op recidief galsteengerelateerde klachten. Of hoogrisicopatiënten met cholecystitis acuta het meest gebaat zijn bij percutane galblaasdrainage of vroege cholecystectomie wordt momenteel onderzocht.

Postoperatieve antibiotische profylaxe blijkt niet zinvol bij patiënten met milde en matig-ernstige acute cholecystitis. Het nut van preoperatieve antibiotische profylaxe wordt momenteel onderzocht.

Casus

Een 79-jarige man met een uitgebreide cardiale voorgeschiedenis en diabetes mellitus type 2 meldt zich op de spoedeisende hulp met hevige pijn in de bovenbuik. De pijn is sinds een dag voortdurend aanwezig. Al een jaar lang heeft hij regelmatig soortgelijke klachten, maar dan van voorbijgaande aard. Ditmaal is de pijn ook heviger. Bij lichamelijk onderzoek is er drukpijn rechtsboven in de buik en een temperatuur van 38,8 ^{o}C. Bloedonderzoek toont een leukocytengetal van 18,1 x 10^{9}/L en een CRP-waarde van 240 mg/L. Echografisch onderzoek toont een drukpijnlijke galblaas en een verdikte wand met vetinfiltratie, een beeld dat past bij cholecystitis acuta. Wat zijn de behandelingsopties en welke behandeling is voor deze patiënt de beste?

Inleiding

Cholecystitis acuta is een veel voorkomende aandoening die in meer dan 90% van de gevallen veroorzaakt wordt door galstenen.[1] In westerse landen komen galstenen voor bij circa 1 op de 10 volwassenen; een prevalentie die lineair toeneemt met leeftijd.[2] Indien galstenen een obstructie van de ductus cysticus veroorzaken kan dit leiden tot een ontsteking van de galblaas: initieel een steriele ontsteking, echter bij 30% - 50% van de patiënten gevolgd door een secundaire infectie door micro-organismen. E. coli en K. pneumoniae zijn hierbij de meest voorkomende.[3] In dit artikel bespreken wij de huidige stand van zaken met betrekking tot de behandeling van cholecystitis acuta.

Zoekstrategie

Wij hebben artikelen gezocht in de online databases van Embase, Medline en de Cochrane library. Als zoektermen hebben wij gehanteerd: ‘acute cholecystitis’ of ‘acute calculous cholecystitis’ in combinatie met ‘cholecystectomy’ of ‘percutaneous drainage’ of ‘cholecystostomy’ of ‘conservative’ of ‘nonoperative’ of ‘antibiotic’.

Diagnose en classificatie

De eerste internationale consensus richtlijn voor de diagnostiek en behandeling van cholecystitis acuta, de zogenoemde ‘Tokyo richtlijn’, verscheen in 2007 en werd in 2012 herzien.[4,5] Volgens deze richtlijn is er sprake van klinische verdenking op cholecystitis acuta bij ten minste één teken van lokale ontsteking (palpabele weerstand/pijn

rechtsboven in de buik of een positief teken van Murphy waarbij de patiënt pijn voelt bij diep inademen tijdens palpatie van de lever of galblaas) in combinatie met ten minste één teken van systemische ontsteking (koorts, verhoogde CRP-waarde of leukocytose) (Tabel 6.1).[4] De definitieve diagnose kan volgens de richtlijn pas worden gesteld met aanvullend beeldvormend onderzoek. Echografie van de bovenbuik is vanwege veiligheid, goede beschikbaarheid en lage kosten de eerste keuze, en heeft een sensitiviteit en specificiteit van respectievelijk 81% en 83%.[1,6] Over de waarde van CT-onderzoek daarentegen zijn slechts beperkte gegevens beschikbaar.[7] De enige studie van voldoende methodologische kwaliteit toonde een sensitiviteit en specificiteit van respectievelijk 92% en 99%.[6,8]

De klinische ernst van cholecystitis acuta wordt volgens de Tokyo richtlijn onderverdeeld in drie gradaties: mild, matig-ernstig en ernstig.[4] Deze indeling is gebaseerd op de mate van lokale en systemische ontsteking (Tabel 6.2). Milde en matig-ernstige cholecystitis acuta worden onderscheiden onder andere op basis van de duur van de klachten (langer dan 72 uur) en het aantal leukocyten (hoger dan 18 x 10^3 cellen/mm^3). Ernstige cholecystitis acuta wordt gekenmerkt door de aanwezigheid van orgaanfalen. Deze criteria echter zijn slechts gebaseerd op enkele retrospectieve studies; de klinische relevantie van de onderverdeling wordt dan ook in recente studies in twijfel getrokken.[9,10] In de richtlijn van de Nederlandse Vereniging voor Heelkunde (NVvH) voor de diagnostiek en behandeling van galsteenlijden, die in 2016 is herzien, zijn bovengenoemde definities en gradering van ernst uit de Tokyo richtlijn overgenomen.[11]

Behandeling

Cholecystectomie

Vroeg versus laat

In Nederland worden de meeste patiënten met cholecystitis acuta behandeld middels een laparoscopische cholecystectomie. Deze procedure kan uitgevoerd worden binnen enkele dagen na het ontstaan van de klachten, een zogeheten ‘vroege cholecystectomie’, of na een ‘afkoelingsperiode’ van enkele weken, een ‘uitgestelde cholecystectomie’. De termijn hiervoor bedraagt in de praktijk veelal zes weken, hoewel gerandomiseerd onderzoek naar de optimale timing van een uitgestelde cholecystectomie ontbreekt. In de Tokyo richtlijn wordt geadviseerd de timing van de cholecystectomie af te stemmen op de ernst van de cholecystitis.[5] Er bestaat echter geen overtuigend bewijs voor deze strategie. Het advies van de NVvH richtlijn is dan ook bij alle patiënten die geen

Tabel 6.1 Diagnostische criteria voor acute cholecystitis volgens de Tokyo richtlijn[5] *

	Criteria
A. Lokale ontsteking	Er is sprake van tenminste één van de volgende criteria: 1. Palpabele weerstand/pijn rechtsboven in de buik 2. Positief teken van Murphy †
B. Systemische ontsteking	Er is sprake van tenminste één van de volgende criteria: 1. Koorts 2. Verhoogde CRP-waarde 3. Leukocytose
C. Beeldvorming	Beeld suggestief voor acute cholecystitis: positief teken van Murphy, galblaaswandverdikking met een gelaagd patroon, hydrops en hyperemie van de galblaaswand, ingeklemde steen in de galblaashals of ductus cysticus, vocht in het galblaasbed

* Vermoedelijke diagnose: 1 item in A + 1 item in B. Definitieve diagnose: 1 item in A + 1 item in B + 1 item in C. † Pijn bij diep inademen tijdens palpatie van de lever of galblaas.

algemene contra-indicatie voor een operatie hebben een vroege cholecystectomie te verrichten. De NVvH richtlijn baseert zich op verschillende trials die vroege en late cholecystectomie met elkaar verlijken.[11] Een meta-analyse uit 2015 van 15 gerandomiseerde studies met 1625 patiënten toonde aan dat vroege cholecystectomie (uitgevoerd binnen 7 dagen na het ontstaan van de klachten) gepaard gaat met minder wondinfecties, een kortere opnameduur, lagere totale kosten en een hogere patiënttevredenheid.[12] Qua risico op conversie en mortaliteit werden geen significante verschillen gevonden.

Het blijft nog de vraag binnen hoeveel dagen een ‘vroege’ cholecystectomie idealiter moet worden verricht. In de Tokyo richtlijn wordt een vroege cholecystectomie gedefinieerd als een cholecystectomie verricht binnen 72 uur na het ontstaan van de klachten.[5] Langer wachten zou leiden tot een toename van ontsteking en daarmee tot een grotere kans op peroperatieve complicaties. Uit recent histopathologisch onderzoek bleek echter dat de mate van ontsteking niet gerelateerd is aan de duur van de klachten.[13] Bovendien werd in een gerandomiseerde studie uit 2016 aangetoond dat ook bij patiënten met klachten langer dan 72 uur een ‘vroege’ cholecystectomie gepaard gaat met minder complicaties en een kortere opname duur dan een uitgestelde cholecystectomie (zes

Tabel 6.2 Diagnostische criteria voor de ernst van acute cholecystitis volgens de Tokyo richtlijn[5]

Ernst	Criteria
Mild	Afwezigheid van de criteria voor een matig-ernstige of ernstige acute cholecystitis.
Matig-ernstig	Er is sprake van tenminste één van de volgende criteria 1. Leukocytose (> 18 x 10^3 cellen/mm^3) 2. Palpabele, gevoelige weerstand in het rechter bovenkwadrant 3. Duur klachten langer dan 72 uur 4. Evidente locale ontsteking (biliaire peritonitis, pericholecystisch abces, hepatisch abces, gangreneuze cholecystitis, emfysemateuze cholecystitis)
Ernstig	Er sprake is van tenminste één van de volgende criteria: 1. Cardiovasculaire dysfunctie (hypotensie welke behandeld moet worden met dopamine of noradrenaline) 2. Neurologische dysfunctie (afname van het bewustzijn) 3. Respiratoire dysfunctie (ratio van partiële arteriële zuurstof druk ten opzichte van ingeademde zuurstof < 300) 4. Renale dysfunctie (oligurie; creatinine > 177 µmol/l) 5. Hepatische dysfunctie (PT-INR, > 1,5) 6. Hematologische dysfunctie (aantal trombocyten < 100 x 10^3/mm^3).

weken na initiële opname).[14] De duur van klachten in de 'vroege' cholecystectomie groep varieerde in dit onderzoek van drie tot zeven dagen met een mediane duur van vier dagen. In de NVvH richtlijn wordt daarom voor een vroege cholecystectomie de tijdslimiet niet beperkt tot 72 uur maar wordt een termijn van een week aanhouden, hoewel bewijs uit klinisch onderzoek voor deze exacte termijn ontbreekt.[11]

Laparoscopische versus open

Een cholecystectomie bij cholecystitis acuta wordt in principe laparoscopisch verricht. Een recente meta-analyse van vier gerandomiseerde studies die laparoscopische met open cholecystectomie vergelijkt bij 310 patiënten toonde aan dat een laparoscopische procedure gepaard gaat met een kleinere kans op complicaties (18% versus 28%; p = 0.03).[15]

De kans dat een laparoscopische cholecystectomie geconverteerd moet worden naar een open procedure is bij cholecystitis acuta, in vergelijking met ongecompliceerd

galsteenlijden, vergroot. De eerder genoemde meta-analyse van 15 gerandomiseerde studies toonde aan dat een vroege cholecystectomie voor cholecystitis acuta gepaard gaat met een conversiepercentage van 13%.[12] Dit is hoger dan het in de literatuur gerapporteerde conversiepercentage van 5% bij een laparoscopische cholecystectomie voor ongecompliceerd galsteenlijden.[16] De reden voor conversie bij cholecystitis blijkt veelal een gebrek aan duidelijk beeld van anatomie van de ductus cysticus en de arteria cystica, de zogeheten 'critical view of safety'.[16]

Met het toenemen van ervaring in laparoscopische chirurgie kunnen ook complexe situaties op minimaal invasieve wijze gehanteerd worden. Men kan bij voorbeeld de galblaas van de fundus richting de hilus uitprepareren, een zogeheten "fundus first" procedure. Ook kan men besluiten om het gebied van de ductus cysticus en grote galwegen te vermijden door een stukje van de galblaas achter te laten.[17] Hierbij kan een endoscopische stapler gebruikt worden om de galblaas dicht te nieten en door te nemen of kan de restgalblaas worden dichtgehecht of zelfs opengelaten worden.

Percutane galblaasdrainage

Een behandeling voor cholecystitis acuta die steeds vaker wordt toegepast is primaire percutane drainage. Hierbij wordt de galblaas onder echo- of CT-geleide via de transhepatische of transperitoneale route aangeprikt en gedraineerd. De procedure wordt uitgevoerd onder lokale anesthesie en kan, indien nodig, worden verricht aan het bed van de patiënt. De drainage kan worden toegepast als definitieve behandeling of als overbrugging naar een uitgestelde cholecystectomie.

Observationele studies tonen aan dat percutane drainage een succesvolle behandeling is in de acute fase van cholecystitis.[18,19] Een meta-analyse uit 2009 met 1751 patiënten liet bij 86% van de patiënten binnen 72 uur na percutane drainage klinische verbetering zien en rapporteerde complicaties bij slechts 6% van de patiënten.[20] De 30-dagen mortaliteit daarentegen was 15%; deels toe te schrijven aan procedurele complicaties (0.4%) en persisterende biliaire infectie (3.6%) maar bij de meerderheid van de patiënten werd de doodsoorzaak niet genoemd. Het hoge percentage is waarschijnlijk het gevolg van 'confounding by indication', omdat met name hoogrisicopatiënten werden behandeld met percutane drainage. Overigens werd bij circa 40% van de initieel percutaan gedraineerde patiënten uiteindelijk alsnog een cholecystectomie verricht, meestal in een subacute of electieve setting.

Vanwege het minimaal invasieve karakter wordt percutane drainage in de praktijk veelal toegepast bij patiënten met een duidelijke contra-indicatie voor een operatie. Het is de vraag of percutane drainage ook de voorkeur geniet boven vroege cholecystectomie bij patiënten met een relatieve contra-indicatie voor een operatie, zoals hoge leeftijd, comorbiditeit (zoals cardiovasculaire/pulmonale aandoeningen en uitgebreide buikoperaties in de voorgeschiedenis) of een slechte klinische toestand als direct gevolg van een ernstige cholecystitis. Voor de groep patiënten waarbij de cholecystitis op basis van een combinatie van deze factoren wordt geclassificeerd als matig-ernstig of ernstig wordt in de Tokyo richtlijn geadviseerd een percutane drainage te verrichten (ernstige cholecystitis) of te overwegen (matig-ernstig cholecystitis). Tot op heden zijn er geen gerandomiseerde of prospectieve studies gepubliceerd die percutane drainage en vroege cholecystectomie met elkaar vergelijken. Recent werd daarom in 11 Nederlandse ziekenhuizen de CHOCOLATE-trial uitgevoerd, een onderzoek waarin hoogrisicopatiënten met cholecystitis acuta worden gerandomiseerd tussen percutane drainage en vroege laparoscopische cholecystectomie.[21] De resultaten van deze trial worden in 2017 verwacht.

Conservatieve behandeling

Aan de andere kant van het behandelspectrum is er mogelijk plaats voor een volledig conservatieve behandeling, met name als het gaat om patiënten met milde cholecystitis acuta. Een recente meta-analyse van observationele studies toonde aan dat een niet-invasieve behandeling tijdens initiële opname succesvol is bij 86% van 1315 patiënten met variërende ernst van cholecystitis, en zelfs bij 96% van de patiënten met milde cholecystitis acuta.[22] Conservatieve behandeling ging gepaard met een mortaliteit van slechts 0,5%. Een nadeel van de conservatieve behandeling zou een langere periode van herstel kunnen zijn. De gemiddelde opnameduur werd gerapporteerd in één studie en was vier dagen.[23] Een ander nadeel is de kans op recidief van galsteengerelateerde klachten. In de bovengenoemde meta-analyse met een follow-up van gemiddeld drie jaar ontwikkelde 22% van de patiënten recidief galsteengerelateerde klachten.[22] Aanvullende prospectieve studies moeten aantonen wat de exacte voor- en nadelen van een conservatief beleid zijn voor verschillende subgroepen van patiënten.

Antibiotica

Het nut van antibiotica bij een conservatieve behandeling van cholecystitis acuta is nooit aangetoond. Een niet placebo-gecontroleerde gerandomiseerde studie uit 2012 met 84 patiënten die een conservatieve behandeling ondergingen liet zien dat het toedienen van antibiotica geen effect heeft op de opnameduur en het risico op complicaties.[23] Hoewel perioperatieve antibiotische profylaxe door zowel de Stichting Werkgroep Antibioticabeleid als de Tokyo richtlijn wordt geadviseerd bij de chirurgische behandeling van cholecystitis acuta ter voorkoming van postoperatieve infecties in het operatie gebied, bestaat ook hiervoor geen overtuigend bewijs.[3,24] Een Franse gerandomiseerde studie met 414 patiënten met milde en matig-ernstige cholecystitis acuta toonde aan dat het toedienen van antibiotische profylaxe gedurende vijf dagen na een vroege cholecystectomie, in aanvulling op een eenmalige preoperatieve gift, niet leidt tot een vermindering van het aantal infectieuze complicaties. De resultaten van de recent gepubliceerde Nederlandse PEANUTS I-trial, waarin 150 patiënten met milde cholecystitis acuta werden gerandomiseerd tussen wel of geen postoperatieve antibiotische profylaxe gedurende drie dagen, bevestigen dit.[25] De waarde van antibiotische profylaxe voorafgaand aan cholecystectomie wordt momenteel onderzocht in de PEANUTS II-trial.

Conclusie

De optimale behandeling van cholecystitis acuta verschilt per patiënt. Bij anderszins gezonde patiënten is een laparoscopische cholecystectomie de aangewezen behandeling, onafhankelijk van de ernst van de cholecystitis. Een vroege cholecystectomie, uitgevoerd binnen één week na aanvang van de klachten, heeft de voorkeur boven een uitgestelde procedure. Postoperatieve antibiotische profylaxe blijkt niet zinvol en ook het nut van preoperatieve antibiotische profylaxe is nooit aangetoond. Bij patiënten met milde klachten lijkt er ruimte voor een volledig conservatieve behandeling. Prospectieve studies moeten evenwel de kans op recidief cholecystitis en de impact daarvan in kaart brengen. Resultaten van een Nederlandse gerandomiseerde studie zullen uitwijzen of hoogrisicopatiënten met cholecystitis acuta het meest gebaat zijn bij percutane drainage of vroege cholecystectomie.

ENGLISH SUMMARY

Treatment for acute cholecystitis: current state of affairs

This review provides an update on the current treatment of acute cholecystitis. Several aspects such as the timing of cholecystectomy, percutaneous catheter drainage, conservative treatment and the use of antibiotic prophylaxis are addressed.

Early cholecystectomy is superior to delayed cholecystectomy because this is associated with lower risk of wound infection, shorter hospital stay, lower hospital costs and greater patient satisfaction.

Percutaneous catheter drainage is a procedure with high short-term success rates, but the high rates of recurrent gallstone-related disease is reason for concern. Whether high-risk patients benefit from percutaneous drainage or early cholecystectomy is currently being investigated in a Dutch randomized multicentre study.

Postoperative antibiotic prophylaxis does not reduce the risk of infectious complications and the role of preoperative antibiotic prophylaxis is also disputable. Intravenous treatment with antibiotics does not improve the outcome in patients with mild acute cholecystitis treated conservatively.

LEERPUNTEN

De klinische ernst van acute cholecystitis is onder te verdelen in mild, matig-ernstig en ernstig gebaseerd op de mate van lokale en systemische inflammatie.

Vroege cholecystectomie is geassocieerd met minder wondinfecties, een kortere opname duur, lagere kosten en hogere patiënttevredenheid dan uitgestelde cholecystectomie.

Laparoscopische cholecystectomie gaat gepaard met sneller postoperatief herstel en een lager complicatierisico dan open cholecystectomie.

Radiologische percutane drainage is succesvol in de acute fase van cholecystitis maar lijkt gepaard te gaan met een hoog risico op recidief galsteen gerelateerde klachten.

Het is onduidelijk of hoogrisicopatiënten met acute cholecystitis meer gebaat zijn bij percutane drainage of vroege cholecystectomie.

Bij patiënten met milde acute cholecystitis lijkt een conservatieve behandeling haalbaar; de exacte voor- en nadelen hiervan moeten worden onderzocht.

Antibiotica hebben geen meerwaarde bij conservatieve behandeling van milde acute cholecystitis.

Postoperatieve antibiotische profylaxe is niet zinvol bij patiënten met milde en matig-ernstige acute cholecystitis. De waarde van preoperatieve antibiotische profylaxe wordt onderzocht.

REFERENTIES

1 Strasberg SM. Acute calculous cholecystitis. N Engl J Med. 2008;358: 2804-11.

2 Schirmer BD, Winters KL, Edlich R. Cholelithiasis and cholecystitis. J Long Term Eff Med. 2005;15.

3 Gomi H, Solomkin JS, Takada T, Strasberg SM, Pitt HA, Yoshida M, et al. TG13 antimicrobial therapy for acute cholangitis and cholecystitis. Journal of hepato-biliary-pancreatic sciences. 2013; 20:60-70.

4 Yokoe M, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Gomi H, et al. TG13 diagnostic criteria and severity grading of acute cholecystitis (with videos). Journal of hepato-biliary-pancreatic sciences. 2013;20:35-46.

5 Miura F, Takada T, Strasberg SM, Solomkin JS, Pitt HA, Gouma DJ, et al. TG13 flowchart for the management of acute cholangitis and cholecystitis. Journal of hepato-biliary-pancreatic sciences. 2013;20:47-54.

6 Kiewiet JJ, Leeuwenburgh MM, Bipat S, Bossuyt PM, Stoker J, Boermeester MA. A systematic review and meta-analysis of diagnostic performance of imaging in acute cholecystitis. Radiology. 2012;264: 708-20.

7 van Santvoort HC. Beeldvorming bij acute cholecystitis. NTVG. 2013.

8 Bennett GL, Rusinek H, Lisi V, Israel GM, Krinsky GA, Slywotzky CM, et al. CT findings in acute gangrenous cholecystitis. Am J Roentgenol. 2002;178:275-81.

9 Amirthalingam V, Low JK, Woon W, Shelat V. Tokyo guidelines 2013 may be too restrictive and patients with moderate and severe acute cholecystitis can be managed by early cholecystectomy too. Surg Endosc. 2016:1-9.

10 Kamalapurkar D, Pang TC, Siriwardhane M, Hollands M, Johnston E, Pleass H, et al. Index cholecystectomy in grade II and III acute calculous cholecystitis is feasible and safe. ANZ J Surg. 2015;85:854-9.

11 The dutch guidelines for the treatment of gallstone disease [Internet].; 2016. Available from: http://heelkunde.nl/sites/-heelkunde.nl/files/richtlijnen-definitief/-RichtlijnGalsteenlijden_09032016.pdf.

12 Wu X, Tian X, Liu M, Wu L, Zhao S, Zhao L. Meta-analysis comparing early versus delayed laparoscopic cholecystectomy for acute cholecystitis. Br J Surg. 2015;102:1302-13.

13 Gomes RM, Mehta NT, Varik V, Doctor NH. No 72-hour pathological boundary for safe early laparoscopic cholecystectomy in acute cholecystitis: A clinicopathological study. Annals of Gastroenterology. 2013; 26:340.

14 Roulin D, Saadi A, Di Mare L, Demartines N, Halkic N. Early versus delayed cholecystectomy for acute cholecystitis, are the 72 hours still the rule?: A randomized trial. Ann Surg. 2016 Jul 15.

15 Coccolini F, Catena F, Pisano M, Gheza F, Fagiuoli S, Di Saverio S, et al. Open versus laparoscopic cholecystectomy in acute cholecystitis. systematic review and meta-analysis. International Journal of Surgery. 2015;18:196-204.

16 Ballal M, David G, Willmott S, Corless D, Deakin M, Slavin J. Conversion after laparoscopic cholecystectomy in england. Surg Endosc. 2009;23:2338.

17 Elshaer M, Gravante G, Thomas K, Sorge R, Al-Hamali S, Ebdewi H. Subtotal cholecystectomy for "difficult gallbladders ":Systematic review and meta-analysis. JAMA surgery. 2015;150:159-68.

18 McKay A, Abulfaraj M, Lipschitz J. Short- and long-term outcomes following percutaneous cholecystostomy for acute cholecystitis in high-risk patients. Surg Endosc. 2012;26:1343-51.

19 Horn T, Christensen SD, Kirkegård J, Larsen LP, Knudsen AR, Mortensen FV. Percutaneous cholecystostomy is an effective treatment option for acute calculous cholecystitis: A 10-year experience. HPB. 2015;17:326-31.

20 Winbladh A, Gullstrand P, Svanvik J, Sandström P. Systematic review of cholecystostomy as a treatment option in acute cholecystitis. HPB. 2009;11:183-93.

21 Kortram K, van Ramshorst B, Bollen TL, Besselink MG, Gouma DJ, Karsten T, et al. Acute cholecystitis in high risk surgical patients: Percutaneous cholecystostomy versus laparoscopic cholecystectomy (CHOCOLATE trial): Study protocol for a randomized controlled trial. Trials. 2012;1

22 Mazeh H, Mizrahi I, Dior U, Simanovsky N, Shapiro M, Freund HR, et al. Role of antibiotic therapy in mild acute calculus cholecystitis: A prospective randomized controlled trial. World J Surg. 2012;36: 1750-9.

23 Loozen CS, Oor JE, van Ramshorst B, van Santvoort HC, Boerma D. Conservative treatment of acute cholecystitis: A systematic review and pooled analysis. Surg Endosc. 2016:1-12.

24 Van Kasteren M, Gyssens I, Kullberg B, Bruining H, Stobberingh E, Goris R. Optimaliseren van het antibioticabeleid in nederland. V. SWAB-richtlijnen voor perioperatieve antibiotische profylaxe. Ned Tijdschr Geneeskd. 2000;144:2049-55.

25 Loozen C, Kortram K, Kornmann V, van Ramshorst B, Vlaminckx B, Knibbe C, et al. Randomized clinical trial of extended versus single-dose perioperative antibiotic prophylaxis for acute calculous cholecystitis. Br J Surg. 2017;104.

PART II

Management of high-risk patients with acute cholecystitis

CHAPTER 7

Acute cholecystitis in elderly patients: a case for early cholecystectomy

Journal of visceral surgery, 2017

C. S. Loozen
B. van Ramshorst
H. C. van Santvoort
D. Boerma

ABSTRACT

Background

Recent advances in laparoscopic techniques and perioperative care have changed the indications for surgery in elderly patients. Consequently, the willingness to offer early surgery for acute cholecystitis continues to increase. This study aims to assess the perioperative outcome of early cholecystectomy for acute calculous cholecystitis in elderly patients.

Methods

All consecutive patients treated by early cholecystectomy for acute calculous cholecystitis in a major teaching hospital, between January 2002 and November 2016, were retrospectively analyzed. The outcome of elderly patients (≥75 years) was compared to that of all others. Conversion rate, 30-day morbidity, 30-day mortality and length of hospital stay were assessed.

Results

Early cholecystectomy for acute calculous cholecystitis was performed in 703 patients: 121 (17%) aged ≥ 75 years and 582 (83%) aged < 75 years. Significantly more elderly patients had an ASA score ≥ 3 (37% vs. 8%, $p<0.001$). Morbidity was higher in the elderly group (17% vs. 8%, $p<0.004$), mainly attributable to the high incidence of cystic stump leakage in this group; a complication that no longer occurred after changing the technique of ligation of the cystic stump. The cardiopulmonary complication rate (4% vs. 3%, $p=0.35$) as well as mortality did not significantly differ (3% vs. 1%, $p=0.07$). The conversion rate was higher in the elderly group (18% vs. 5%, $p<0.001$) and the median postoperative length of hospital stay was longer (5.0 vs. 3.0 days, $p<0.001$).

Conclusion

Early laparoscopic cholecystectomy is a treatment well suited to elderly patients with mild and moderate acute cholecystitis.

INTRODUCTION

Acute cholecystitis is a common condition that accounts for approximately one-third of all emergency admissions to surgical wards.[1] More than 90% of the cases are associated with cholelithiasis;[2] a condition that affects 10% to 15% of the general population.[3-5] Previous studies showed that the development of gallstones and acute cholecystitis is strongly related to age.[4,6,7] As the global population ages, the number of patients presenting with acute cholecystitis is expected to rise.

While early cholecystectomy has been firmly established as the procedure of choice for acute cholecystitis in young and fit patients,[8,9] controversy exists in the surgical management of elderly.[10-13] Due to comorbidities and reduced physiological reserves, elderly are thought to be at risk for increased perioperative morbidity and mortality. Many clinicians esteem elderly patients to be better off with percutaneous catheter drainage, as it avoids any surgery related complications. This, however, is not substantiated by clinical evidence. In fact, literature shows that the 30-day mortality of percutaneous drainage is higher than that of cholecystectomy.[14]

Recent advances in laparoscopic techniques and perioperative care have changed the indications for surgery in elderly patients in general. As a result, the willingness to offer early surgery for acute cholecystitis continues to increase. The present study aims to assess the perioperative outcome of early cholecystectomy for acute calculous cholecystitis in elderly patients (≥75 years). The outcome is compared to that in younger patients, operated by the same group of surgeons during the same time period.

METHODS

All consecutive patients treated by early cholecystectomy for acute calculous cholecystitis in a large teaching hospital, between January 2002 and November 2016, were retrospectively identified from a prospectively collected database. All patients had been admitted through the emergency department and were operated on during the same admission. Before data collection, approval was obtained from the Institutional Review Board of the St. Antonius Hospital in Nieuwegein, the Netherlands.

Diagnosis

Acute cholecystitis had been diagnosed according to the criteria of the Tokyo Guidelines.[15] Patients had to meet the following inclusion criteria: (1) local sign of inflammation including Murphy's sign or right upper quadrant pain, (2) systemic signs of inflammation including fever (body temperature > 38.3), elevated C-reactive protein (> 3 mg/dL) and/or elevated white blood cell count (higher than the upper limit of normal), (3) imaging findings characteristic of acute cholecystitis. Patients who did not meet all three inclusion criteria as well as patients with acalculous cholecystitis were excluded. The severity of acute cholecystitis was graded as mild (grade I), moderate (grade II) or severe (grade III) according to the severity assessment criteria of the Tokyo Guidelines.[15]

Data collection

The following data were collected from medical charts: age, sex, body-mass index (BMI), laboratory data (i.e. white blood cell count and C-reactive protein), time since onset of symptoms and the severity of acute cholecystitis according to the Tokyo Guidelines.[15] The risk of perioperative morbidity was assessed according to the American Society of Anesthesiologists (ASA) classification. Associated medical conditions including ischemic heart disease, chronic obstructive pulmonary disease, diabetes mellitus (type I and II), chronic renal failure and previous abdominal surgery were derived from the medical records of the patients.

Surgical procedure

Cholecystectomy was performed laparoscopically using the standard four-port technique. If the treating surgeon considered a laparoscopic approach to be contraindicated, an open procedure was adopted from the outset. Routine intra-operative cholangiography was not employed. Specific aspects of the surgical procedure such as the approach, the duration, the need for conversion and the occurrence of intraoperative complications were collected from the surgical reports. Patients received a single dose of antibiotic prophylaxis before surgery. Whether or not antibiotic therapy was postoperatively continued was dependent on the preference of the attending surgeon.

Outcome parameters

The outcome parameters to be assessed were need for conversion, operating time, 30-day morbidity (including intraoperative complications), 30-day mortality and post-operative length of hospital stay. Complications were assessed according to Clavien-Dindo classification.[16]

Statistical analysis

Statistical analysis was carried out using SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA). The chi-square test, or where appropriate the Fisher exact test, was used for univariable analysis of categorical data. The Mann-Whitney U-test was used to assess continues variables. All tests were two sided; a p-value of < 0.05 was considered to be statistically significant. Categorical data were described as frequencies (%) and continuous data as mean (±SD) or median (range).

RESULTS

Patient characteristics and operative details

A total of 5654 consecutive patients underwent a cholecystectomy during the study period. The aforementioned criteria for acute calculous cholecystitis were met in 703 patients: 121 (17%) aged ≥75 years and 582 (83%) aged < 75 years. The baseline characteristics of the elderly and non-elderly patients are depicted in Table 7.1. Elderly patients were more likely to have cardiovascular disease (28% vs. 11%, $p < 0.001$), pulmonary disease (23% vs. 7%, $p < 0.001$) and diabetes (19% vs. 11%, $p = 0.02$). Significantly more elderly patients had an ASA score ≥ 3 (37% vs. 8%, $p < 0.001$). The severity of cholecystitis did not significantly differ between the two groups ($p = 0.82$). The median duration from onset of symptoms in both groups was 2 days ($p = 0.07$). In the elderly and non-elderly group, patients were treated by attempted laparoscopic cholecystectomy in 98% and 99%, respectively. Primary open cholecystectomy was performed in three patients in both groups.

Perioperative outcome

Data on the perioperative outcomes are summarized in Table 7.2. Perioperative mor-

Table 7.1 Baseline characteristics of elderly and non-elderly patients treated by early cholecystectomy for acute cholecystitis

Patient characteristics	≥ 75 years (n = 121)	< 75 years (n = 582)	P-value
Age - years	80.1 ± 4.2	52.8 ± 13.2	< 0.001
Male sex	59 (49)	264 (45)	0.50
Body-mass index - kg/m2	27.2 ± 4.1	29.0 ± 5.8	0.02
Coexisting conditions †			
Cardiovascular disease	30 (28)	58 (11)	< 0.001
Pulmonary disease	25 (23)	39 (7)	< 0.001
Chronic renal insufficiency	3 (3)	6 (1)	0.18
Diabetes	21 (19)	62 (11)	0.02
Previous abdominal surgery †	35 (32)	139 (25)	0.15
ASA classification			< 0.001
I: Healthy status	7 (6)	222 (38)	
II: Mild systemic disease	69 (57)	314 (54)	
III: Severe systematic disease	45 (37)	46 (8)	
Severity of acute cholecystitis * ‡			0.82
Mild (grade I)	52 (57)	281 (58)	
Moderate (grade II)	39 (43)	195 (41)	
Severe (grade III)	0 (0)	5 (1)	
Disease severity			
White blood cell count (x109/L)	14.7 ± 5.4	13.6 ± 5.2	0.06
C-reactive protein (mg/L)	173.8 ± 170.0	112.0 ± 106.4	< 0.001
Time since onset of symptoms - days	2 (1-6)	2 (1-6)	0.07

Data are presented as n (%), mean ± SD or median (range).

* According to the Tokyo Guidelines.[15] † 12 missing values in the elderly group, 34 missing values in the non-elderly group. ‡ 30 missing values in the elderly group, 101 missing values in the non-elderly group.

ASA denotes American Society of Anesthesiologists.

bidity was higher in the elderly group (17% vs. 8%, p = 0.004) whereas the cardiopulmonary complication rate (4% vs. 3%, p = 0.35) as well as mortality did not significantly differ (3% vs. 1%, p = 0.07). The mean operating time was comparable

between the two groups ($p = 0.53$). The conversion rate from laparoscopic to open cholecystectomy was significantly higher in the elderly group (18% vs. 5%, $p < 0.001$), predominately due to concerns about anatomy and intraperitoneal adhesions. The median postoperative length of hospital stay was longer in the elderly group (5.0 vs. 3.0 days, $p < 0.001$).

In the elderly group, postoperative bile leakage was the most common complication, occurring in eight patients (7%) (Table 7.2). Seven of these patients had a leakage of the cystic stump, whereas one patient appeared to have a tangential lesion of the common bile duct. All but one patient were treated successfully by endoscopic stent placement or sphincterotomy; the remaining patient deteriorated clinically and died despite emergency laparotomy and intensive care admission. Two other patients in the elderly group died from the consequences of diffuse liver bed bleeding and congestive heart failure, respectively. According to the Clavien-Dindo classification, three complications were grade 5, 12 complications were grade 3A, two complications were grade 3B and nine complications were grade 2.

In the non-elderly group, intra-abdominal abscesses (3%) and wound infections (2%) were the most common complications (Table 7.2). Postoperative bile leakage occurred in five patients (0.9%). Three patients died (1%); one as a consequence of iatrogenic bowel injury and two as a consequence of a thromboembolic complication. According to the Clavien-Dindo classification, three complications were grade 5, four complications were grade 3B, 12 complications were grade 3A and 34 complications were Clavien-Dindo grade 2.

DISCUSSION

The present study, which includes the largest consecutive series of elderly patients undergoing early surgery for acute cholecystitis in literature, demonstrates that early cholecystectomy is a valuable treatment option in elderly patients with mild and moderate acute cholecystitis, with a perioperative morbidity of 17% and a mortality of 3%. As expected, in non-elderly patients operated by the same group of surgeons during the same time period, these rates were more favorable; 8% and 1%, respectively. The difference in outcome is mainly attributable to the surprisingly high incidence of cystic

Table 7.2 Perioperative outcome of early cholecystectomy for acute cholecystitis in elderly and non-elderly patients

Outcome	≥ 75 years (n = 121)	< 75 years (n = 582)	P-value
Conversion to open surgery †	21 (18)	27 (5)	< 0.001
Perioperative morbidity *	20 (17)	47 (8)	0.004
Surgical complication	17 (14)	35 (6)	0.002
Common bile duct lesion	1 (0.8)	2 (0.3)	
Cystic stump leakage	7 (6)	3 (0.5)	
Intra-abdominal abscess	5 (4)	15 (3)	
Wound infection	3 (3)	14 (2)	
Bleeding requiring transfusion or reintervention	3 (3)	0 (0)	
Iatrogenic bowel injury	0 (0)	3 (0.5)	
Cardiopulmonary complication	5 (4)	15 (3)	0.35
Pneumonia	2 (2)	9 (2)	
Arrhythmia	3 (3)	4 (0.7)	
Congestive heart failure	2 (2)	1 (0.2)	
Thromboemobolic complication	0 (0)	2 (0.3)	
Mortality *	3 (3)	3 (1)	0.07
Operating time - min	75.1 ± 28.9	73.2 ± 29.8	0.53
Duration of hospital stay - days	5.0 (1-42)	3.0 (1-62)	< 0.001

Data are presented as n (%), mean ± SD or median (range). * within 30 postoperative days. † In both groups, three patients were treated by primary open cholecystectomy

stump leakage in the elderly group; a complication that no longer occurred after changing the technique of ligation of the cystic stump from metal to vascular clips (in 2013). If, in the present series, stump leakage is not taken into account, morbidity of early cholecystectomy for acute cholecystitis does not significantly differ between the two groups.

In recent years, a small number of retrospective studies have been performed to compare the outcome of early cholecystectomy for acute cholecystitis in elderly with that in younger patients.[17-20] In general, elderly appeared to be sicker at presentation and proved to have more comorbidities, which is consistent with our findings. Although one

would expect more complications to occur in the elderly group, especially those of cardiac and respiratory nature, most studies demonstrated that both groups did not significantly differ in terms of perioperative outcome.[17-19] Nikfarjam et al.[20], on the contrary, demonstrated age ≥ 80 years to be independently associated with increased complications following early cholecystectomy for acute cholecystitis, the majority of complications being cardiac and respiratory in nature. Our study, however, showed that the cardiopulmonary complication rate did not differ between both groups.

Another striking difference between the elderly and the younger patients is the conversion rate from laparoscopic to open cholecystectomy (18% vs. 5%). This is in accordance with literature, showing that advanced age entails the risk of conversion to an open procedure.[21] Although open compared to laparoscopic cholecystectomy for acute cholecystitis is associated with increased risk of complications[22], in the present study, patients in whom the procedure was converted did not show worse perioperative outcomes (data not shown). Previous studies showed that patients operated upon by a laparoscopic surgeon have a greater chance of a laparoscopically completed cholecystectomy. Therefore, postponing the procedure should be considered in order to have it performed by a laparoscopic surgeon.[23,24]

The question is whether complications can be avoided by choosing a non-operative treatment strategy for acute cholecystitis in the elderly. A small prospective study of 53 elderly patients with acute cholecystitis treated conservatively demonstrated that 30% suffered from biliary sepsis requiring emergency surgery and 2% died.[25] A prospective study of 42 elderly patients with acute cholecystitis and an APACHE-II score ≥ 12 showed that 7 patients (17%) suffered from ongoing sepsis, all of whom died.[26] A recently published systematic review, which did not specifically focus on elderly patients, showed conservative treatment to be very successful in patients with mild (grade I) acute cholecystitis.[27] Whether this accounts for elderly patients with mild acute cholecystitis too should be subject of future research.

Also percutaneous drainage may offer a less-invasive alternative for the treatment of acute cholecystitis, avoiding the risk of surgical morbidity. A systematic review conducted in 2009 demonstrated that the 30-day mortality of patients treated with percutaneous drainage (15%) was higher than that of patients treated with cholecystectomy (5%).[14] This, however, could be attributed to confounding by indication as it is to be expected that patients treated with drainage were in a worse

clinical condition than those treated with cholecystectomy.[14] On the other hand, more than 40% of patients treated with percutaneous drainage eventually underwent cholecystectomy, which indicates that percutaneous drainage is not a definitive treatment in a large proportion of patients.

Although increased morbidity and mortality are inextricably linked to any treatment strategy for acute cholecystitis in elderly patients, the outcome of early cholecystectomy in elderly patients may be improved by careful patient selection. A large retrospective study of patients who underwent laparoscopic cholecystectomy showed that prediction of individual outcome based on a patient's individual risk profile and optimization of comorbidities may help to prevent specific post-operative complications.[28] In addition, anticipation of a complication should be an important incentive to focus on concrete measures to reduce specific complications in patients at risk.

In conclusion, early laparoscopic cholecystectomy is a treatment well suited to elderly patients with mild and moderate acute cholecystitis. To determine the optimal treatment of elderly patients with severe illness or severe comorbidities, a prospective randomized trial comparing early cholecystectomy with percutaneous drainage is currently being conducted (CHOCOLATE trial, NTR2666).[29] The results of this trial will become available this year.

Acknowledgements

None

REFERENCES

1 Browning JD, Horton JD. Gallstone disease and its complications. Semin Gastrointest Dis 2003 Oct;14(4):165-177.

2 Kimura Y, Takada T, Strasberg SM, Pitt HA, Gouma DJ, Garden OJ, et al. TG13 current terminology, etiology, and epidemiology of acute cholangitis and cholecystitis. Journal of hepato-biliary-pancreatic sciences 2013;20(1):8-23.

3 Shaffer EA. Epidemiology and risk factors for gallstone disease: has the paradigm changed in the 21st century? Curr Gastroenterol Rep 2005;7(2):132-140.

4 Schirmer BD, Winters KL, Edlich R. Cholelithiasis and cholecystitis. J Long Term Eff Med 2005;15(3).

5 Tazuma S. Epidemiology, pathogenesis, and classification of biliary stones (common bile duct and intrahepatic). Best practice & research Clinical gastroenterology 2006;20(6):1075-1083.

6 Glenn F. Surgical management of acute cholecystitis in patients 65 years of age and older. Ann Surg 1981 Jan;193(1):56-59.

7 Cho JY, Han H, Yoon Y, Ahn KS. Risk factors for acute cholecystitis and a complicated clinical course in patients with symptomatic cholelithiasis. Archives of Surgery 2010;145(4):329-333.

8 Gurusamy KS, Davidson C, Gluud C, Davidson BR. Early versus delayed laparoscopic cholecystectomy for people with acute cholecystitis. Cochrane Database Syst Rev 2013;6.

9 Gurusamy K, Samraj K, Gluud C, Wilson E, Davidson B. 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.

10 Nazeer MA, Ali M, Ahmed K, SALEEM R. Outcomes of laparoscopic cholecystectomy in the elderly versus young patients. Pak J Med Health Sci 2012;6(3):544-546.

11 Bergman S, Sourial N, Vedel I, Hanna WC, Fraser SA, Newman D, et al. Gallstone disease in the elderly: are older patients managed differently? Surg Endosc 2011;25(1):55-61.

12 McGillicuddy E, Schuster K, Barre K, Suarez L, Hall M, Kaml G, et al. Non-operative management of acute cholecystitis in the elderly. Br J Surg 2012;99(9):1254-1261.

13 Nielsen LBJ, Harboe KM, Bardram L. Cholecystectomy for the elderly: no hesitation for otherwise healthy patients. Surg Endosc 2014;28(1):171-177.

14 Winbladh A, Gullstrand P, Svanvik J, Sandström P. Systematic review of cholecystostomy as a treatment option in acute cholecystitis. HPB 2009;11(3):183-193.

15 Yokoe M, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Gomi H, et al. TG13 diagnostic criteria and severity grading of acute cholecystitis (with videos). Journal of hepato-biliary-pancreatic sciences 2013;20(1):35-46.

16 Dindo D, Demartines N, Clavien P. 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.

17 Ambe PC, Weber SA, Christ H, Wassenberg D. Primary cholecystectomy is feasible in elderly patients with acute cholecystitis. Aging clinical and experimental research 2015;27(6):921-926.

18 Fuks D, Duhaut P, Mauvais F, Pocard M, Haccart V, Paquet J, et al. A retrospective comparison of older and younger adults undergoing early laparoscopic cholecystectomy for mild to moderate calculous cholecystitis. J Am Geriatr Soc 2015;63(5):1010-1016.

19 Fukami Y, Kurumiya Y, Mizuno K, Sekoguchi E, Kobayashi S. Cholecystectomy in octogenarians: be careful. Updates in surgery 2014;66(4):265-268.

20 Nikfarjam M, Yeo D, Perini M, Fink MA, Muralidharan V, Starkey G, et al. Outcomes of cholecystectomy for treatment of acute cholecystitis in octogenarians. ANZ J Surg 2014;84(12):943-948.

21 Philip Rothman J, Burcharth J, Pommergaard HC, Viereck S, Rosenberg J. Preoperative Risk Factors for Conversion of Laparoscopic Cholecystectomy to Open Surgery - A Systematic Review and Meta-Analysis of Observational Studies. Dig Surg 2016;33(5):414-423.

22 Coccolini F, Catena F, Pisano M, Gheza F, Fagiuoli S, Di Saverio S, et al. Open versus laparoscopic cholecystectomy in acute cholecystitis. Systematic review and meta-analysis. International Journal of Surgery 2015;18:196-204.

23 Kortram K, Reinders JSK, van Ramshorst B, Wiezer MJ, Go PM, Boerma D. Laparoscopic cholecystectomy for acute cholecystitis should be performed by a laparoscopic surgeon. Surg Endosc 2010; 24(9):2206-2209.

24 Boddy A, Bennett J, Ranka S, Rhodes M. Who should perform laparoscopic cholecystectomy? A 10-year audit. Surg Endosc 2007;21(9):1492-1497.

25 Vracko J, Markovic S, Wiechel K. Conservative treatment versus endoscopic sphincterotomy in the initial management of acute cholecystitis in elderly patients at high surgical risk. Endoscopy 2006;38(08): 773-778.

26 Hatzidakis AA, Prassopoulos P, Petinarakis I, Sanidas E, Chrysos E, Chalkiadakis G, et al. Acute cholecystitis in high-risk patients: percutaneous cholecystostomy vs conservative treatment. Eur Radiol 2002;12(7):1778-1784.

27 Loozen CS, Oor JE, van Ramshorst B, van Santvoort HC, Boerma D. Conservative treatment of acute cholecystitis: a systematic review and pooled analysis. Surg Endosc 2016:1-12.

28 Donkervoort S, Kortram K, Dijksman L, Boermeester M, van Ramshorst B, Boerma D. Anticipation of complications after laparo-scopic cholecystectomy: prediction of individual outcome. Surg Endosc 2016:1-7.

29 Kortram K, van Ramshorst B, Bollen TL, Besselink MG, Gouma DJ, Karsten T, et al. Acute cholecystitis in high risk surgical patients: percutaneous cholecystostomy versus laparoscopic cholecystectomy (CHOCOLATE trial): study protocol for a randomized controlled trial. Trials 2012;13(1):1

CHAPTER 8

Early cholecystectomy for acute cholecystitis in the elderly population: a systematic review and meta-analysis

Digestive surgery, 2017

C. S. Loozen
B. van Ramshorst
H. C. van Santvoort
D. Boerma

ABSTRACT

Background

In the era of advanced surgical techniques and improved perioperative care, the willingness to perform emergency operations in elderly patients continues to increase. This systematic review aimed to assess the clinical outcomes of early cholecystectomy in elderly patients with acute cholecystitis.

Methods

MEDLINE, Embase and Cochrane Library databases were systematically searched for studies reporting on early cholecystectomy for acute cholecystitis in patients aged ≥70 years. The conversion rate, perioperative morbidity and mortality were calculated using a random-effects model.

Results

Eight articles fell within the scope of this study. In total, 592 patients were identified. The mean age was 81 years. Early cholecystectomy was performed laparoscopically in 316 patients (53%) and open in 276 patients (47%). The procedure was associated with a conversion rate of 23% (95% CI 18.6 - 28.3), a perioperative morbidity of 24% (95% CI 20.5 - 27.5) and a mortality of 3.5% (95% CI 2.3 - 5.4).

Conclusion

Early cholecystectomy seems to be a feasible treatment in elderly patients with acute cholecystitis. To reduce morbidity, patients who may benefit from surgery ought to be selected carefully. Future prospective studies should compare early cholecystectomy with alternative treatments to investigate which treatment is most appropriate for elderly patients.

INTRODUCTION

Acute calculous cholecystitis is a complication of cholelithiasis; a condition that afflicts more than 20 million Americans annually.[1] The prevalence of gallstones increases with age: in patients aged ≥ 60 the prevalence ranges from 20% to 30%[2,3] and increases to 80% in institutionalized individuals aged ≥ 90.[4] In the United States, the population aged 65 and over has been estimated to be 43.1 million in 2012 and is projected to be 82.7 million in 2050.[5] As a result, the incidence of acute calculous cholecystitis will also increase.

In young and otherwise healthy patients, early cholecystectomy is generally accepted as the standard treatment of acute cholecystitis.[6-11] It is preferred over delayed cholecystectomy since the latter is associated with higher complication rates, longer hospital stay, higher costs and lower patient satisfaction.[12] In elderly patients, the optimal treatment of acute cholecystitis remains controversial. In view of the ageing population, addressing this controversy becomes a matter of increasing urgency.

Due to comorbidities and reduced physiological reserves, elderly are thought to be at risk for increased perioperative morbidity and mortality. In daily practice, percutaneous drainage is often preferred over cholecystectomy in the elderly population. However, no randomized controlled trials have been published to substantiate this practice. A systematic review published in 2009 analysed the safety and efficacy of percutaneous drainage for acute cholecystitis in elderly and critically ill patients and reported a mortality rate of up to 15%.[13]

In this era of advanced surgical techniques and improved perioperative care, the willingness to offer surgery at initial presentation to elderly patients and those with significant comorbidities continues to increase. This systematic review aims to assess the clinical outcomes of early cholecystectomy in elderly patients with acute cholecystitis.

METHODS

A systematic review was conducted following the guidance of the Centre for Reviews and Dissemination with respect to reviews in health care, and was reported in accordance with the PRISMA statement.[14,15]

Literature search

In July 2016, a literature search was performed by two independent reviewers (CS and DB) to identify studies reporting on early laparoscopic cholecystectomy for acute cholecystitis in the elderly. MEDLINE, Embase and Cochrane Library databases were searched for articles containing the following keywords and/or synonyms: "acute cholecystitis" or "acute calculous cholecystitis" in combination with "cholecystectomy" and "aged" or "geriatrics" or "elderly" or "eldest" or "septuagenarian" or "octogenarian" or "nonagenarian" or "centenarian" or "supercentenarian" or "old" or "older". The search had been limited to articles in English and Dutch and published after January 1990 in order to represent current clinical practice.

Study selection

Duplicates were removed. Titles and abstracts were independently screened by the reviewers (CS and DB) to assess the relevance of the publications. Subsequently, full-text articles were retrieved and checked. The remaining articles were surveyed by cross-reference-search in order to detect studies possibly missed. In case methods or results were unclear, authors were contacted to seek clarification. Excluded were reviews, case-reports and articles of which no full text was available (Figure 8.1). All studies concerning elderly patients (i.e. aged ≥ 70 years) treated with early cholecystectomy for acute calculous cholecystitis were considered eligible for inclusion. The criteria for the diagnosis of acute cholecystitis had to be defined in the article, and acute cholecystitis had to be proven either by ultrasound or histologically.

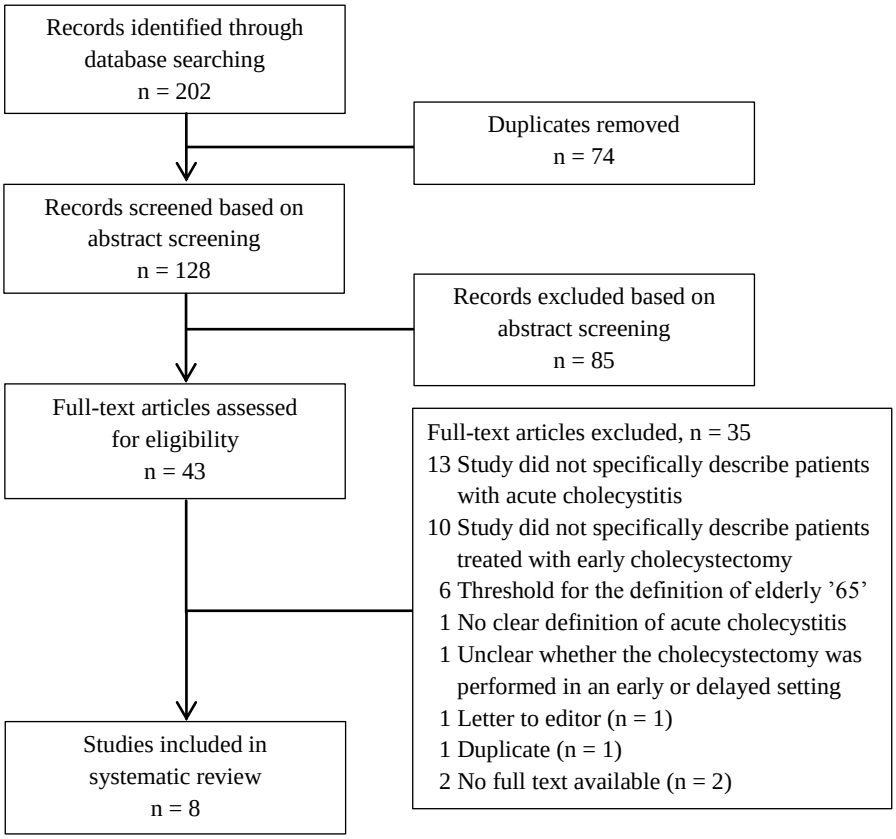
Data collection

Data were extracted from the full-text articles by both reviewers independently. The MINORS (methodological index for non-randomized studies) score was used to assess the risk of bias. The global ideal score being 16 for non-comparative studies and 24 for comparative studies.[16]

Outcomes

The specific outcomes to be assessed were conversion rate from laparoscopic to open cholecystectomy, perioperative morbidity and mortality, and length of hospital stay.

Figure 8.1 PRISMA flow diagram of study selection process



Statistical analysis

The perioperative outcomes were valued based on the proportion of events and the 95% confidence interval. In comparative studies in which data of only one group were relevant, data of only that group were used for the analysis. The estimated pooled event rates were calculated by means of a random-effects model, using meta-analysis software version 3.1. Statistical heterogeneity between the included studies was determined by using forest plots and by performing a X^2 ("chi-squared") heterogeneity test and by calculating the I^2-index. A high I^2-index represents a high suspicion of heterogeneity. All pooled event rates were shown in forest plots, regardless the level of heterogeneity.

RESULTS

Study selection

Figure 8.1 shows the article selection in accordance with the PRISMA statement.[14,15] A total of 202 references were identified through electronic search. Cross-reference-search did not lead to new articles. Seventy-four duplicates were removed and the remaining potentially relevant articles were screened on title and abstract. Eighty-five articles were excluded because of irrelevancy. The remaining 43 manuscripts were assessed for eligibility based on full-text. Eight studies met the inclusion criteria and were used in the final analysis. The reasons for excluding articles are shown in Figure 8.1. Regarding the inclusion of studies, total agreement among both authors (CS and DB) existed.

Characteristics of the included studies

The characteristics of the eight included studies[17-24] are visualized in Table 8.1. Six studies[17-19,21,22,24] identified patients retrospectively, one study[20] retrospectively identified patients from a prospectively maintained database and one study[23] had a prospective design using standardized case report forms to collect data.

Five of the included studies[17-21] were designed to compare the perioperative outcomes of early cholecystectomy for acute cholecystitis in elderly and younger patients. Two studies[22,23] were designed to compare laparoscopic with open cholecystectomy in the early treatment of elderly patients with acute cholecystitis. The remaining study[24] aimed to determine the feasibility of open cholecystectomy in the elderly population.

Risk of bias

Table 8.2 shows the methodological quality assessment of the included studies, all of which had a non-randomized design.

Outcomes

In total, 592 elderly patients treated with early cholecystectomy for acute cholecystitis were identified (Table 8.3). The mean age was 81 years. Nearly half of the patients (44%) had an ASA (American Society of Anaesthesiologist) score ≥ 3. Early cholecystectomy was primarily performed laparoscopically in 316 patients (53%) and open in 276 patients (47%). The operating time varied from 72 to 134 minutes.

Table 8.1 Demographic information of the included studies

Study	Year	Country	Design	N	Threshold for the definition of elderly, years	Mean age, years	Patients with ASA score ≥3, %
Ambe[17]	2015	Germany	R	74	70	78	73
Fuks[18]	2015	France	R	78	75	82	62
Fukami[19]	2014	Japan	R	24	80	NR	12
Nikfarjam[20]	2013	Australia	RP	71	80	NR	51
Fujikawa[21]	2012	Japan	R	27	70	77 *	26
Chau[22]	2002	Hong Kong	R	73	75	80	32
Pessaux[23]	2001	France	P	139	75	82	36
Makinen[24]	1993	Finland	R	106	70	NR	NR

Data are presented as mean unless stated otherwise, * median.

N denotes number of patients, ASA American Society of Anesthesiologist, R retrospective study, P prospective study, RP retrospective analysis of prospectively collected data and NR not reported.

Conversion rate

Seven studies[17-23] reported on the conversion rate from laparoscopic to open cholecystectomy, ranging from 7% to 36%. In total, 69 of the 316 (22%) laparoscopic procedures were converted. The most commonly reported reasons for conversion were concerns regarding anatomy, the presence of common bile duct stones and difficulties with the dissection of Calot's triangle due to severe inflammation. The estimated pooled conversion rate was 23% (95% CI 18.6 - 28.3) (Figure 8.2). Heterogeneity was low between the included studies ($I^2 = 47\%$).

Perioperative morbidity

The perioperative complication rate was reported in all included studies, ranging from 4% to 31% (Table 8.3). Complications either directly or indirectly related to the surgical procedure were seen in 136 (23%) of the 592 patients. A total of 155 complications were reported, being pulmonary complications (n = 43), wound complications (n = 37) cardiac complications (n = 13) bile leakages (n = 12), intra-abdominal abscesses (n = 7), fever of

Table 8.2 Methodological quality of the included studies (MINORS)

Study	Year	Country	Design	N	Threshold for the definition of elderly, years	Mean age, years	Patients with ASA score ≥3, %
Ambe[17]	2015	Germany	R	74	70	78	73
Fuks[18]	2015	France	R	78	75	82	62
Fukami[19]	2014	Japan	R	24	80	NR	12
Nikfarjam[20]	2013	Australia	RP	71	80	NR	51
Fujikawa[21]	2012	Japan	R	27	70	77 *	26
Chau[22]	2002	Hong Kong	R	73	75	80	32
Pessaux[23]	2001	France	P	139	75	82	36
Makinen[24]	1993	Finland	R	106	70	NR	NR

Data are presented as mean unless stated otherwise, * median.

MINORS: methodological index for non-randomised studies. The items are scored as follows: 0 = not reported, 1 = reported but inadequate, 2 = reported and adequate. The global ideal score being 16 for non-comparative studies and 24 for comparative studies.[16]

unknown origin (n = 6), intraperitoneal haemorrhages (n = 5), retained stones (n = 4), septicaemia (n = 4), urinary tract infections (n = 4), delayed gastric emptying (n = 3), acute renal failures (n = 2), pancreatitis (n = 2), strokes (n = 2), thromboembolic complications (n = 1), psychosis (n = 1), iatrogenic complication (n = 1) and non-specified complications (n = 8). The estimated pooled morbidity was 23.8% (95% CI 20.5 - 27.5) (Figure 8.3). The included studies showed a low degree of heterogeneity (I^2 = 27%).

Mortality

All included studies[17-24] reported on the perioperative mortality, ranging from 0 to 5% (Table 8.3). Nineteen of the 592 elderly patients died following early cholecystectomy (3%). The causes of death being pulmonary complications (n = 5), cardiac complications (n = 4), multisystem organ failure (n = 1) and disseminated intravascular coagulopathy due to chronic liver cirrhosis (n = 1). In eight patients the cause of death was not due to chronic liver cirrhosis (n = 1). In eight patients the cause of death was not

Table 8.3 Perioperative outcome of early cholecystectomy for acute cholecystitis in elderly

Study	N	Patients treated with LC/OC, n	Conversion, n (%)	Overall morbidity, n (%)	Mortality, n (%)	Post-operative LOS, days
Ambe[17]	74	65/9	15 (23)	18 (24)	2 (3)	13
Fuks[18]	78	64/14	10 (16)	17 (22)	1 (1)	7 *
Fukami[19]	24	11/13	1 (9)	4 (17)	1 (4)	9
Nikfarjam[20]	71	68/3	14 (21)	22 (31)	3 (4)	7
Fujikawa[21]	27	27/0	2 (7)	1 (4)	0	7
Chau[22]	73	31/42	11 (36)	21 (29)	3 (4)	9
Pessaux[23]	139	50/89	16 (32)	27 (19)	4 (3)	11
Makinen[24]	106	0/106	NA	26 (25)	5 (5)	NR
	592	316/276	69 (22)	136 (23)	19 (3)	

Data are presented as mean unless stated otherwise, * median.

N denotes number of patients, LC laparoscopic cholecystectomy, OC open cholecystectomy, NA not applicable, NR not reported and LOS length of hospital stay.

specified. Three studies (18,19,23) reported the characteristics of the patients who died, showing that they all suffered from severe pre-existent comorbidities or had a poor clinical pre-operative condition. The estimated pooled mortality was 3.5% (95% CI 2.3 - 5.4). There was no heterogeneity between the included studies ($I^2 = 0\%$) (Figure 8.4).

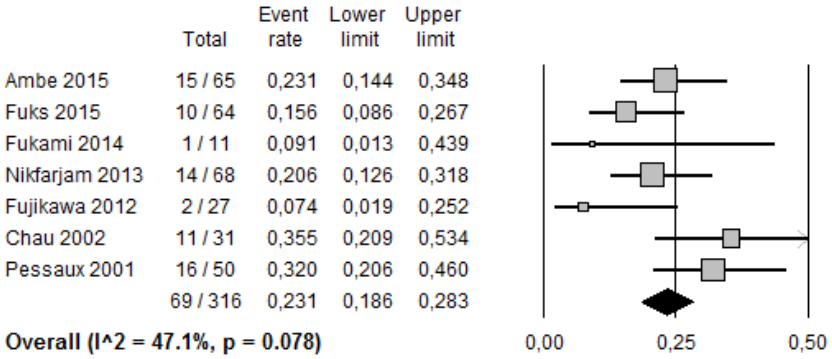
Postoperative length of hospital stay

Seven studies described the postoperative length of hospital stay[17-23]; two[18,20] reported a median duration of seven days and five[17,19,21-23] reported a mean duration of 11 days, ranging from 7 up to 13 days.

DISCUSSION

This systematic review demonstrated that early cholecystectomy for acute cholecystitis in patients aged 70 and older is associated with a perioperative morbidity of 24% and a

Figure 8.2 Forest plot of the conversion rate of early laparoscopic cholecystectomy for acute cholecystitis in elderly patients



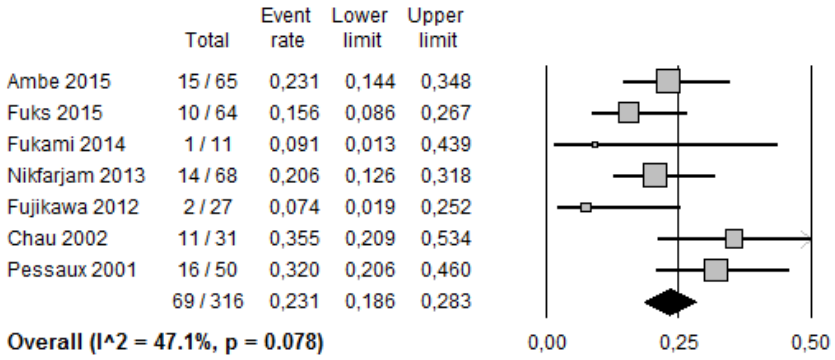
mortality of 3.5%.

These rates are higher than reported for non-elderly patients undergoing emergency cholecystectomy for acute cholecystitis, which has been extensively investigated in previous studies, being approximately 15% and <1%, respectively.[25] Yet, four of the five included studies comparing perioperative outcomes of early cholecystectomy in elderly and younger patients showed no significant difference in terms of perioperative morbidity or mortality.[17-19,21] Only one study proved older age to be independently associated with increased morbidity.[20]

Elderly patients may have more comorbidity and often present with clinical signs of a more severe cholecystitis in terms of systemic sequelae, as compared to younger patients.[17-21] Many of the complications encountered in this meta-analysis, such as pulmonary and cardiac complications as well as death, could be attributed to reduced physiological reserves and pre-existent comorbidities rather than to the surgical procedure itself. Minor complications such as wound infections were also frequently encountered but had minor impact on the final outcome. It is noteworthy that only two studies[17,19] reported on the severity of each complication, both by using the Clavien-Dindo classification.[26] The remaining studies neither mentioned the severity of the complications nor whether or not patients fully recovered from the complications.

Studies focusing on non-elderly patients undergoing early cholecystectomy for acute cholecystitis demonstrated a conversion rate from laparoscopic to open cholecystectomy

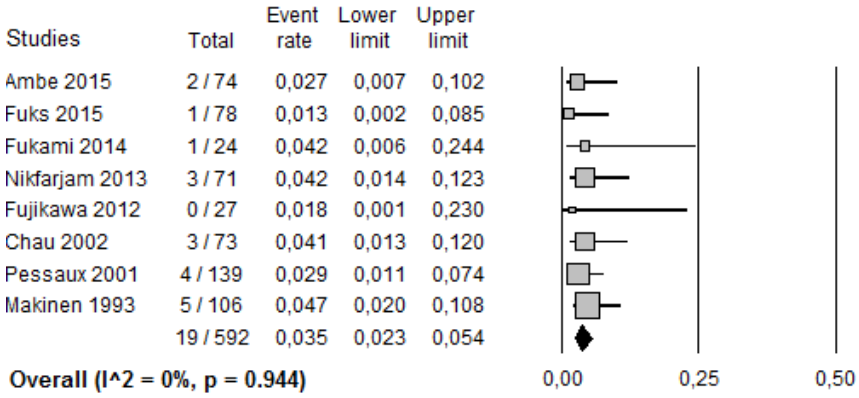
Figure 8.3 Forest plot of the complication rate of early cholecystectomy for acute cholecystitis in elderly patients



of 13%.[25] The present study showed a conversion rate of 23%. This high rate may have resulted in increased perioperative morbidity, as open compared to laparoscopic cholecystectomy for acute cholecystitis is associated with increased risk of complications (28% versus 18%, p = 0.03).[27] A recent meta-analysis of observational studies showed that advanced age is associated with increased risk of conversion, although no obvious explanation is given.[28] Dense adhesions due to previous episodes of complicated gallstone disease or previous abdominal surgery, or perioperative cardiopulmonary complications may be the reason.[19,21] In the present review, only two studies[22,23] reported on the morbidity in the converted patients, showing no significant difference in morbidity with patients successfully treated with laparoscopic cholecystectomy.

An alternative for urgent cholecystectomy in elderly patients is percutaneous drainage in addition to appropriate systemic support and antibiotic treatment. This minimally invasive procedure avoids the risk associated with general anesthesia and can be performed either as a bridge to surgery or as a definitive treatment.[29,30] In the literature, it is described as a rather uncomplicated procedure with low complication rates and high success rates.[31-33] The reported 30-day mortality, however, is higher than that of acute cholecystectomy, but this may likely be a result of selection bias since the available literature is mainly retrospective.[13] Eventually, almost half of the patients treated with percutaneous drainage eventually underwent a cholecystectomy, which indicates that for a large proportion of patients drainage alone is not the definitive treatment.[13] Early

Figure 8.4 Forest plot of the mortality of early cholecystectomy for acute cholecystitis in elderly patients



cholecystectomy in this respect provides a one-shot definitive treatment. Whether emergency cholecystectomy is a better choice than percutaneous drainage remains unclear. A clinical trial comparing both treatment strategies is currently being conducted (CHOCOLATE trial, NTR2666).[34] The results of this trial will become available in 2017.

Conservative management (i.e. non-invasive management) is another option for the treatment of elderly patients with acute cholecystitis. Since the source of infection is not controlled using this approach, though, many patients might still develop biliary sepsis. A prospective study of 53 elderly patients with acute cholecystitis treated conservatively showed that 16 patients (30%) suffered from biliary sepsis requiring emergency surgery, one of whom died.[35] A prospective study of 42 elderly patients with acute cholecystitis and an APACHE-II score $\geq$ 12 showed that 7 patients (17%) suffered from ongoing sepsis, all of whom died.[36] In addition, since the gallbladder is left in situ, there is a chance of recurrent gallstone related disease of at least 22%.[37]

Although increased morbidity and mortality are inextricably linked to any treatment strategy for acute cholecystitis in elderly patients, the outcome of early cholecystectomy in elderly patients may be improved by several measures.

Firstly, applying strict criteria to select patients who might benefit from early cholecystectomy may contribute to a better perioperative outcome. Fuks et al.[18] assessed the perioperative outcome of early cholecystectomy in elderly patients and included only patients with grade I and grade II acute cholecystitis based on the severity assessment

criteria of the Tokyo Guidelines.[38] Patients with either grade III acute cholecystitis (i.e. cholecystitis accompanied by organ dysfunction) or complaints lasting longer than 5 days were excluded. Early cholecystectomy in the grade I and II group turned out to be associated with a perioperative outcomes similar to that observed in their younger counterparts, and is assumed to be appropriate and safe. To reduce the risk of perioperative morbidity and mortality, a severity assessment of pre-existing comorbid conditions should be performed. This review showed that patients who died had been suffering from severe pre-existent comorbidities or a poor clinical preoperative condition.[18,19,23] Careful selection of elderly patients who may benefit from surgery, i.e. patients in good physical health with few comorbidities, may contribute to a better perioperative outcome.

Secondly, elderly surgical patients require a different level of perioperative care than younger patients. To provide optimal care, a thorough preoperative assessment of the individual's health status is essential to identify factors associated with increased risks of specific complications and to recommend a management plan that could minimize these risks.[39] Specialists from multiple disciplines should be involved in the preoperative optimization of comorbidities and the correction of system deficits.

Thirdly, early cholecystectomy in elderly patients with acute cholecystitis should be performed with the utmost care and prudence. A laparoscopic procedure rather than an open procedure is preferred.[27] Previous studies have shown that laparoscopic cholecystectomy is more succesful if carried out by a laparoscopy-oriented surgeon.[40,41] In the present study, the conversion rate appeared to be 18% if only studies reporting on early cholecystectomy performed by experienced laparoscopic surgeons or performed in a centre specialized in laparoscopic surgery were considered.[17,18,20,21]

Lastly, elderly patients require specialized postoperative care since they are prone to developing postoperative complications including pulmonary complications, under nutrition, urinary tract infections, ulcers, delirium and functional decline.[39] Education of health care providers in core geriatric principles, risk factors, the incorporation of evidence-based interventions and interdisciplinary communication may contribute to improvement of postoperative outcome.

Conclusions based on this systematic review should be drawn with caution. Firstly, all but one study had a retrospective design, carrying the risk of selection bias. The choice of treatment was mostly made at the surgeon's discretion and there was a lack of clear

criteria for the assignment of patients to early cholecystectomy. The included studies were methodologically of an estimated poor to moderate quality as demonstrated by the MINORS scores in Table 8.2. Secondly, the definition of early cholecystectomy was not unequivocal. Four studies[17,19,21,23] used this term to indicate cholecystectomy performed within three days of onset of symptoms, one study[18] used this term to indicate surgery within five days, whereas three studies[20,22,24] used the term 'urgent cholecystectomy without specifying the duration of complaints prior to surgery. Furthermore, data possibly relevant in the treatment of elderly such as rate of perioperative delirium, rate of functional decline and rate of exacerbation of underlying comorbid conditions were not available.

This is the first systematic review examining the clinical outcomes of early cholecystectomy for acute cholecystitis in elderly patients. Based on the best available evidence, early surgical management seems to be a feasible treatment in this patient group. To reduce the risk of perioperative complications, elderly who may benefit from surgery should be carefully selected, the procedure should be performed by an experienced laparoscopic surgeon and appropriate perioperative care should be available. Whether early cholecystectomy or percutaneous drainage is better suited in elderly patients with acute cholecystitis will be demonstrated by an ongoing randomized trial.[34]

REFERENCES

1. Everhart JE, Khare M, Hill M, Maurer KR. Prevalence and ethnic differences in gallbladder disease in the United States. Gastroenterology 1999;117(3):632-639.

2. Lirussi F, Nassuato G, Passera D, Toso S, Zalunardo B, Monica F, et al. Gallstone disease in an elderly population: the Silea study. Eur J Gastroenterol Hepatol 1999;11(5):485-492.

3. Festi D, Dormi A, Capodicasa S, Staniscia T, Attili AF, Loria P, et al. Incidence of gallstone disease in Italy: results from a multicenter, population-based Italian study (the MICOL project). World J Gastroenterol 2008;14(34):5282-5289.

4. Ratner J, Lisbona A, Rosenbloom M, Palayew M, Szabolcsi S, Tupaz T. The prevalence of gallstone disease in very old institutionalized persons. JAMA 1991;265 (7):902-903.

5. Ortman JM, Velkoff VA, Hogan H. An aging nation: the older population in the United States. Washington, DC: US Census Bureau 2014:25-1140.

6. Papi C, Catarci M, D'ambrosio L, Gili L, Koch M, Grassi GB, et al. Timing of cholecystectomy for acute calculous cholecystitis: a meta-analysis. Am J Gastroenterol 2004;99(1):147-155.

7. Gurusamy KS, Davidson C, Gluud C, Davidson BR. Early versus delayed laparoscopic cholecystectomy for people with acute cholecystitis. Cochrane Database Syst Rev 2013;6.

8. Gurusamy K, Samraj K, Gluud C, Wilson E, Davidson B. 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.

9. Gutt CN, Encke J, Koninger J, Harnoss JC, Weigand K, Kipfmuller K, et al. Acute cholecystitis: early versus delayed cholecystectomy, a multicenter randomized trial (ACDC study, NCT00447304). Ann Surg 2013 Sep;258(3):385-393.

10. Kolla S, Aggarwal S, Kumar A, Kumar R, Chumber S, Parshad R, et al. Early versus delayed laparoscopic cholecystectomy for acute cholecystitis: a prospective randomized trial. Surgical Endoscopy and Other Interventional Techniques 2004;18 (9):1323-1327.

11. Banz V, Gsponer T, Candinas D, Guller U. Population-based analysis of 4113 patients with acute cholecystitis: defining the optimal time-point for laparoscopic cholecystectomy. Ann Surg 2011 Dec;254 (6):964-970.

12. Song G, Bian W, Zeng X, Zhou J, Luo Y, Tian X. Laparoscopic cholecystectomy for acute cholecystitis: early or delayed?: Evidence from a systematic review of discordant meta-analyses. Medicine 2016; 95(23):e3835.

13. Winbladh A, Gullstrand P, Svanvik J, Sandström P. Systematic review of cholecystostomy as a treatment option in acute cholecystitis. HPB 2009;11(3):183-193.

14. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;151(4):W-65-W-94.

15. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009; 151(4):264-269.

16. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (MINORS): development and validation of a new instrument. ANZ J Surg 2003;73(9): 712-716.

17. Ambe PC, Weber SA, Christ H, Wassenberg D. Primary cholecystectomy is feasible in elderly patients with acute cholecystitis. Aging Clin Exp Res 2015 Dec;27(6):921-926.

18. Fuks D, Duhaut P, Mauvais F, Pocard M, Haccart V, Paquet JC, et al. A retrospective comparison of older and younger adults undergoing early laparoscopic cholecystectomy for mild to moderate calculous cholecystitis. J Am Geriatr Soc 2015 May;63(5):1010-1016.

19. Fukami Y, Kurumiya Y, Mizuno K, Sekoguchi E, Kobayashi S. Cholecystectomy in octogenarians: be careful. Updates Surg 2014 Dec;66(4):265-268.

20. Nikfarjam M, Yeo D, Perini M, Fink MA, Muralidharan V, Starkey G, et al. Outcomes of cholecystectomy for treatment of acute cholecystitis in octogenarians. ANZ J Surg 2014 Dec;84(12): 943-948.

21. Fujikawa T, Tada S, Abe T, Yoshimoto Y, Maekawa H, Shimoike N, et al. Is early laparoscopic cholecystectomy feasible for acute cholecystitis in the elderly? J Gastroenterol Hepatol 2012 /;1(10):247-251.

22. Chau CH, Tang CN, Siu WT, Ha JP, Li MK. Laparoscopic cholecystectomy versus open cholecystectomy in elderly patients with acute cholecystitis: retrospective study. Hong Kong Med J 2002 Dec;8(6): 394-399.

23. Pessaux P, Regenet N, Tuech JJ, Rouge C, Bergamaschi R, Arnaud JP. Laparoscopic versus open cholecystectomy: a prospective comparative study in the elderly with acute cholecystitis. Surg Laparosc Endosc Percutan Tech 2001 Aug;11(4): 252-255.

24. Makinen AM, Nordback I. Conventional cholecystectomy in elderly patients. Ann Chir Gynaecol 1993;82(4):241-244.

25. Cao AM, Eslick GD, Cox MR. Early cholecystectomy is superior to delayed cholecystectomy for acute cholecystitis: a meta-analysis. Journal of Gastrointestinal Surgery 2015;19(5):848-857.

26. Dindo D, Demartines N, Clavien P. 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.

27. Coccolini F, Catena F, Pisano M, Gheza F, Fagiuoli S, Di Saverio S, et al. Open versus laparoscopic cholecystectomy in acute cholecystitis. Systematic review and meta-analysis. International Journal of Surgery 2015;18:196-204.

28. Philip Rothman J, Burcharth J, Pommergaard HC, Viereck S, Rosenberg J. Preoperative Risk Factors for Conversion of Laparoscopic Cholecystectomy to Open Surgery - A Systematic Review and Meta-Analysis of Observational Studies. Dig Surg 2016;33(5): 414-423.

29. Simorov A, Ranade A, Parcells J, Shaligram A, Shostrom V, Boilesen E, et al. Emergent cholecystostomy is superior to open cholecystectomy in extremely ill patients with acalculous cholecystitis: a large multicenter outcome study. The American Journal of Surgery 2013;206(6): 935-941.

30. Kapan M, Onder A, Tekbas G, Gul M, Aliosmanoglu I, Arikanoglu Z, et al. Percutaneous cholecystostomy in high-risk elderly patients with acute cholecystitis: a lifesaving option. Am J Hosp Palliat Care 2013 Mar;30(2):167-171.

31. Melloul E, Denys A, Demartines N, Calmes J, Schäfer M. Percutaneous drainage versus emergency cholecystectomy for the treatment of acute cholecystitis in critically ill patients: does it matter? World J Surg 2011;35(4):826-833.

32. McKay A, Abulfaraj M, Lipschitz J. Short- and long-term outcomes following percutaneous cholecystostomy for acute cholecystitis in high-risk patients. Surg Endosc 2012;26(5):1343-1351.

33. Horn T, Christensen SD, Kirkegård J, Larsen LP, Knudsen AR, Mortensen FV. Percutaneous cholecystostomy is an effective treatment option for acute calculous cholecystitis: a 10-year experience. HPB 2015;17(4):326-331.

34. Kortram K, van Ramshorst B, Bollen TL, Besselink MG, Gouma DJ, Karsten T, et al. Acute cholecystitis in high risk surgical patients: percutaneous cholecystostomy versus laparoscopic cholecystectomy (CHOCOLATE trial): study protocol for a randomized controlled trial. Trials 2012; 13(1):1.

35. Vracko J, Markovic S, Wiechel K. Conservative treatment versus endoscopic sphincterotomy in the initial management of acute cholecystitis in elderly patients at high surgical risk. Endoscopy 2006;38 (08):773-778.

36. Hatzidakis AA, Prassopoulos P, Petinarakis I, Sanidas E, Chrysos E, Chalkiadakis G, et al. Acute cholecystitis in high-risk patients: percutaneous cholecystostomy vs conservative treatment. Eur Radiol 2002;12(7):1778-1784.

37. Loozen CS, Oor JE, van Ramshorst B, van Santvoort HC, Boerma D. Conservative treatment of acute cholecystitis: a systematic review and pooled analysis. Surg Endosc 2016:1-12.

38. Yokoe M, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Gomi H, et al. TG13 diagnostic criteria and severity grading of acute cholecystitis (with videos). Journal of hepato-biliary-pancreatic sciences 2013;20(1):35-46.

39. ACS NSQIP/American Geriatrics Society. Optimal Perioperative Management of the Geriatric Patient. Available at: https://www.facs.org/~/media/files/quality%20programs/geriatric/acs%20nsqip%20geriatric%202016%20guidelines.ashx.

40. Boddy A, Bennett J, Ranka S, Rhodes M. Who should perform laparoscopic cholecystectomy? A 10-year audit. Surg Endosc 2007;21(9):1492-1497.

41. Kortram K, Reinders JSK, van Ramshorst B, Wiezer MJ, Go PM, Boerma D. Laparoscopic cholecystectomy for acute chole-cystitis should be performed by a laparoscopic surgeon. Surg Endosc 2010; 24(9):2206-2209.

CHAPTER 9

Laparoscopic cholecystectomy versus percutaneous catheter drainage for high-risk patients with acute cholecystitis

Submitted

C. S. Loozen
H. C. van Santvoort
P. van Duijvendijk
M. G. H. Besselink
D. J. Gouma
G. A. P. Nieuwenhuijzen
J. C. Kelder
S. C. Donkervoort
N. A. W. van Geloven
P. M. Kruyt
D. Roos
K. Kortram
V. N. N. Kornmann
A. Pronk
D. L. van der Peet
R. M. Crolla
B. van Ramshorst
T. L. Bollen
D. Boerma

ABSTRACT

Background

Previous studies have suggested that laparoscopic cholecystectomy in high-risk patients with acute cholecystitis is associated with high morbidity and mortality. Percutaneous catheter drainage is gaining popularity as a less invasive alternative treatment, but evidence to support this strategy is limited.

Methods

We performed a nationwide randomized trial comparing laparoscopic cholecystectomy to percutaneous catheter drainage in high-risk patients with acute calculous cholecystitis. High-risk was defined as an APACHE-II score ≥7. The primary end point was a composite of major complications within 30 days and reintervention (i.e., surgical, radiological or endoscopic), readmission or death within one year.

Results

The trial was concluded early after a planned interim-analysis. Data from 134 randomized patients were analyzed. The primary end point occurred in 10 of 66 patients (15%) assigned to laparoscopic cholecystectomy and in 46 of 68 patients (68%) assigned to percutaneous catheter drainage (risk ratio with laparoscopic cholecystectomy, 0.22; 95% confidence interval, 0.12 to 0.41; P<0.001). In the percutaneous drainage group, 45 patients (66%) required a reintervention, as compared with 8 patients (12%) in cholecystectomy group (P<0.001). Readmissions occurred more often in the percutaneous drainage group (62% versus 11%, P<0.001) and the median length of hospital stay was longer (9 days versus 5 days, P<0.001). The rate of death did not differ between groups (9% versus 3%, P=0.70).

Conclusion

Laparoscopic cholecystectomy, as compared with percutaneous catheter drainage, reduced the rate of the composite end point of major complications, reintervention, readmission and death in high-risk patients with acute cholecystitis (Netherlands Trial Register Number, NTR2666).

INTRODUCTION

Acute cholecystitis is a common indication for hospital admission and an increasing burden on the Western health care system. In the United States, the total number of hospital admissions for acute cholecystitis from 1997 to 2012 increased by 44% from 149,661 to 215,995.[1]

In young, otherwise healthy patients early laparoscopic cholecystectomy is considered the treatment of choice for acute calculous cholecystitis.[2] In high-risk patients the management of acute cholecystitis remains controversial. Cholecystectomy in these patients can lead to serious morbidity and mortality due to reduced physiologic reserve.[3-8] Therefore, imaging-guided percutaneous catheter drainage is increasingly being performed as an alternative to early cholecystectomy. This minimally invasive radiological procedure resolves local and systemic inflammation without the risks of surgery. According to international guidelines, it is a valuable treatment in high-risk patients and in patients with moderate and severe cholecystitis.[9] A drawback of percutaneous catheter drainage, however, is that it is not a definitive treatment since the gallbladder is not removed. This may lead to recurrent cholecystitis and other biliary complications with severe clinical impact.[10,11]

There are no randomized studies comparing laparoscopic cholecystectomy with percutaneous catheter drainage in patients with acute cholecystitis. It therefore remains unclear which treatment should be preferred in terms of clinical and economical outcomes. In daily practice, both cholecystectomy and percutaneous catheter drainage are performed according to the preference of the treating surgeon, gastroenterologist or other clinicians.

We performed a nationwide randomized trial (CHOCOLATE) to assess whether laparoscopic cholecystectomy is superior to percutaneous catheter drainage in high-risk patients with acute calculous cholecystitis.

METHODS

Study design

The protocol and rationale of this study have been previously described.[12] Adult patients with acute calculous cholecystitis and a high surgical risk were enrolled in 11 teaching

hospitals in the Netherlands. Acute cholecystitis was defined according to the Tokyo Guidelines.[13] Risk assessment was based on the APACHE-II severity of disease classification system.[14] High risk was defined as an APACHE-II score of ≥7. This cut-off was chosen based on the systematic evaluation of a number of imaginary case scenarios by a multicenter, multidisciplinary expert panel of surgeons, gastroenterologists and radiologists. Patients with an APACHE-II score ≥15 were excluded because the risk of mortality in these patients was deemed too high, i.e., disease severity and/or co-morbidity presented a strict contra-indication for surgery. We also excluded patients with symptoms that lasted longer than 7 days at time of first presentation, since these patients should undergo delayed cholecystectomy according to the Dutch treatment guidelines.[15] Other exclusion criteria were pregnancy, decompensated liver cirrhosis, admission to the ICU at the time of diagnosis of cholecystitis and mental illness prohibiting informed consent.

Patients were randomly assigned to either laparoscopic cholecystectomy or percutaneous catheter drainage, both to be performed within 24 hours after randomization. Randomization was performed using an online module. Permuted-block randomization with varying block sizes with a maximum block size of four patients was used. Randomization was stratified according to treatment center.

Study oversight

The study was investigator-initiated and conducted in accordance with the principles of the Declaration of Helsinki. The protocol was approved by the institutional review board of each participating center. The safety and efficacy of the trial was monitored by a data safety monitoring board (DSMB) consisting of three independent, non-participating clinicians and an independent epidemiologist. All patients or their legal representatives provided written informed consent.

Procedures

Laparoscopic cholecystectomy was performed by the four-trocar technique with transection of the cystic duct and artery after reaching the critical view of safety as described in the national and international guidelines.[15,16] The procedures were performed by surgeons experienced in laparoscopic surgery, defined as performing more than 100 laparoscopic procedures on a yearly basis. Patients received a single dose of preoperative antibiotic prophylaxis according to the local hospital protocol.

Percutaneous catheter drainage was performed under aseptic circumstances with image guidance using either ultrasound or computed tomography. The transhepatic or transperitoneal route was used depending on the preference of the interventional radiologist and the location of the gallbladder. Emergency cholecystectomy was performed in case of clinical deterioration, persisting fever or an increase in the serum white blood cell count or C-reactive protein within 48 hours, despite accurate position and function of the drain.

Patients were discharged with the percutaneous drain. The drain was left in place during a period of three weeks. Before removal of the drain, antegrade cholangiography was performed to assess whether there was duodenal backflow and a patent cystic duct. Further treatment was left to the discretion of the treating clinician.

Data collection and outcomes

The primary end point was a composite of major complications within 30 days and reintervention (i.e., surgical, radiological or endoscopic), readmission or death within one year. Detailed definitions are given in Table 9.1. Reinterventions and readmissions had to be directly/indirectly related to acute cholecystitis. The secondary end points included the individual components of the primary outcome, minor complications, difficulty of cholecystectomy (as scored by VAS 1 to 10), health care resource utilization and total costs. Details on cost calculation are provided in the Supplementary Appendix.

Follow-up took place at the outpatient clinic three weeks after discharge and subsequently by means of a phone call once every month during one year. Data collection was performed by local clinicians using case record forms. The study coordinator verified all completed forms in accordance with on-site source data. Discrepancies detected by the study coordinator were resolved through consensus by two investigators not involved in patient care.

A blinded assessment of primary and secondary outcomes was performed by an adjudication committee consisting of four experienced surgeons and one radiologist. Each committee member individually evaluated the data of every patient presented in a standardized format, including all available data collected during follow-up. Disagreement was resolved in a plenary consensus meeting with concealment of the treatment assignment.

Table 9.1 Definitions of the Primary End Point

End Point	Definition	Comment
Major complication		Within 30 days after randomization
Intra-abdominal abscess	Fever and/or elevated CRP and/or WBC and intra-abdominal fluid collection on CT-imaging or ultrasound	
Biliary injury	All injuries of the intra- and extrahepatic biliary ducts including leakage of the biliary tree according to the Amsterdam classification[32]	Type A: leakage of the minor hepatic ducts or cystic duct, Type B: leakage of CBD without stricture, Type C: stricture of the CBD without bile leakage, Type D: complete transection of the CBD with or without resection of a part of it.
Bleeding	Drop in haemoglobin level requiring transfusion and/or reintervention	
Pneumonia	Coughing or dyspnoea, radiography with infiltrative abnormalities, elevated infection parameters and positive sputum culture	
Myocardial infarction	Symptomatic elevated cardiac enzymes and abnormalities on electrocardiography or cardiac ultrasound	
Cerebrovascular	(Temporary) loss of function of any body part or sense caused by cerebral ischemia or bleeding, proven on cerebral CT-imaging	
Thrombo-embolic	Symptomatic deep venous thrombosis or pulmonary embolism, radiologically proven	

Reintervention	Surgical, endoscopic or radiological reintervention	Within one year after randomization. Before analysis, the adjudication committee decided to only report reinterventions and readmissions directly/indirectly related to acute cholecystitis. A routine elective cholecystectomy after percutaneous catheter drainage was not included in the primary endpoint (i.e. only cholecystectomies for recurrent gallstone related complications were included).
Readmission		Within one year after randomization. Before analysis, the adjudication committee decided to only report reinterventions and readmissions directly/indirectly related to acute cholecystitis. Readmission for a routine elective cholecystectomy after percutaneous catheter drainage was not included in the primary end point.
Death		Within one year after randomization.

CRP denotes C-reactive protein, WBC white blood cell, CT computed tomography and CBD common bile duct.

Statistical analysis

The sample size calculation was based on an expected reduction of the primary end point from 28% in the percutaneous drainage group to 15% in the cholecystectomy group.[12] This was based on the results of a Dutch retrospective cohort study and a systematic review analyzing the safety and effectiveness of percutaneous drainage in elderly and critically ill patients.[8,17] To show this effect with 80% power, a two-sided alpha level of 5% and a loss-to follow-up of 1%, at least 284 patients in total were needed.

Primary analyses were performed in accordance with a pre-established analysis plan and according to the intention-to-treat principle. Differences between groups were expressed as risk ratios with corresponding 95% confidence interval. For continuous variables, differences were calculated with the student's t test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. A two-tailed P value < 0.05 was considered statistically significant. All P values are two-sided and not corrected for multiple testing.

In the original study protocol,[12] an interim-analysis for efficacy was specified after the first year of inclusion because it was anticipated that half the number of required patients would have been randomized at that time. The accrual rate was, however, slower than expected. Therefore, the interim analysis was conducted at a later stage at the time when half the sample size had been reached. The occurrence of the primary end point was compared between the treatment groups. The Peto approach was followed, meaning that the study would only be stopped for beneficial effects in case of a P value <0.001. The results of the interim analysis were evaluated by the independent DSMB.

RESULTS

Premature termination of the study

In December 2015, a formal interim analysis for the primary end point was performed. Data on 138 patients were reviewed, 118 of whom had completed follow-up. The P value of the difference between both groups was below the pre-specified threshold value of 0.001. Motivated by considerations of the beneficial effect of laparoscopic cholecystectomy and concerns about negative outcomes in the percutaneous drainage group, on February 26, 2016, the DSMB recommended termination of the trial. All

patients who had undergone randomization before this date were followed until study completion.

Study participants

Between February 2011 and February 2016, a total of 790 patients with acute calculous cholecystitis were assessed for eligibility, 142 of whom underwent randomization and completed follow-up. A total of 8 patients were excluded from subsequent analyses because they revoked informed consent or did not meet the inclusion criteria in retrospect. (Figure 9.1). Baseline characteristics of the treatment groups were similar, with the exception of mean age (71.4±10.6 versus 74.9±8.6, P=0.04) and the number of patients with cardiovascular disease (58% versus 78%, P=0.01) (Table 9.2).

Laparoscopic cholecystectomy

Laparoscopic cholecystectomy was performed in 64 out of 66 in this group. One patient underwent endoscopic retrograde cholangiopancreatography (ERCP) because of concomitant cholangitis and one patient was treated conservatively because of hyponatremia. Both underwent elective cholecystectomy several weeks after discharge. In 11 patients (17%), the laparoscopic procedure had to be converted to an open cholecystectomy. The median difficulty of the operation as scored by the performing surgeon was 8 (range, 1 to 10). Details are provided in the Supplementary Appendix.

Percutaneous catheter drainage

Percutaneous catheter drainage was performed in all 68 patients assigned to this group. The procedure was technically successful in 65 patients (96%). In three patients the radiologist failed to place the percutaneous tube into the gallbladder lumen; two of these patients were treated conservatively until resolution of symptoms and one required emergency cholecystectomy due to gallbladder perforation with extravasation of contrast fluid resulting in severe abdominal pain. Clinical improvement within 48 hours occurred in 63 of the 68 patients (93%). In one patient an emergency cholecystectomy was performed due to clinical deterioration.

Table 9.2 Baseline Characteristics of the Included Patients * †

Characteristics	Laparoscopic cholecystectomy (n = 66)	Percutaneous drainage (n = 68)
Age - yr	71.4±10.6	74.9±8.6
Male sex - no. (%)	41 (62)	44 (65)
Body-mass index ‡	28.7±5.3	29.0±5.5
Coexisting conditions - no. (%)		
Cardiovascular disease	38 (58)	53 (78)
Pulmonary disease	13 (20)	14 (21)
Chronic renal insufficiency	3 (5)	5 (7)
Diabetes	13 (20)	16 (24)
Previous abdominal surgery - no. (%)	16 (24)	10 (15)
ERCP before randomization - no. (%)	3 (5)	4 (6)
ASA classification on admission - no. (%)		
I: healthy status	10 (15)	4 (6)
II: mild systemic disease	33 (50)	37 (54)
III: severe systemic disease	23 (35)	24 (35)
IV: severe systemic disease that is a constant threat to life	0	3 (4)
Disease severity		
APACHE-II score §	9.5±1.9	9.4±2.0
C-reactive protein - mg/liter	218.5±117.2	214.7±123.8
White blood cell count - x10 -9/liter ¶	17.0±5.1	17.2±5.2
Body temperature - ºC ‖	37.7±1.1	37.8±0.9
Time since onset of symptoms - days **		
Median	3	2
Range	1-5	1-7

* Plus–minus values are means ±SD. † The baseline characteristics were similar in the two treatment groups, with the exception of mean age (P=0.04) and proportion of patients with cardiovascular disease (P=0.01). ‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data on the body-mass index were missing for 12 patients in the cholecystectomy group and 9 patients in the drainage group. § Scores on the Acute Physiologic and Chronic Health Evaluation II (APACHE II) scale range from 0 to 71, with higher scores indicating

more severe disease. ¶ Data on the white blood cell count were missing for 1 patient in the drainage group. ‖ Data on the body temperature were missing for 5 patients in the cholecystectomy group and 2 patients in the drainage group. ** The time since onset of symptoms was 7 days or less in all patients. In 5 patients in the drainage group, however, data on the exact number of days were missing.

ERCP denotes endoscopic retrograde cholangiopancreatography and ASA American Society of Anaesthesiologists.

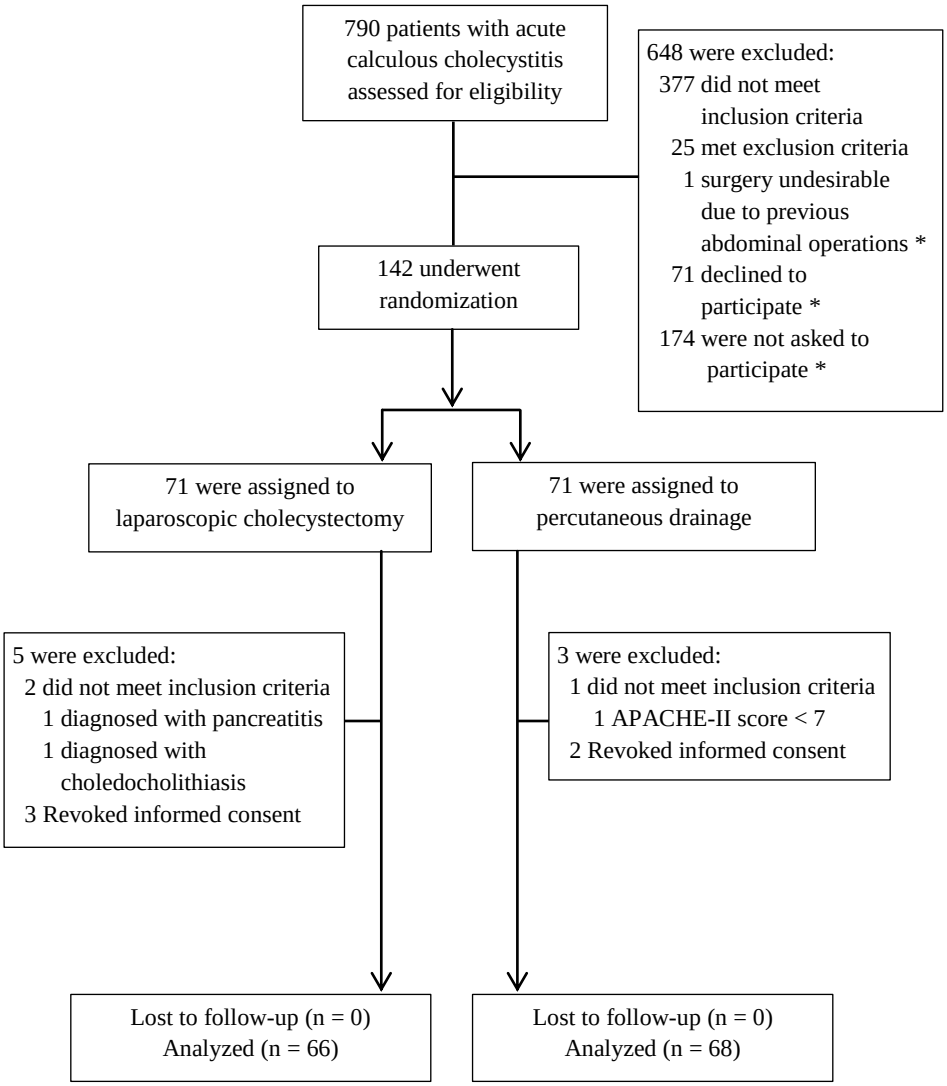
Study outcomes

The composite primary end point of major complications, reintervention, readmission or death occurred in 10 of the 66 patients (15%) assigned to laparoscopic cholecystectomy and in 46 of the 68 patients (68%) assigned to percutaneous drainage (risk ratio with laparoscopic cholecystectomy, 0.22; 95% confidence interval, 0.12 to 0.41; P<0.001) (Table 9.3). These results did not change after *post hoc* adjustment for baseline differences in age and cardiovascular disease using multivariable logistic regression (adjusted odds ratio with laparoscopic cholecystectomy, 0.08; 95% confidence interval, 0.03 to 0.20; P<0.001).

The rate of major and minor complications between the two treatment groups did not significantly differ (Table 9.3). Reinterventions related to cholecystitis, however, were performed less often after laparoscopic cholecystectomy as compared with percutaneous drainage (12% versus 66%, P<0.001) (Table 9.3). Readmissions related to cholecystitis also occurred less often in patients assigned to laparoscopic cholecystectomy (11% versus 62%, P<0.001), including emergency admissions (8% versus 43% P<0.001) (Table 9.3).

The rate of death did not significantly differ between the two treatment groups; two patients (3%) in the cholecystectomy group and six patients (9%) in the percutaneous drainage group died (P=0.27). Deaths in the cholecystectomy group occurred during follow-up and were related to oesophageal and colorectal cancer. In the percutaneous drainage group two patients died during index admission as a result of ongoing sepsis due to the acute cholecystitis, one patient died during readmission from sepsis due to recurrent cholecystitis and one patient died at home by an unknown cause, one week after removal of the percutaneous drain. The remaining two patients died during follow-up from mesothelioma and intestinal ischemia.

Figure 9.1 Enrollment, Randomization and Follow-up of the Study Patients



* Patients who were eligible for inclusion but did not participate in the trial. The baseline characteristics of these patients were similar to those of the included patients, with the exception of the APACHE-II score, which was higher in the included group (9.4 versus 9.0, P=0.01) (Table S9.2 in the Supplementary Appendix).

APACHE denotes acute physiology and chronic health evaluation.

Health care resource utilization and costs

The total length of hospital stay (including readmissions) was five days (range, 2 to 54) in the cholecystectomy group and nine days (range, 2 to 52) in the percutaneous drainage group (P<0.001) (Table 9.3). The total number of emergency room visits was seven and 56, respectively (P<0.001). The total number of readmissions was nine in the cholecystectomy group and 67 in the percutaneous drainage group (P<0.001) and the total number of reinterventions 21 and 64, respectively (P<0.001).

The mean direct medical costs per patient during a follow-up period of one year after randomization were €5568 ($6125) for laparoscopic cholecystectomy and €8283 ($9111) for percutaneous drainage, with a mean absolute difference of €2715 ($2987) per patient. Details of costs are given in Table S9.1 in the Supplementary Appendix.

DISCUSSION

This study showed that laparoscopic cholecystectomy is superior to percutaneous catheter drainage in the treatment of high-risk patients with acute calculous cholecystitis. Cholecystectomy not only reduced the rate of the composite end point of major complications, reintervention, readmission and death, but also reduced health care resource utilization and costs by more than 30%.

Previous studies demonstrated that percutaneous catheter drainage for acute cholecystitis in high-risk patients has a high short-term success rate.[8,18-23] Our study supports these findings with prompt clinical improvement in over 90% of patients undergoing percutaneous drainage. However, the high rate of recurrent gallstone related disease in our study is reason for concern. More than half of the patients in the percutaneous drainage group developed recurrent symptoms requiring (emergency) readmissions and/or reinterventions, a much higher rate than reported in previous studies.[19,20,24,25] This may be explained by the randomized design of our study and the fact that we only included high-risk patients.

The rate of recurrent gallstone related symptoms after percutaneous catheter drainage could have been lower if all patients would have undergone elective cholecystectomy. Routine elective cholecystectomy was not part of the study design because one of the advantages of percutaneous catheter drainage is the avoidance of complications related to surgery. For that reason, several authors suggest that elective cholecystectomy after

Table 9.3 Primary and Secondary End Points

Outcome	Laparoscopic cholecystectomy (n = 66)	Percutaneous drainage (n = 68)	Risk Ratio (95% CI)	P-Value
Primary composite end point *				
Major complication, reintervention, readmission, or death - no (%)	10 (15)	46 (68)	0.22 (0.12-0.41)	<0.001
Secondary end points *				
Major complication - no. (%)	6 (9)	4 (6)	1.55 (0.46-5.23)	0.53
Intra-abdominal abscess	4 (6)	2 (3)		
Biliary injury	4 (6)	2 (3)		
Pneumonia	2 (3)	1 (2)		
Reintervention - no. (%)	8 (12)	45 (66)	0.18 (0.09-0.36)	<0.001
Surgical intervention - no. (%)	3 (5)	32 (47)	0.10 (0.03-0.30)	<0.001
Emergency cholecystectomy	NA	11 (16)		
Clinical deterioration	NA	2 (3)		
Recurrent cholecystitis	NA	9 (13)		
Elective cholecystectomy †	2 (2)	20 (29)		
Recurrent gallstone related disease	NA	15 (22)		
Dysfunctional drain ‡	NA	1 (2)		
Absence of duodenal backflow revealed by cholangiography ‡	NA	4 (6)		
Cholecystectomy not performed during index admission ‡	2 (2)	NA		
Diagnostic laparoscopy	1 (2)	1 (2)		

Endoscopic intervention - no. (%)	6 (9)	11 (16)	0.56 (0.22-1.43)	0.22
ERCP	6 (9)	11 (16)		
Choledocholithiasis	2 (3)	9 (13)		
Biliary injury	4 (6)	2 (3)		
Removal biliary stent	1 (2)	0		
Radiological intervention - no. (%)	4 (6)	15 (22)	0.28 (0.10-0.79)	0.008
Percutaneous catheter drainage	NA	8 (12)		
Recurrent cholecystitis	NA	6 (9)		
Dysfunctional drain	NA	2 (3)		
Drainage abscess	3 (5)	4 (6)		
Drainage biloma	2 (3)	0		
Drainage ascites	0	1 (2)		
Antegrade cholangiography	NA	4 (6)		
Contrast image PTC tube	1 (2)	0		
Readmission - no (%) §	7 (11)	42 (62)	0.17 (0.08-0.36)	<0.001
Emergency readmission - no. (%)	5 (8)	29 (43)	0.18 (0.07-0.43)	<0.001
Recurrent gallstone related disease	4 (6)	29 (43)		
Pneumonia	1 (2)	0		
Planned readmission - no. (%)	4 (6)	21 (31)	0.20 (0.07-0.54)	<0.001
Elective cholecystectomy §	2 (3)	20 (23)		
Elective ERCP	2 (3)	2 (3)		

Table 9.3 Primary and Secondary End Points (*continued)*

Outcome	Laparoscopic cholecystectomy (n = 66)	Percutaneous drainage (n = 68)	Risk Ratio (95% CI)	P-Value
Death - no. (%)	2 (3)	6 (9)	0.34 (0.07-1.64)	0.27
Directly/indirectly related to acute cholecystitis	0	3 (4)		
Unrelated to acute cholecystitis	2 (3)	2 (3)		
Unknown cause of death	0	1 (2)		
Minor complication - no. (%)	0	4 (6)		0.12
Wound infection	0	2 (3)		
Bleeding without need for transfusion	0	0		
Urinary tract infection	0	2 (3)		
Health care utilization				
Length of stay after randomization - days				0.01
Median	4	6		
Range	2-54	2-25		
Total length of hospital stay - days				<0.001
Median	5	9		
Range	2-54	2-52		
Total length of stay in ICU - days				0.16
Median	0	0		
Range	0-36	0-2		
Total no. of ER visits				<0.001

Per study group	7	56	
Range per patient	0-1	0-5	
Total no. of reinterventions			<0.001
Per study group	21	64	
Range per patient	0-6	0-4	
Total no. of readmissions			<0.001
Per study group	9	67	
Range per patient	0-2	0-5	

* Multiple events in the same patient were considered as one end point. † Elective cholecystectomies were not included in the primary end point, unless performed for recurrent gallstone related disease. ‡ These procedures were not included in the primary end point because the adjudication committee judged the indication debatable. § Readmissions to undergo elective cholecystectomy were not included in the primary end point, unless the procedure was performed for recurrent gallstone related disease.

LC denotes laparoscopic cholecystectomy, PD percutaneous drainage, ERCP endoscopic retrograde cholangiopancreatography, PTC percutaneous transhepatic cholangiography, ICU intensive care unit, ER emergency room and NA not applicable.

percutaneous catheter drainage should not be performed in high-risk patients.[22,26-28] Our findings, however, support routine cholecystectomy in all patients who have undergone percutaneous catheter drainage, as promoted by others.[29-31] Alternatively, only patients who are especially at risk for recurrent gallstone related disease could undergo cholecystectomy. There are, however, no studies that have evaluated clinical, biochemical or radiological predictors for failure of percutaneous catheter drainage in acute cholecystitis. Antegrade cholangiography may help to select patients who benefit from elective surgery. Our study, however, was not designed to evaluate the value of cholangiography following percutaneous catheter drainage. Further prospective studies on this topic are needed.

Although other studies have reported considerable morbidity and mortality for emergency laparoscopic cholecystectomy in high-risk patients (up to 41% and 5%, respectively),[3-8] our study shows that immediate cholecystectomy in patients with an APACHE-II score of ≥7 is safe. Major complications occurred in 9% of patients which seems acceptable in this category of severely ill patients. Our results do not apply to patients with an APACHE-II score ≥15 because these patients were excluded. During the entire study period, however, only 10 patients were excluded on the basis of this criterion. This implies that virtually all patients with acute calculous cholecystitis can safely undergo early laparoscopic cholecystectomy. As opposed to percutaneous catheter drainage, cholecystectomy is a definitive treatment for gallstone related disease which does not require readmissions and other interventions that impact patient's quality of life and are a burden on hospital capacity for emergency and elective care.

In conclusion, among high-risk patients with acute cholecystitis, laparoscopic cholecystectomy, as compared with percutaneous drainage, is the preferred treatment strategy from both a clinical and economical point of view.

REFERENCES

1 Wadhwa V, Jobanputra Y, Garg SK, Patwardhan S, Mehta D, Sanaka MR. Nationwide trends of hospital admissions for acute cholecystitis in the United States. Gastroenterol Rep (Oxf) 2016;.

2 Keus F, Gooszen HG, van Laarhoven CJ. Open, small-incision, or laparoscopic cholecystectomy for patients with symptomatic cholecystolithiasis. An overview of Cochrane Hepato-Biliary Group reviews. The Cochrane Library 2010;.

3 Ambe PC, Weber SA, Christ H, Wassenberg D. Primary cholecystectomy is feasible in elderly patients with acute cholecystitis. Aging clinical and experimental research 2015;27:921-6.

4 Fukami Y, Kurumiya Y, Mizuno K, Sekoguchi E, Kobayashi S. Cholecystectomy in octogenarians: be careful. Updates in surgery 2014;66:265-8.

5 Nikfarjam M, Yeo D, Perini M, et al. Outcomes of cholecystectomy for treatment of acute cholecystitis in octogenarians. ANZ J Surg 2014;84:943-8.

6 Kirshtein B, Bayme M, Bolotin A, Mizrahi S, Lantsberg L. Laparoscopic cholecystectomy for acute cholecystitis in the elderly: is it safe? Surg Laparosc Endosc Percutan Tech 2008;18:334-9.

7 Decker G, Goergen M, Philippart P, Mendes da Costa P. Laparoscopic cholecystectomy for acute cholecystitis in geriatric patients. Acta Chir Belg 2001; 101:294-9.

8 Winbladh A, Gullstrand P, Svanvik J, Sandström P. Systematic review of cholecystostomy as a treatment option in acute cholecystitis. HPB 2009;11:183-93.

9 Miura F, Takada T, Strasberg SM, et al. TG13 flowchart for the management of acute cholangitis and cholecystitis. Journal of hepato-biliary-pancreatic sciences 2013; 20:47-54.

10 Jang WS, Lim JU, Joo KR, Cha JM, Shin HP, Joo SH. Outcome of conservative percutaneous cholecystostomy in high-risk patients with acute cholecystitis and risk factors leading to surgery. Surg Endosc 2015;29:2359-64.

11 Sanjay P, Mittapalli D, Marioud A, White RD, Ram R, Alijani A. Clinical outcomes of a percutaneous cholecystostomy for acute cholecystitis: a multicentre analysis. HPB 2013;15:511-6.

12 Kortram K, van Ramshorst B, Bollen TL, et al. Acute cholecystitis in high risk surgical patients: percutaneous cholecystostomy versus laparoscopic cholecystectomy (CHOCOLATE trial): study protocol for a randomized controlled trial. Trials 2012;13:1.

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

14 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.

15 Dutch Guidelines for the treatment of gallstone disease 2007. NVvH.

16 Yamashita Y, Takada T, Strasberg SM, et al. TG13 surgical management of acute cholecystitis. Journal of hepato-biliary-

pancreatic sciences 2013;20:89-96.

17 Kortram K, de Vries Reilingh T, Wiezer M, van Ramshorst B, Boerma D. Percutaneous drainage for acute calculous cholecystitis. Surg Endosc 2011;25:3642-6.

18 Chang YR, Ahn Y, Jang J, et al. Percutaneous cholecystostomy for acute cholecystitis in patients with high comorbidity and re-evaluation of treatment efficacy. Surgery 2014;155:615-22.

19 McKay A, Abulfaraj M, Lipschitz J. Short- and long-term outcomes following percutaneous cholecystostomy for acute cholecystitis in high-risk patients. Surg Endosc 2012;26:1343-51.

20 Horn T, Christensen SD, Kirkegård J, Larsen LP, Knudsen AR, Mortensen FV. Percutaneous cholecystostomy is an effective treatment option for acute calculous cholecystitis: a 10-year experience. HPB 2015;17:326-31.

21 Ha JP, Tsui KK, Tang CN, Siu WT, Fung KH, Li MK. Cholecystectomy or not after percutaneous cholecystostomy for acute calculous cholecystitis in high-risk patients. Hepatogastroenterology 2008;55: 1497-502.

22 Griniatsos J, Petrou A, Pappas P, et al. Percutaneous cholecystostomy without interval cholecystectomy as definitive treatment of acute cholecystitis in elderly and critically ill patients. South Med J 2008;101:586-90.

23 Melloul E, Denys A, Demartines N, Calmes J, Schäfer M. Percutaneous drainage versus emergency cholecys tectomy for the treatment of acute cholecystitis in critically ill patients: does it matter? World J Surg 2011;35:826-33.

24 Jang WS, Lim JU, Joo KR, Cha JM, Shin HP, Joo SH. Outcome of conservative percutaneous cholecystostomy in high-risk patients with acute cholecystitis and risk factors leading to surgery. Surg Endosc 2015;29:2359-64.

25 Boules M, Haskins I, Farias-Kovac M, et al. What is the fate of the cholecystostomy tube following percutaneous cholecystostomy? Surg Endosc 2016;1-6.

26 Granlund A, Karlson B, Elvin A, Rasmussen I. Ultrasound-guided percutaneous cholecystostomy in high-risk surgical patients. Langenbeck's Archives of Surgery 2001;386:212-7.

27 Chok KS, Chu FS, Cheung TT, et al. Results of percutaneous transhepatic cholecystostomy for high surgical risk patients with acute cholecystitis. ANZ J Surg 2010;80:280-3.

28 Leveau P, Andersson E, Carlgren I, Willner J, Andersson R. Percutaneous cholecystostomy: a bridge to surgery or definite management of acute cholecystitis in high-risk patients? Scand J Gastroenterol 2008;43:593-6.

29 Welschbillig-Meunier K, Pessaux P, Lebigot J, et al. Percutaneous cholecystostomy for high-risk patients with acute cholecystitis. Surgical Endoscopy And Other Interventional Techniques 2005;19:1256-9.

30 Koebrugge B, van Leuken M, Ernst MF, van Munster I, Bosscha K. Percutaneous cholecystostomy in critically ill patients with a cholecystitis: a safe option. Dig Surg 2010;27:417-21.

31 Morse BC, Brandon Smith J, Lawdahl RB, Roettger RH. Management of acute cholecystitis in critically ill patients:

contemporary role for cholecystostomy and subsequent cholecystectomy. Am Surg 2010;76:708-12.

32 Bergman JJ, van den Brink GR, Rauws EA, et al. Treatment of bile duct lesions after laparoscopic cholecystectomy. Gut 1996;38:141-7.

CHAPTER 9

Supplementary appendix to:
Laparoscopic cholecystectomy versus percutaneous catheter drainage for high-risk patients with acute cholecystitis

METHODS

Postoperative antibiotics

Antibiotic therapy was not routinely continued postoperatively unless the performing surgeon had indications to do so (e.g. sepsis, hemodynamic instability). In these cases, the primary investigator was notified and the indications well documented.

Costs

To determine economic differences between laparoscopic cholecystectomy and percutaneous catheter drainage, the direct medical cholecystitis-related costs during a follow-up period of one year after randomization were taken into account. Primary data were used to assess the use of health care resources. For each patient, the following health care resources were assessed: the number of days of admission (on the general ward and intensive care unit), radiography, surgical procedures, endoscopic procedures, and the use of other medical services (outpatient clinic visits, telephonic consultations and emergency room visits). No volumes of haematological, biochemical or microbiological blood tests were taken into account as no differences were expected based on their low unit costs.

Unit costs for admission days, outpatient visits and emergency room visits were based on the 2015 Dutch manual for costing in health care research.[1] Unit costs of radiologic and endoscopic procedures were derived from the St. Antonius Hospital tariffs ledger (2016), which included personnel, material and overhead costs. Unit costs for cholecystectomy were calculated from specialists' fees for surgeon and anaesthesiologist, personnel costs, purchase prices of materials used and overhead costs.[2] Unit costs are presented in Table S9.1.

Costs were calculated as the product sum of the volumes of resources used and their respective unit costs.

RESULTS

Eligible atients

During the study period, 246 patients were eligible but did not participate in the trial (Figure 9.1). The baseline characteristics of these patients were comparable to the

Table S9.1 Total Direct Medical Costs *

		Laparoscopic cholecystectomy (N = 66)		Percutaneous drainage (N = 68)	
	Price per unit†	**N**	**Total (€)**	**N**	**Total (€)**
Hospital stay[1]					
General ward (per day)	476	417	198,492	833	396,508
Intensive care unit (per day) †	1186	47	55,742	2	2372
Radiology ‡					
Abdominal ultrasound	76	15	1140	55	4180
CT scan	216	11	2376	35	7560
Cranial CT scan	198	2	396	1	198
MRI scan	279	6	1674	2	558
X-ray thorax	52	41	2132	33	1716
X-ray abdomen	52	1	52	9	468
US or CT guided drainage	437	9	3933	85	37,145
Paracentesis	168	0	0	1	168
Thoracentesis	101	0	0	2	202
Antegrade cholangiography	401	3	1203	68	27,268
Endoscopy ‡					
ERCP	876	8	7008	12	10,512
Gastroscopy or duodenoscopy	405	1	405	3	1215
Enteral feeding tube placement	459	1	459	3	1377
Endoscopic ultrasound	125	0	0	1	125
Surgery[2]					
Cholecystectomy	1256	66	82,896	31	38,936
Diagnostic laparoscopy	1114	1	1114	1	1114
Other[1]					
Outpatient visits	91	71	6461	185	16,835
Tel. outpatient consultation	15	13	195	21	315
Emergency room visits	259	7	1813	56	14.504
Total			367,491		563,276
Health care costs per patient *			**€ 5568**		**€ 8283**

* For conversion to US dollars multiply by 1.10. † Exclusive diagnostic tests, procedures, radiography and medication. ‡ Unit costs based on the St. Antonius hospital ledger (2016).

LC denotes laparoscopic cholecystectomy, PD percutaneous drainage, CT computed tomography, MRI magnetic resonance imaging, US ultrasound and ERCP endoscopic retrograde cholangiopancreatography.

characteristics of the included patient, except for APACHE-II score (9.0 versus 9.4, P=0.01) (Table S9.2).

Details on laparoscopic cholecystectomies

Fifty-five of the 64 patients (86%) received antibiotic prophylaxis before surgery, six patients (9%) did not receive antibiotics prophylaxis and in three patients (5%) it was unclear whether they received preoperative antibiotics. The mean duration of the procedure was 81.5±29.0 minutes.

The reason for conversion included difficulty in identifying the anatomy either due to extensive inflammation or poor vision in all patients, in addition to fibrosis of Calot's triangle in two patients, a perforated cystic duct in one patient and a ruptured gallbladder in one patient.

Details on percutaneous catheter drainages

Percutaneous catheter drainage was performed with image guidance using ultrasound in 62 patients (91%), computed tomography in 2 patients (3%) and X-per guide in 4 patients (6%). The transperitoneal route was used in 57 patients (84%), the transhepatic route in eight patients (12%), and in three patients (4%) the route was unclear. The median drain size was 8.5 French (range, 5 to 12). The mean duration of the procedure was 20.9±7.6 minutes. The median difficulty of the procedure as scored by the radiologist was 3 (range, 0 to 9) (as scored by VAS 1 to 10). The drain was removed after a mean period of 20.9±7.6 days.

Table S9.2 Baseline Characteristics of the Included and Non-included Eligible Patients * †

Characteristics	**Included Patients (N = 134)**	**Non-included Patients (N = 246)**
Age - yr	73.2±9.7	73.2±10.8
Male sex - no. (%)	85 (63)	134 (55)
Coexisting conditions - no. (%)		
Cardiovascular disease	91 (68)	154 (63)
Pulmonary disease	27 (20)	38 (15)
Chronic renal insufficiency	8 (6)	12 (5)
Diabetes	29 (22)	50 (20)
Previous abdominal surgery - no. (%)	26 (19)	40 (16)
ASA classification on admission - no. (%)		
I: Healthy status	14 (10)	40 (16)
II: Mild systemic disease	70 (52)	121 (49)
III: Severe systematic disease	47 (35)	82 (33)
IV: Severe systemic disease that is a constant threat to life	3 (2)	3 (1)
Disease severity		
APACHE-II score ‡	9.4±2.0	9.0±1.8

* Plus–minus values are means ±SD. † The baseline characteristics were similar in the two groups, with the exception of the APACHE-II score, which was higher in the included group (9.4 versus 9.0, P=0.01). ‡ Scores on the Acute Physiologic and Chronic Health Evaluation II (APACHE II) scale range from 0 to 71, with higher scores indicating more severe disease.

ASA denotes American Society of Anaesthesiologists and APACHE Acute Physiology and Chronic Health Evaluation.

REFERENCES

1 Hakkaart-van Roijen L, Van der Linden N, Bouwmans C, Kanters T, Tan S. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg (geactualiseerde versie 2015). opdracht van Zorginstituut Nederland 2015.

2 Da Costa D, Dijksman L, Bouwense S, et al. Cost-effectiveness of same-admission versus interval cholecystec-tomy after mild gallstone pancreatitis in the PONCHO trial. Br J Surg 2016.

PART III

Surgical treatment of common bile duct stones

CHAPTER 10

Surgical treatment of common bile duct stone

Gallstones: recent advance in epidemiology, pathogenesis, diagnosis and management, 2016

C. S. Loozen
D. Boerma

ABSTRACT

Over the past century, the management of common bile duct (CBD) stones has evolved considerably, and endoscopic as well as surgical options are currently available. This chapter describes the surgical techniques, and its complications, that are currently available, focusing on the laparoscopic approach. In patients with CBD stones and concomitant gallbladder stones, laparoscopic cholecystectomy can be performed in combination with laparoscopic exploration of the CBD. This so called "single-stage" approach can be accomplished through a transcystic or a transductal approach. A transcystic approach is generally used in cases of small stones in small bile ducts. The CBD is reached via an opening in the cystic duct and actual extraction is performed with an extraction device (e.g. atraumatic grasper, Fogarty balloon catheter or wire basket) under visual guidance. A transductal approach is preferred in cases of large, occluding or multiple CBD stones, stones in the proximal ductal system, or in cases of small or tortuous cystic ducts. A choledochotomy is made and stones can be extracted by using any of the aforementioned devices. The choledochotomy should be closed primarily using an absorbable suture. Laparoscopic CBD exploration can be performed with high efficiency and minimal morbidity and mortality. Yet, it should only be performed by experienced laparoscopic surgeons since laparoscopic CBD exploration, especially through the transductal approach, requires advanced laparoscopic skills. Therefore the default procedure in many hospitals remains ERCP, performed either before or after laparoscopic cholecystectomy in separate sessions, a so-called "two-stage" approach. ERCP can also be performed intraoperatively in a rendezvous fashion, which allows easy and fast cannulation and less manipulation.

INTRODUCTION

The prevalence of common bile duct (CBD) stones in patients with symptomatic gallstone disease is 3% - 10%.[1-4] Most CBD stones originate from the gallbladder, only a small percentage are developed de novo. Over the past century, the management of CBD stones has evolved considerably. Historically, CBD stones were treated with open bile duct exploration, a procedure carried out by many general surgeons on a regular basis. It was associated with low morbidity and mortality rates and associated with a low percentage of retained stones (1-3%).[5-8] During long term follow-up, approximately 10% of the patients required surgical revision. After the introduction and rapid uptake of endoscopic retrograde cholangiopancreatography (ERCP) in the late 1970s, endoscopic treatment of CBD stones prior to cholecystectomy supplanted open bile duct exploration, and open bile duct clearance has decreased dramatically.[9,10]

In the era of minimally invasive surgery and the emergence of laparoscopic techniques, there has been a gradual increase in laparoscopic CBD exploration, and numerous techniques have been developed. Laparoscopic bile duct exploration, however, requires advanced laparoscopic skills and experience. Therefore, the default procedure in many hospitals remains ERCP, performed either before or after laparoscopic cholecystectomy. Endoscopic treatment of CBD stones obviously has advantages: it is minimally invasive and it is associated with high success rates; if performed by a competent endoscopist, stones are successfully removed in more than 90%. Disadvantages of endoscopic stone removal are a morbidity rate of approximately 10%, including post-operative ERCP, and mortality rate of at least 0.5%, mainly as a consequence of the frequently performed additional endoscopic sphincterotomy.[11-13] Moreover, it should be noted that in patients with concomitant gallbladder stones, a subsequent surgical intervention is still required. Conservative treatment of CBD stones also remains being practised. It is feasible in patients with non-obstructing choledocholithiasis, since some stones never cause clinical complaints and may even pass spontaneously. A prospective study on the incidence of choledocholithiasis in 997 patients undergoing laparoscopic cholecystectomy, showed that, based on intraoperatively performed cholangiography, CBD stones were present in 3.4% of the patients.[1] Within six weeks of operation, more than one third of the stones passed spontaneously, which appeared not to be dependent on number or size of the stones or the diameter of the bile duct. Only 2.2% of the patients had persistent CBD stones at six weeks after laparoscopic cholecystectomy, requiring ERCP. So, in the

management of clinically silent choledocholithiasis, a short-term expectant approach may be feasible.[1]

In summary, several treatment options for choledocholithiasis are available, including conservative management, ERCP, open bile duct exploration and laparoscopic bile duct exploration. This chapter explores the surgical techniques, and its complications, that are currently available, focusing on the laparoscopic approach.

SURGICAL CBD EXPLORATION - APPROACHES

Laparoscopic CBD exploration – technique

Instrumentation

Appropriate instrumentation should be readily available, including a choledochoscope, a laparoscopic ultrasound probe to evaluate the presence of stones and the biliary anatomy, extraction devices (e.g., atraumatic graspers, baskets, suction-irrigation devices), dilators (e.g., balloon dilatation catheters, Fogarty catheters) and drains.

Positioning of the patient Perioperative morbidity

The patient is placed in supine position with the legs apart.[14,15] The surgeon stands between the patients legs (French position). The left arm placed in 90 degrees and the right arm alongside the body. The first assistant stands on the left side of the patient. The operating table is positioned in reverse Trendelenburg, with a left lateral tilt.

Trocar placement

The optical trocar is positioned in the umbilical area.[14,15] The operating trocars, used to introduce surgical devices such as scissors, graspers and dissection devices, are positioned in the right and left hypochondrium. The retractor trocar is positioned in the epigastric area through which retracting instruments as well as suction-irrigation devices can be introduced. In addition to these four trocars usually used for cholecystectomies, a fifth trocar may be required for introduction of instrumentation such as the choledochoscope to perform choledochoscopy. This trocar is placed in the right subcostal area in the axis of the cystic duct, halfway between the xiphoid and the right subcostal trocar.[14,15]

Exposure and dissection

After introduction of the laparoscope, adequate exposure of the subhepatic area is obtained by suspension of the liver and caudal retraction of the duodenum. The infundibulum of the gallbladder is retracted upward and laterally. To ensure safe dissection, good exposure of the anterior surface of Calot's triangle is essential. Calot's triangle is stretched open by retracting the fundus of the gallbladder superiorly and stretching the cystic duct laterally. After identification and exposure, the cystic artery is clipped proximally and distally and the cystic duct is clipped close to the junction with the gallbladder.

Intraoperative cholangiography

Imaging of the biliary tract by cholangiography is an essential part of CBD exploration. In this way, the anatomy of the biliary tract, as well as the number, size and location of the bile duct stones can be determined. The cystic duct is incised on its anterior surface, one centimetre from the junction with the CBD. Subsequently, the cholangiocatheter is introduced and fluorescent fluid is injected into the bile ducts until a complete cholangiogram is obtained.[14,15] If the cholangiogram demonstrates radiolucent defects, crescent-shaped blockage of contrast, dilatation of the bile ducts or absence of passage of contrast into the duodenum, the presence of CBD stones is suspected, and laparoscopic exploration of the bile duct could be performed. If no stones are detected, the cystic duct is closed and a completion cholecystectomy is performed.

Approach

Laparoscopic bile duct exploration can be accomplished through a transcystic or a transductal approach. In a transcystic approach, the CBD is reached via an opening in the cystic duct, whereas in the transductal approach the CBD itself is incised and opened. The decision whether to perform a transcystic or a transductal procedure depends not only on the location, number and size of the stones and anatomic features, but also on the availability of equipment and the surgeons' preference and expertise (table 10.1). A transcystic approach is generally used in cases of small stones in small bile ducts, whereas a transductal approach is preferred in cases of large, occluding or multiple CBD stones, stones in the proximal ductal system, or in cases of small or tortuous cystic ducts.[16] Since transductal stone retrieval is more invasive and requires specific skills in

suturing and knot-tying, this approach is often used in patients in whom a transcystic approach has failed.

Transcystic approach

If the decision is made to proceed with a transcystic CBD exploration, the first manoeuvre is flushing warm saline through the cystic duct, in an attempt to force small CBD stones or debris through the ampulla into the duodenum. Intravenous glucagon may be used to relax the sphincter of Oddi.

To achieve an adequate diameter of the cystic duct, large enough to reach the CBD for stone extraction, dilatation by means of an atraumatic forceps, a balloon catheter or a flexible atraumatic dilator can be performed.[15] These devices can cause serious damage to the cystic duct and should therefore be used with caution.

The actual extraction of stones can be performed 'blindly', but is mostly done under fluoroscopic guidance. Various extraction techniques can be used. In the event that stones are easily accessible through the cystic duct orifice, an atraumatic grasper can be used.[15] A Fogarty balloon catheter technique can be used to retrieve stones that are less accessible, and is especially useful to dislodge impacted stones and in patients with a dilated cystic ducts.[17] The Fogarty catheter is guided through the cystic duct into the duodenum. The balloon on the tip of the catheter is inflated and pulled back until resistance at the sphincter is felt. Subsequently, the balloon is deflated and the catheter withdrawn one centimetre to ensure a position just proximal of the sphincter. After re-inflation of the balloon, the catheter is gently withdrawn to drag along stones and debris through the cystic duct orifice, to be removed with a forceps. To avoid perforation of the ductal system, this procedure should always be performed with great care and gentle manipulation. The drawback to this technique is the potential for the stone to be pulled into the common hepatic duct, beyond the reach of an endoscope. If this happens, changing the position of the operating table combined with irrigation of the duct will usually return the stone in the proximal system, i.e. within reach of the endoscope.

Another technique to extract stones from the CBD is by using a wire basket.[15] The basket is advanced under fluoroscopic guidance through the cystic duct into the CBD. The entrapment and extraction of the stone(s) can be visualized and stones can subsequently be removed. To avoid bile duct injury, a spiral wire basket with flexible leaders should be

used.[17] According to retrospective studies, fluoroscopic wire basket stone retrieval is successful in more than 90% of the patients.[18,19]

The most advanced method of laparoscopic transcystic CBD exploration allows stone capture under direct vision with a choledochoscope (figure 10.1). The scope is inserted under direct vision through the cystic duct into the CBD. If the cystic duct is not large enough for scope insertion, it should first be balloon-dilated, which should be performed by closely monitoring the physical changes in the cystic duct while the dilatation proceeds to avoid unexpected duct injuries. Visualisation can be facilitated by continuously infusing saline, which simultaneously distends the lumen of the duct. Via the working channel of the scope, a stone basket is advanced into the CBD.[16] The stone is then retrieved by the basket and securely held against the tip of the endoscope. Subsequently, the choledochoscope is carefully withdrawn with the basket under continual view. Intrahepatic stones and stones that defy capture with a basket are better off with the combined use of a choledochoscope and balloon catheter. The balloon is advanced past the stone, inflated and withdrawn towards the scope. The scope, stone and balloon are withdrawn through the ductal orifice. If extraction of the stone through the cystic duct is impossible due to the size of the stone, a longitudinal incision along the cystic duct may have to be made.

Once all stones are extracted, complete clearance of the CBD has to be confirmed with the choledochoscope or by cholangiography or ultrasound; of which cholangiography is recommended if stones are suspected proximal of the junction of cystic and CBD. Finally, a simple closure of the cystic duct using a ligature, suture or clipping technique is performed. To prevent postoperative obstruction caused by significant inflammation or oedema of the papilla, a drain can be placed.

Transductal approach

The cystic duct is dissected down to the level of the CBD. The anterior surface of the CBD is exposed and with laparoscopic scissors, a 1-2 cm longitudinal incision (choledochotomy) is made, long enough to allow insertion of the choledochoscope and at least the size of the largest stone. A transvers incision is rarely used in laparoscopy, but can be considered in specific cases such as a very dilated CBD.[14]

When the CBD is opened, stones often clear spontaneously.[14] Residual stones can be extracted through one of the aforementioned blind techniques (e.g. saline infusion, high-

Table 10.1 Factors influencing the approach of duct exploration[4]

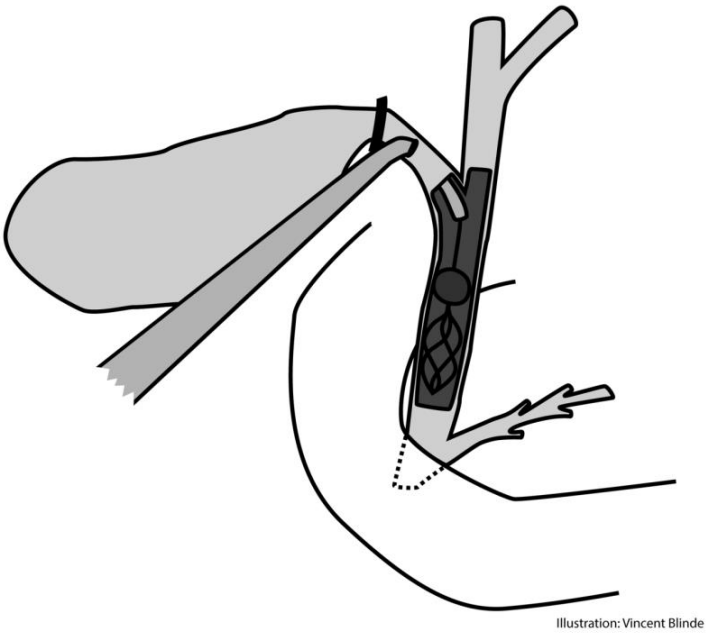
Factor	Trans-cystic approach	Trans-ductal approach
Single stone	Yes	Yes
Multiple stones	Yes	Yes
Stones < 6 mm diameter each	Yes	Yes
Stones > 6 mm diameter each	No	Yes
Intrahepatic stones	No	Yes
Diameter of cystic duct < 4 mm	No	Yes
Diameter of cystic duct > 4 mm	Yes	Yes
Diameter of CBD < 6 mm	Yes	No
Diameter of CBD > 6 mm	Yes	Yes
Cystic duct entrance - lateral	Yes	Yes
Cystic duct entrance - posterior	No	Yes
Cystic duct entrance - distal	No	Yes
Inflammation - mild	Yes	Yes
Inflammation - marked	Yes	No
Suturing ability - poor	Yes	No
Suturing ability - good	Yes	Yes

pressure suction-irrigation or retrieval with a atraumatic grasper, Fogarty catheter or wire basket) or under visual guidance with use of fluoroscopy or a choledochoscope. Each extracted stone is placed in an endoscopic extraction bag that is placed in the abdominal cavity, close to the choledochotomy. Complete clearance of the CBD should always be confirmed either endoscopically or radiographically.[14]

After CBD exploration and stone removal, the choledochotomy should be closed primarily using an absorbable suture (figure 10.2). This closure method carries the risk of CBD stenosis, and therefore a transcystic or antegrade drain (attached to the cystic stump) should be placed if any postoperative obstruction of the CBD due to inflammation or oedema is to be expected.[14]

An alternative to primary closure is closure with T-tube drainage, which has often been used in the era of open bile duct surgery to reduce the risk of postoperative bile leakage. The use of this technique however, is no longer recommended since it provokes many

Figure 10.1 Transcystic stone removal from the common bile duct. The flexible scope is inserted through the cystic duct into the common bile duct. Under direct vision, a spiral wire basket is advanced into the common bile duct via the working channel of the scope. The basket is placed distal from the stone, opened and gently withdrawn. After the stone is captured, the choledochoscope is carefully withdrawn through the ductal orifice with the basket under continual view.



complications such as localized pain, fluid and electrolyte disturbances, dislodgment of the tube, biliary stricture and bile leak with the T-tube in situ or after removal of the tube.[20,21] In a systematic review Gurusamy et al. compared T-tube drainage with primary closure after laparoscopic CBD exploration.[22] In three randomized controlled trials, a total of 295 patients were included. Serious morbidity did not significantly differ between both groups; 11.3% and 6.1%, respectively, whereas T-tube drainage turned out to be associated with significantly longer operating time and hospital stay compared with primary closure. Therefore, the routing use of T-tube drainage cannot be justified. A closed suction drain is frequently used after transductal CBD exploration to detect leakage. The drain can usually be removed within 24 hours, provided that the output is not bilious.

Lithotripsy

Electrohydraulic lithotripsy can be used to fragment impacted bile duct stones or stones that are too large to be captured via the conventional way. Once the fragments are small enough, conventional stone retrieval techniques are used to complete duct clearance. Electrohydraulic lithotripsy is effective in tackling difficult stones and is relatively inexpensive. Yet, it must be used with great caution to avoid damage to the bile duct wall. Laser lithotripsy for bile duct stones has not been widely adopted due to the high costs and limited availability of required equipment.[23]

Completion cholangiography

After finishing bile duct exploration, completion cholangiography should be performed to ensure full clearance of the duct. Failure of contrast to pass to the duodenum and visual intraluminal opacities usually indicates either sludge or retained stones, or stricture of the CBD. If attempts to remove this material are unsuccessful, the surgeon must decide to either perform a choledochoenterostomy, convert to open CBD exploration, or leave the stones in place and resort to postoperative ERCP.

Postoperative care

As soon as the patient has recovered from anaesthesia, oral intake can be restarted. The patient can be discharged based on the clinical condition.

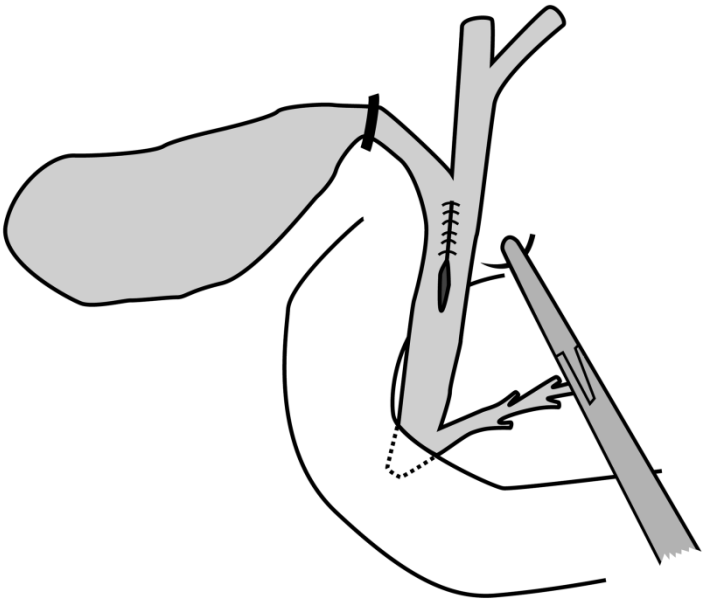
Contraindications

Contraindications to perform laparoscopic CBD exploration include clinical instability of the patient, conditions in the porta hepatis that would make exploration hazardous, but most of all, insufficient skilfulness of the surgeon in performing a laparoscopic exploration due to a lack of training or expertise.

OPEN CBD EXPLORATION - TECHNIQUE

Open CBD exploration starts with ligating the proximal cystic duct to prevent stones from migrating from the gallbladder into the CBD. Subsequently, dissection down to the anterior surface of the CBD is carried out, and a longitudinal choledochotomy is created.

Figure 10.2 Primary closure of the choledochotomy after transductal common bile duct exploration.



Stones can then be extracted using various techniques such as manual manipulation, saline infusion and balloon extraction. In the unlikely event that these procedures are unsuccessful, choledochoscopy with wire basket retrieval can be performed.

In the era of minimally invasive surgery, open surgical exploration should not be considered a primary option in the treatment of CBD stones, but should only be performed in case laparoscopic and endoscopic CBD exploration are unsuccessful or unavailable, in case of severe inflammation of the triangle of Calot, or in patients with choledochocystolithiasis who already undergo open cholecystectomy. Open exploration should also be considered if a stone is impacted at the ampulla of Vater or in case of a dilated CBD or multiple stones; in these cases either a surgical sphincterotomy or a choledochoenterostomy should be performed.[16]

A surgical sphincterotomy starts with mobilisation of the duodenum. Subsequently, a duodenotomy is made at the level of the ampulla. Than the distal part of the sphincter musculature is incised over a length of approximately one centimetre, which should not extend beyond the outer wall of the duodenum.[16] A dilator may be used to bring the

ampulla into the operative field, where it is incised along the anterosuperior side to be able to remove impacted stones.[16]

The most common choledochoenterostomy is a side-to-side anastomosis between the CBD and the duodenum.[16] This approach is usually performed in the setting of a dilated CBD with multiple stones because a large opening between the bile duct and duodenum can be created. After a Kocher manoeuvre and exposure of the CBD, a 2-3 centimetre choledochotomy is made close to the lateral border of the duodenum, followed by a similar-sized incision at the adjacent duodenum wall.[16] Subsequently, a diamond shaped anastomosis is made with interrupted absorbable sutures. This procedure is a well-established and relatively simple to perform, although it is prone to duodenobiliary reflux and occasional symptomatic inspissation with food debris causing cholangitis (the so called 'sump syndrome').[16,24] Studies comparing choledocho-duodenostomy with transduodenal sphincterotomy have shown similar results, so the decision to perform one or the other procedure should depend on the experience and preference of the surgeon.[25]

SURGICAL CBD EXPLORATION - FAILURE AND COMPLICATIONS

Failure to clear the CBD

Surgical bile duct exploration is successful in clearing the CBD in the vast majority of patients. A prospective study which randomized 118 patients to open bile duct exploration, reported a success rate of 96% in clearing the CBD and a mean length of hospital stay of 13 days.[26] The efficacy of laparoscopic exploration in clearing the CBD from stones has been studied by many. Just recently, Zhu et al. carried out a meta-analysis which compared single-stage versus two-stage laparoscopic approach in the treatment of concomitant gallstones and CBD stones.[27] Eight trials with in total 1130 patients were included. Laparoscopic CBD exploration was successful in clearing the CBD in approximately 90% of the patients. A recent systematic review by Reinders et al. however, compared transcystic versus transductal stone extraction and showed that the success rate of bile duct clearance varied from 80% to 100% for a transcystic exploration and from 58% to 100% for a transductal exploration.[28]

Unsuccessful CBD clearance may be the result of several reasons such as large or multiple stones, impacted stones, intrahepatic stones, severe inflammation of the porta hepatis, obesity of the patient or inadequate or failure of equipment. Stromberg et al.

examined the factors that may attribute to stone clearance failure in laparoscopic transcystic CBD exploration.[29] Data of 155 consecutive patients were prospectively collected. Laparoscopic transcystic CBD exploration proved to be successful in 85% of the patients, whereas retained stones, visualised with cholangiography, were present in the remaining 15%. Reasons for failure were: large stones (n = 8), guide wire failure in reaching the CBD (n = 6), impacted stones (n = 5), stones displaced to intrahepatic duct (n = 1), equipment failure (n = 1) and other (n = 2). The odds ratio for failure in stone clearance among patients with a bile duct diameter greater than 6 mm was 6.90 (95% CI: 0.87-54.61) compared to patients with a bile duct diameter of 6 mm or less. Furthermore, there was a significant threefold increase in risk among patients with stones greater than 5 millimetre diameter compared to those with stones of 5 millimetres or less. In this study, large stones and small ducts are risk factors for failure of stone clearance.

Laparoscopic CBD exploration can be considered as a demanding procedure that requires considerable surgical experience. The surgeon's skill thus is an important factor related to success. In the hands of experienced laparoscopic surgeons, it has emerged as the favourable choice, and nowadays many surgeons are encouraged to practise it. However, it takes time to gain enough skilfulness to apply this approach and, furthermore, the use of this procedure is limited, which makes it difficult to gain actual experience.

Complications

Laparoscopic stone removal is associated with several complications, including bile leakage, injury of the CBD, postoperative pancreatitis and abscess formation. The morbidity rate of laparoscopic CBD exploration is 7%-10% in a transcystic approach and 16%-27% in a transductal approach.[28] Open bile duct exploration is associated with a morbidity rate of approximately 13%.[26]

Bile leakage

Postoperative bile leakage is the most common complication after laparoscopic CBD exploration. It occurs in approximately 11% of patients who undergo transductal exploration, and in approximately 2% of patients who undergo transcystic exploration.[28] If not detected in a postoperative drain, patients with bile leakage often present with fever or other parameters suggestive of infection, generalised peritonitis, increased bilirubin

concentration in the drain fluid, and a biliary collection on ultrasound or additional scan. Bile may leak from the gallbladder bed, the cystic duct orifice, the cystic duct or the CBD itself, and may be the result of dissection or manipulation of the biliary tract during laparoscopic (or open) bile duct exploration. To reduce the incidence of bile leak, it is essential to operate carefully with gentle tissue handling techniques and perfect vision. Additionally, the cystic duct should be secured adequately, which may require suture ligation. Hua et al. performed a retrospective study to identify the potential risk factors for postoperative bile leakage after primary closure following laparoscopic CBD exploration via choledochotomy.[30] Postoperative bile leakage occurred in 3.8% (6/157). Univariate analysis revealed that successful duct clearance ($p = 0.010$) and small diameter of the CBD ($p < 0.001$) were significant risk factors for bile leakage.

Percutaneous drainage may be necessary in case bile leakage is suspected and a biliary collection is proven on ultrasound. Since most leaks are self-limiting and can be managed without surgery, drainage allows a period of observation. In a retrospective study, Estellés et al. showed that in more than half of the patients with bile leakage, no further action was required and that the leak closed spontaneously.[31] Postoperative ERCP with sphincterotomy or stent placement may be necessary in case of a distal obstruction of the CBD caused by spasm, oedema or debris, and relaparoscopy in case the leak does not seal or in case the patients clinically deteriorate.

CBD injury

The most worrying complication related to surgical CBD exploration is an injury of the CBD. This may be caused by several factors including inflammation of/in the porta hepatis, variable biliary anatomy, inappropriate exposure and aggressive attempts to achieve haemostasis. Multiple classifications have been developed to classify bile duct injuries. According to the Amsterdam classification, bile duct injuries are classified as follows: type A - cystic duct leakage; B - CBD leakage; C - bile duct stricture; type D - complete transsection of the bile duct.[32] In the presence of a skilled and experienced hepatobiliary surgical team, intraoperative bile duct injuries should be repaired immediately. If no such team is available, the patient should be referred to an expertise centre. If not diagnosed at time of surgery, patients with bile duct injuries often come to medical attention early in the postoperative period, often within the first week. Most of the patients with significant bile leaks present with abdominal pain, fever or other sepsis

signs. Some bile leaks however, may not become apparent for several weeks and patients may present with non-specific complaints such as fatigue or weakness.

To avoid manoeuvres that damage the CBD during dissection and exploration, a thorough knowledge of biliary anatomy and possible anomalies is essential. This can be accomplished by performing intraoperative cholangiography. In addition, the procedure should always be performed with great care and gentle manipulations. If the cystic duct is not large enough to insert the choledochoscope or other instruments, it should first be dilated. Subsequent introduction of instruments into the CBD must be done with care to avoid perforation of the ductal wall. If a choledochotomy is made, the incision must be long enough to allow insertion of the choledochoscope and extraction of the stones. Too short an incision carries the risk of posterior injury of the CBD and tearing of the CBD during stone extraction or choledochoscope manipulation.

Postoperative pancreatitis

Postoperative acute pancreatitis after bile duct surgery might occur due to retraction or manipulation of the CBD during surgical exploration. As mentioned before, choledochoscope and extraction devices (e.g. wire basket, balloon) have to be used very carefully. The incidence of postoperative pancreatitis however, turns out to be surprisingly low.[31] A randomized controlled trail that included 256 patients who underwent either laparoscopic or open bile duct exploration even showed that none of the patients developed pancreatitis.[26] The surprising absence of postoperative pancreatitis may be explained by the large amount of successful transcystic laparoscopic CBD explorations and by the use of a flexible choledochoscope enabling direct visualization of the entire intra-biliary procedure, thus preventing any potential trauma of the ampulla of Vater.[26] Balloon dilatation of the sphincter of Oddi can often be avoided.

In the vast majority of patients, acute pancreatitis is self-limiting. Aggressive hydration and adequate analgesia should be given to all patients, unless precluded by cardiovascular or renal comorbidities.[33] Patients with severe pancreatitis may develop multi-organ system failure and may require admission to an intensive care.[33]

Abscess

In the retrospective study among 160 patients who underwent laparoscopic CBD

exploration with primary closure after choledochotomy, Vidagany et al. showed that five patients (3.1%) developed an abdominal abscess, of whom two had been treated with antibiotics and three with percutaneous drainage.[31] In randomized controlled trial comparing laparoscopic CBD exploration with open surgery, Grubnik et al showed that intra-abdominal abscesses occurred in respectively 1.5% (2/138) and 3.4% (4/118).[26]

Prior to completion of the surgical intervention, the perihepatic space should be thoroughly freed of stones, debris and bile. Moreover, a suction drain should be placed in case of severe inflammation or bile spill. In patients who underwent bile duct exploration, symptoms like persistent abdominal pain, fever, tachycardia, ileus and leucocytosis may suggest an intra-abdominal abscess, although the clinical presentation can be highly variable and many of these features may be absent. The diagnosis should be confirmed with ultrasonography or computed tomography. Treatment of intra-abdominal abscess includes administration of parenteral empirical antibiotics and percutaneous drainage. In the unlikely event that percutaneous drainage fails or if the collection is not amenable to catheter drainage, surgical drainage may be performed.

Wound infection

The change from open to laparoscopic surgery has significantly reduced the occurrence of wound related complications, although wound infections and trocar site hernias are still reported with an incidence of 1%-22% in all kinds of laparoscopic procedures.[34-37] In the previously mentioned randomized controlled trial, Grubnik et al. showed that wound infections were present in only 0.7% of the patients who underwent laparoscopic CBD exploration and in 5.9% of the patients who underwent an open procedure.[26] Most wound infections show up within the first 30 days after surgery. Risk factors for wound related problems include obesity, diabetes, nicotine abuse, steroid use and malnutrition, as well as type and technical performance of the surgical procedure.[35-38] Wound infections should be treated with antibiotics and, if necessary, with incision and drainage.

Complications related to cholecystectomy

Complications can occur not only during surgical bile duct exploration but also during subsequent (open or laparoscopic) cholecystectomy. These complications include haemorrhage, biliary injury, bile leaks and iatrogenic bowel injury. Conversion of

laparoscopic to open surgery should take place in case of unclear anatomy, occurrence of complications and in the event that no reasonable progress can be made in a timely fashion.

CHOLEDOCHOLITHIASIS - ENDOSCOPIC AND SURGICAL MANAGEMENT

Over the past century, the management of choledocholithiasis has evolved considerably, and several options are currently available. The removal of stones from the CBD can be performed either endoscopically or surgically. Open CBD exploration was considered the standard care in former times, but since the introduction of ERCP, endoscopic management has gained much ground in the treatment of CBD stones. Even though its use has declined since the introduction of laparoscopic CBD exploration, ERCP still plays an important role in the treatment of choledocholithiasis due to the high success rates of endoscopic stone extraction.[39]

ERCP is associated with several complications such as pancreatitis, cholangitis, perforation of the duodenum, and bleeding. Concerning ERCP, reported morbidity rates vary between 3% and 23% and mortality rates between 0% and 6%.[40-44] During long term follow-up, in about 10%-15% of the patients late complications occur, such as stone recurrence and cholangitis.[42,43,45] Acute pancreatitis represents the most common complication, leading to a significant increase in morbidity, mortality and prolonged hospitalization. Historically, acute pancreatitis following ERCP was seen in 5%-10 % of the patients, but over the past 15 years the risk of post-ERCP pancreatitis has decreased to 2%-4%.[46,47] Gentle injection of contrast into the pancreatic duct and performance by an experienced endoscopist can minimize its occurrence. In high-risk patients, pancreatic duct stents and nonsteroidal anti-inflammatory drug suppository are used.[33]

In 2008, Bailey et al. conducted a randomized controlled trial comparing primary deep biliary cannulation via a guide wire with conventional contrast-assisted cannulation, aiming to examine which approach is associated with a lower rate of post-ERCP pancreatitis.[39]

Post-ERCP pancreatitis occurred in 7.0% (29/413). The incidence of post-ERCP pancreatitis was not reduced by the guide-wire technique (16 vs 13, p= 0.48), although it increased incrementally with each attempt at the papilla (OR 1.4 per attempt, P = 0.04).

Open CBD exploration versus ERCP

Historically, the standard treatment for choledocholithiasis consisted of open CBD exploration, but since the introduction of ERCP and endoscopic sphincterotomy in the late 1970s, endoscopic management of CBD stones rapidly gained ground.[9,10,48-50] In a systematic review in 2013, Dasari et al. included eight randomized controlled trials that compared open bile duct surgery with endoscopic treatment of CBD stones.[51] Morbidity and mortality did not significantly differ. Yet, open exploration showed significant smaller number of retained stones compared to ERCP (6% (20/313) vs. 16% (47/296), p= 0.0002). Yet, in the context of modern medical practice these results have to be interpreted carefully, since all included studies were performed in the past century, so the results might have been influenced by the early experience and limited competence of the endoscopists in performing the ERCP.[51]

Open CBD exploration versus laparoscopic CBD exploration

With advancing technology, laparoscopic biliary surgery has become safe, efficient and cost-effective and has supplanted open biliary surgery.[52] In 2012, Grubnic et al. conducted a randomized controlled trial, aiming to compare open with laparoscopic CBD exploration.[26] A total of 256 patients were included, of whom 118 underwent open exploration and 138 laparoscopic exploration of the CBD. Laparoscopic exploration was performed trough the cystic duct in case of easily accessible small stones (n=76) and through a choledochotomy in case of large or numerous stones, stones located above the cystic duct implantation into the CBD, or after failure of transcystic exploration (n=62). Open compared to laparoscopic CBD exploration did not significantly differ in terms of stone clearance or duration of surgery. Morbidity turned out to be higher in the open group (12.7% vs. 6.5%), although the difference was not significant. Duration of hospital stay on the other hand, turned out to be significantly longer in the open group (12.6 vs. 4.2 days, $p < 0.01$).[26]

COMBINED CHOLEDOCHOCYSTOLITHIASIS - ENDOSCOPIC AND SURGICAL MANAGEMENT

In patients with CBD stones and concomitant gallbladder stones, several treatment options are available. Laparoscopic cholecystectomy can be performed in combination

with preoperative or postoperative ERCP (the so called "two-stage approach") or with laparoscopic surgical bile duct exploration or intraoperative ERCP (the so called "single-stage approach).

Two-stage approach

Preoperative ERCP with laparoscopic cholecystectomy

In patients who undergo ERCP for CBD stones and who have concomitant gallbladder stones, the fate of the gallbladder has been subject of study. In 2002, we conducted a randomized controlled trial to assess whether cholecystectomy deferral (wait-and-see policy) after endoscopic stone removal is justified.[53] After successful endoscopic sphincterotomy and extraction of CBD stones, patients were allocated to either a wait-and-see policy or elective laparoscopic cholecystectomy. During two year follow-up, recurrent biliary symptoms occurred in 47% (27/49) of the patients allocated to the wait-and-see policy and in 2% (1/49) of the patients allocated to cholecystectomy. Morbidity turned out to be 32% and 14%, respectively.[53] In a systematic review published in 2007, McAlister et al. included five randomized controlled trial on this subject, with a total of 662 patients.[54] The mortality rate was 14% (47/334) in the wait-and-see group compared to 8% (26/328) in the cholecystectomy group ($p = 0.010$). Patients in the wait-and-see group had higher rates of recurrent biliary pain ($P < 00001$), jaundice or cholangitis ($p = 0.03$), and repeat ERCP or other forms of cholangiography ($p = 0.005$). Cholecystectomy was eventually performed in 35% of patients in the wait-and-see group. Ever since, laparoscopic cholecystectomy is advised after successful ERCP in patients with residual gallbladder stones.

In 2010, we performed a randomized controlled trial to investigate the optimal timing of cholecystectomy after endoscopic sphincterotomy in patients with choledocho-cystolithiasis.[55] Patients were randomly assigned to either undergo a cholecystectomy within 72 hours or 6-8 weeks after endoscopic sphincterotomy. In the early group, 2% (1/47) of the patients developed recurrent biliary events prior to laparoscopic cholecystectomy, versus 36% (17/49) of the patients in the delayed group ($P < 0.001$). Both groups did not significantly differ with regard to conversion rate, difficulty of surgery, operating time or hospital stay. Laparoscopic cholecystectomy within 72 hours appears to be safe and prevents the majority of biliary events in this period following sphincterotomy.

In conclusion, cholecystectomy reduces the risk of recurrent biliary symptoms (e.g. biliary colics, acute cholecystitis, recurrent CBD stones with cholangitis or biliary pancreatitis) and should therefore be offered to patients whose gallbladders remain in-situ after endoscopic management of CBD stones, shortly after CBD clearance. In patients with contraindications for surgery (e.g. advanced age or severe comorbidities) though, endoscopic CBD management is still considered an acceptable definitive treatment, even though biliary events are to be expected.

Laparoscopic cholecystectomy with postoperative ERCP

In case intraoperative cholangiography during laparoscopic cholecystectomy reveals CBD stones, the surgeon can leave the stones in place for subsequent ERCP. If a well-trained laparoscopic surgeon as well as adequate equipment is available however, a laparoscopic approach should first be attempted, since laparoscopic exploration is associated with decreased morbidity and less expensive.

Nathanson et al. conducted a randomized controlled trial to determine the optimal treatment of patients with CBD stones in whom transcystic duct exploration had failed.[56] A total of 86 patients were intraoperatively randomized to undergo either laparoscopic choledochotomy (n=41) or postoperative ERCP (n=45). Both treatment strategies did not significantly differ in terms of stone clearance or significant morbidity. Bile leakage on the other hand occurred in six patients having choledochotomy and did not occur in patients having ERCP (p=0.01). The decision to perform either one of the treatment options should depend on the availability of an expert endoscopist and on the preference and experience of the surgeon.

In patients with CBD stones detected after cholecystectomy, postoperative ERCP usually is the preferred treatment. In the unlikely event that ERCP is unsuccessful, surgical exploration of the CBD can be performed.

Single-stage approach

Laparoscopic cholecystectomy with laparoscopic common bile duct exploration

Laparoscopic CBD exploration at the time of laparoscopic cholecystectomy has gained much attention in the treatment of choledochocystolithiasis. This so single-stage surgical strategy offers the possibility to treat the patient for both gallstones and CBD stones in

one single session and can be performed with high efficiency and minimal morbidity and mortality. In the hands of experienced laparoscopic surgeons, the single-stage laparoscopic technique may be the favourable treatment.

In the past decade, many randomized controlled trials were conducted to evaluate the feasibility of the single-stage versus the two-stage approach in the treatment of concomitant gallstones and CBD stones. Zhu et al. performed a meta-analysis of eight randomized controlled trails on this subject, and included a total of 1130 patients.[27] Both treatment modalities were equivalent in terms of clinical complications (15%) and mortality (1.4%). Yet, single-stage management turned out to be more successful in clearing the CBD (90% vs. 86%, $p = 0.03$)[27] and more cost-effective as a result of a reduced hospital stay (4.6 vs. 5.3 days, $p = 0.03$).[27,57,58]

Even though single-stage management in itself is superior to two-stage management in treating patients with choledochocystolithiasis, the choice of treatment is often determined by factors such as the presence of professional expertise and the availability of adequate equipment on the one hand, and the anatomy of the biliary tract and the number and size of CBD stones on the other, rather than by a real superiority of one strategy over another.[52,59] Laparoscopic CBD exploration involves advanced laparoscopic skills and procedures, including intracorporeal suturing and knotting and choledochoscopy, which takes a long time to master.[27] As a result, in the majority of hospitals worldwide, the two-stage approach remains the preferred management strategy for choledochocystolithiasis. Notwithstanding the fact that this approach requires two separate procedures and is associated with prolonged hospital stay.

Laparoscopic cholecystectomy with intraoperative ERCP

Another option in the treatment of combined choledochocystolithiasis is laparoscopic cholecystectomy and endoscopic sphincterotomy at the same time, the so called "rendezvous' technique. During laparoscopy, a transcystic inserted guidewire is positioned through the ampulla to allow easy and fast access of the sphincterotome into the CBD. This method allows easy and fast cannulation, thus avoiding papillary oedema and pancreatic trauma.

The effectiveness and safety of this (combined endoscopic-laparoscopic) rendezvous technique in the treatment of uncomplicated choledocho-cystolithiasis has been assessed in several studies. In a randomized controlled trial, Hong et al. compared the rendezvous

technique with laparoscopic cholecystectomy with laparoscopic CBD exploration.[60] No difference was found in terms of surgical success rate, duration of surgery, postoperative complications, retained bile duct stones and length of hospital stay. Both minimally invasive procedures were shown to be safe and effective in the treatment of choledochocystolithiasis.

Lella et al. randomly assigned patients with choledochocystolithiasis to either the rendezvous technique (n=60) or preoperative ERCP (with endoscopic sphincterotomy) followed by laparoscopic cholecystectomy (n=60).[61] All included patients had one or more risk factors for post-ERCP pancreatitis. None of the patients who underwent the combined laparoscopic-endoscopic procedure developed postoperative pancreatitis, whereas in the pre-operative ERCP group six cases of acute pancreatitis occurred. The rendezvous technique seems to prevent post-ERCP pancreatitis in patients with risk factors for this complication.

In a similar trial, Morino et al. randomly assigned patients to either the laparoscopic-endoscopic procedure or the preoperative ERCP followed by laparoscopic cholecystectomy in the same hospital admission.[62] Stone clearance, morbidity and mortality did not significantly differ between both groups, whereas the rendezvous technique was associated with significant shorter hospital stay (4 days versus 8 days, $p < 0.0001$) and reduction of total costs (2829 vs 3834 euro ($p < 0.05$).

The rendezvous technique turns out to be a feasible treatment for patients with concomitant gallstones and CBD stones.[60-62] However, since the endoscopist and surgeon must cooperate closely at the same time, this minimally invasive option requires considerable organisational effort and is not always an available option.

CONCLUSIONS

In patient with concomitant gallstones and CBD stones, laparoscopic CBD exploration at the same time as cholecystectomy offers the possibility to treat both problems simultaneously. This so-called single stage approach requires routine intraoperative cholangiography, and since this already is the first step in performing transcystic stone removal, it seems logical to use this approach in a first attempt to extract (small) stones. If transcystic stone clearance is unsuccessful, the surgeon can proceed with transductal CBD exploration. Yet, this method requires advanced laparoscopic skills and should be

performed only by experienced laparoscopic surgeons. Ideally, intraoperative ERCP would be the next step, and can be performed in a rendezvous fashion.[28] The transcystic inserted guidewire is positioned through the ampulla to allow easy and fast cannulation and less manipulation. This combined endoscopic-laparoscopic procedure however, requires considerable organisational effort since the endoscopist and surgeon have to work closely together at the same time, and therefore not always an available option.

Although laparoscopic CBD exploration is slowly gaining ground in the treatment of combined CBD and gallbladder stones, many surgeon still prefer a two-stage approach in which laparoscopic cholecystectomy and ERCP are carried out in separate sessions. This approach is successful, but disadvantages are increased costs as result of a prolonged hospital stay and the need for another surgical intervention in case postoperative ERCP fails to clear the CBD.

REFERENCES

1 Collins C, Maguire D, Ireland A, Fitzgerald E, O'Sullivan GC. A prospective study of common bile duct calculi in patients undergoing laparoscopic cholecystectomy: natural history of choledocholithiasis revisited. Ann Surg 2004 Jan;239(1):28-33.

2 Hemli JM, Arnot RS, Ashworth JJ, Curtin AM, Simon RA, Townend DM. Feasibility of laparoscopic common bile duct exploration in a rural centre. ANZ J Surg 2004 Nov;74(11):979-982.

3 Fiore NF, Ledniczky G, Wiebke EA, Broadie TA, Pruitt AL, Goulet RJ, et al. An analysis of perioperative cholangiography in one thousand laparoscopic cholecystectomies. Surgery 1997 Oct;122(4):817-21; discussion 821-3.

4 Petelin JB. Laparoscopic common bile duct exploration. Surg Endosc 2003 Nov; 17(11):1705-1715.

5 Gonzalez JJ, Sanz L, Grana JL, Bermejo G, Navarrete F, Martinez E. Biliary lithiasis in the elderly patient: morbidity and mortality due to biliary surgery. Hepatogastroenterology 1997 Nov-Dec; 44(18):1565-1568.

6 Hammarstrom LE, Holmin T, Stridbeck H, Ihse I. Long-term follow-up of a prospective randomized study of endoscopic versus surgical treatment of bile duct calculi in patients with gallbladder in situ. Br J Surg 1995 Nov;82(11):1516-1521.

7 Neoptolemos JP, Carr-Locke DL, Fossard DP. Prospective randomised study of preoperative endoscopic sphincterotomy versus surgery alone for common bile duct stones. Br Med J (Clin Res Ed) 1987 Feb 21;294(6570):470-474.

8 Targarona EM, Ayuso RM, Bordas JM, Ros E, Pros I, Martinez J, et al. Randomised trial of endoscopic sphincterotomy with gallbladder left in situ versus open surgery for common bileduct calculi in high-risk patients. Lancet 1996 Apr 6; 347(9006):926-929.

9 Kawai K, Akasaka Y, Murakami K, Tada M, Koli Y. Endoscopic sphincterotomy of the ampulla of Vater. Gastrointest Endosc 1974 May;20(4):148-151.

10 Classen M, Demling L. Endoscopic sphincterotomy of the papilla of vater and extraction of stones from the choledochal duct (author's transl). Dtsch Med Wochenschr 1974 Mar 15;99(11):496-497.

11 Himal HS. Common bile duct stones: the role of preoperative, intraoperative, and postoperative ERCP. Semin Laparosc Surg 2000 Dec;7(4):237-245.

12 Binmoeller KF, Schafer TW. Endoscopic management of bile duct stones. J Clin Gastroenterol 2001 Feb;32(2):106-118.

13 Vitale GC, Zavaleta CM. Endoscopic retrograde cholangiopancreatography for surgeons. Semin Laparosc Surg 2003 Mar; 10(1):19-27.

14 Bacal D, Berthou JC, Mutter D, Jourdan I. Laparoscopic common bile duct exploration: choledochotomy approach. 2003; Available at: http://www.websurg.com/doi-ot02en013a.htm. Accessed 12/22/2015.

15 Bacal D, Berthou JC, Mutter D, Jourdan I. Laparoscopic common bile duct explo-

ration: transcystic approach. 2003; Available at: http://www.web-surg.com/doi-ot02en014a.htm. Accessed 12/22/2015.

16 Hungness ES, Soper NJ. Management of common bile duct stones. J Gastrointest Surg 2006 Apr;10(4):612-619.

17 Lyass S, Phillips EH. Laparoscopic transcystic duct common bile duct exploration. Surg Endosc 2006 Apr;20 Suppl 2:S441-5.

18 ElGeidie A, Atif E, Naeem Y, ElEbidy G. Laparoscopic Bile Duct Clearance Without Choledochoscopy. Surg Laparosc Endosc Percutan Tech 2015 Oct;25(5):e152-5.

19 Paganini AM, Guerrieri M, Sarnari J, De Sanctis A, D'Ambrosio G, Lezoche G, et al. Thirteen years' experience with laparoscopic transcystic common bile duct exploration for stones. Effectiveness and long-term results. Surg Endosc 2007 Jan;21(1):34-40.

20 Martin IJ, Bailey IS, Rhodes M, O'Rourke N, Nathanson L, Fielding G. Towards T-tube free laparoscopic bile duct exploration: a methodologic evolution during 300 consecutive procedures. Ann Surg 1998 Jul;228(1):29-34.

21 Gharaibeh KI, Heiss HA. Biliary leakage following T-tube removal. Int Surg 2000 Jan-Mar;85(1):57-63.

22 Gurusamy KS, Koti R, Davidson BR. T-tube drainage versus primary closure after laparoscopic common bile duct exploration. Cochrane Database Syst Rev 2013 Jun 21;6:CD005641.

23 DiSario J, Chuttani R, Croffie J, Liu J, Mishkin D, Shah R, et al. Biliary and pancreatic lithotripsy devices. Gastrointest Endosc 2007 May;65(6):750-756.

24 Cuschieri A, Adamson GD. Multimedia article. Laparoscopic transection choledochoduodenostomy. Surg Endosc 2005 May;19(5):728.

25 Baker AR, Neoptolemos JP, Leese T, James DC, Fossard DP. Long term follow-up of patients with side to side choledochoduodenostomy and trans-duodenal sphincteroplasty. Ann R Coll Surg Engl 1987 Nov;69(6):253-257.

26 Grubnik VV, Tkachenko AI, Ilyashenko VV, Vorotyntseva KO. Laparoscopic common bile duct exploration versus open surgery: comparative prospective randomized trial. Surg Endosc 2012 Aug; 26(8):2165-2171.

27 Zhu HY, Xu M, Shen HJ, Yang C, Li F, Li KW, et al. A meta-analysis of single-stage versus two-stage management for concomitant gallstones and common bile duct stones. Clin Res Hepatol Gastroenterol 2015 Oct;39(5):584-593.

28 Reinders JS, Gouma DJ, Ubbink DT, van Ramshorst B, Boerma D. Transcystic or transductal stone extraction during single-stage treatment of choledochocystolithiasis: a systematic review. World J Surg 2014 Sep;38(9):2403-2411.

29 Stromberg C, Nilsson M, Leijonmarck CE. Stone clearance and risk factors for failure in laparoscopic transcystic exploration of the common bile duct. Surg Endosc 2008 May;22(5):1194-1199.

30 Hua J, Lin S, Qian D, He Z, Zhang T, Song Z. Primary closure and rate of bile leak following laparoscopic common bile duct exploration via choledochotomy. Dig Surg 2015;32(1):1-8.

31 Estelles Vidagany N, Domingo Del Pozo C, Peris Tomas N, Diez Ares JA, Vazquez Tarragon A, Blanes Masson F. Eleven years of primary closure of common bile duct after choledochotomy for choledocholithiasis. Surg Endosc 2015 Jul 23.

32 Bergman JJ, van den Brink GR, Rauws EA, de Wit L, Obertop H, Huibregtse K, et al. Treatment of bile duct lesions after laparoscopic cholecystectomy. Gut 1996 Jan;38(1):141-147.

33 Tenner S, Baillie J, DeWitt J, Vege SS, American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol 2013 Sep;108(9) :1400-15; 1416.

34 Masoomi H, Buchberg B, Nguyen B, Tung V, Stamos MJ, Mills S. Outcomes of laparoscopic versus open colectomy in elective surgery for diverticulitis. World J Surg 2011 Sep;35(9):2143-2148.

35 Lal P, Vindal A, Sharma R, Chander J, Ramteke VK. Safety of open technique for first-trocar placement in laparoscopic surgery: a series of 6,000 cases. Surg Endosc 2012 Jan;26(1):182-188.

36 Swank HA, Mulder IM, la Chapelle CF, Reitsma JB, Lange JF, Bemelman WA. Systematic review of trocar-site hernia. Br J Surg 2012 Mar;99(3):315-323.

37 Boldo E, Perez de Lucia G, Aracil JP, Martin F, Escrig J, Martinez D, et al. Trocar site hernia after laparoscopic ventral hernia repair. Surg Endosc 2007 May;21(5):798-800.

38 Fernandez AZ,Jr, DeMaria EJ, Tichansky DS, Kellum JM, Wolfe LG, Meador J, et al. Experience with over 3,000 open and laparoscopic bariatric procedures: multivariate analysis of factors related to leak and resultant mortality. Surg Endosc 2004 Feb;18(2):193-197.

39 Bailey AA, Bourke MJ, Williams SJ, Walsh PR, Murray MA, Lee EY, et al. A prospective randomized trial of cannulation technique in ERCP: effects on technical success and post-ERCP pancreatitis. Endoscopy 2008 Apr;40(4):296-301.

40 Coppola R, Riccioni ME, Ciletti S, Cosentino L, Coco C, Magistrelli P, et al. Analysis of complications of endoscopic sphincterotomy for biliary stones in a consecutive series of 546 patients. Surg Endosc 1997 Feb;11(2):129-132.

41 Tranter SE, Thompson MH. Comparison of endoscopic sphincterotomy and laparoscopic exploration of the common bile duct. Br J Surg 2002 Dec;89(12): 1495-1504.

42 Tanaka M. Bile duct clearance, endoscopic or laparoscopic? J Hepatobiliary Pancreat Surg 2002;9(6):729-732.

43 Sugiyama M, Atomi Y. Follow-up of more than 10 years after endoscopic sphincterotomy for choledocholithiasis in young patients. Br J Surg 1998 Jul;85(7):917-921.

44 Sees DW, Martin RR. Comparison of preoperative endoscopic retrograde cholangiopancreatography and laparoscopic cholecystectomy with operative management of gallstone pancreatitis. Am J Surg 1997 Dec;174(6):719-722.

45 Tanaka M, Takahata S, Konomi H, Matsunaga H, Yokohata K, Takeda T, et al. Long-term consequence of endoscopic sphincterotomy for bile duct stones. Gastrointest Endosc 1998 Nov;48(5):465-469.

46 Badalov N, Tenner S, Baillie J. The Prevention, recognition and treatment of post-ERCP pancreatitis. JOP 2009 Mar 9; 10(2):88-97.

47 Freeman ML, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, et al. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. Gastrointest Endosc 2001 Oct;54(4):425-434.

48 Hill J, Martin DF, Tweedle DE. Risks of leaving the gallbladder in situ after endoscopic sphincterotomy for bile duct stones. Br J Surg 1991 May;78(5):554-557.

49 Davidson BR, Neoptolemos JP, Carr-Locke DL. Endoscopic sphincterotomy for common bile duct calculi in patients with gall bladder in situ considered unfit for surgery. Gut 1988 Jan;29(1):114-120.

50 Cotton PB, Geenen JE, Sherman S, Cunningham JT, Howell DA, Carr-Locke DL, et al. Endoscopic sphincterotomy for stones by experts is safe, even in younger patients with normal ducts. Ann Surg 1998 Feb;227(2):201-204.

51 Dasari BV, Tan CJ, Gurusamy KS, Martin DJ, Kirk G, McKie L, et al. Surgical versus endoscopic treatment of bile duct stones. Cochrane Database Syst Rev 2013 Dec 12;12:CD003327.

52 Topal B, Aerts R, Penninckx F. Laparoscopic common bile duct stone clearance with flexible choledochoscopy. Surg Endosc 2007 Dec;21(12):2317-2321.

53 Boerma D, Rauws EA, Keulemans YC, Janssen IM, Bolwerk CJ, Timmer R, et al. Wait-and-see policy or laparoscopic cholecystectomy after endoscopic sphincterotomy for bile-duct stones: a randomised trial. Lancet 2002 Sep 7;360(9335): 761-765.

54 McAlister VC, Davenport E, Renouf E. Cholecystectomy deferral in patients with endoscopic sphincterotomy. Cochrane Database Syst Rev 2007 Oct 17;(4)(4): CD006233.

55 Reinders JS, Goud A, Timmer R, Kruyt PM, Witteman BJ, Smakman N, et al. Early laparoscopic cholecystectomy improves outcomes after endoscopic sphincterotomy for choledochocystolithiasis. Gastroenterology 2010 Jun; 138(7):2315-2320.

56 Nathanson LK, O'Rourke NA, Martin IJ, Fielding GA, Cowen AE, Roberts RK, et al. Postoperative ERCP versus laparoscopic choledochotomy for clearance of selected bile duct calculi: a randomized trial. Ann Surg 2005 Aug; 242(2):188-192.

57 Bansal VK, Misra MC, Rajan K, Kilambi R, Kumar S, Krishna A, et al. Single-stage laparoscopic common bile duct exploration and cholecystectomy versus two-stage endoscopic stone extraction followed by laparoscopic cholecystectomy for patients with concomitant gallbladder stones and common bile duct stones: a randomized controlled trial. Surg Endosc 2014 Mar;28(3):875-885.

58 Topal B, Vromman K, Aerts R, Verslype C, Van Steenbergen W, Penninckx F. Hospital cost categories of one-stage versus two-stage management of common bile duct stones. Surg Endosc 2010 Feb; 24(2):413-416.

59 Bencini L, Tommasi C, Manetti R, Farsi M. Modern approach to cholecysto-choledocholithiasis. World J Gastrointest Endosc 2014 Feb 16;6(2):32-40.

60 Hong DF, Xin Y, Chen DW. Comparison of laparoscopic cholecystectomy combined with intraoperative endoscopic sphincterotomy and laparoscopic exploration of the common bile duct for cholecystocholedocholithiasis. Surg Endosc 2006 Mar; 20(3):424-427.

61 Lella F, Bagnolo F, Rebuffat C, Scalambra M, Bonassi U, Colombo E. Use of the laparoscopic-endoscopic approach, the so-called "rendezvous" technique, in cholecystocholedocholithiasis: a valid method in cases with patient-related risk factors for post-ERCP pancreatitis. Surg Endosc 2006 Mar;20(3):419-423.

62 Morino M, Baracchi F, Miglietta C, Furlan N, Ragona R, Garbarini A. Preoperative endoscopic sphincterotomy versus laparo-endoscopic rendezvous in patients with gallbladder and bile duct stones. Ann Surg 2006 Dec;244(6):889-93; discussion 893.

CHAPTER 11

Summary and general discussion

SUMMERY AND GENERAL DISCUSSION

PART I: Treatment strategies for acute calculous cholecystitis

Many patients undergoing surgery for acute cholecystitis receive *postoperative* antibiotic prophylaxis with the intent to reduce infectious complications. To determine the effect of this prophylaxis on postoperative infections in patients undergoing emergency cholecystectomy for mild acute calculous cholecystitis, we conducted a randomized controlled, multicenter, non-inferiority trial (PEANUTS-I trial). The results of this trial are provided in **Chapter 2**. A total of 150 patients with mild acute cholecystitis were randomly assigned to either a single preoperative dose of cefazoline (2000 mg, IV) or antibiotic prophylaxis for three days after surgery (cefuroxime 750 mg + metronidazole 500 mg, IV, three times daily) in addition to this single dose. The primary endpoint was defined as a composite of all infectious complications within 30 days after cholecystectomy. The absence of extended antibiotic prophylaxis appeared not to lead to an increase of complications; 3 of 77 patients (4%) in the extended antibiotic group and 3 of 73 (4%) patients in the standard prophylaxis group developed infectious complications (absolute difference 0.2%; 95% CI -8.2 to 8.9). Although non-inferiority of standard single-dose prophylaxis compared with extended prophylaxis could not be proven, extending antibiotics seems clinically irrelevant considering the low overall infection rate. In patients with mild acute cholecystitis, *postoperative* antibiotic prophylaxis may therefore be omitted. Even in patients with moderate acute cholecystitis the use of *postoperative* antibiotic prophylaxis is disputable. A recent randomized controlled trial demonstrated no beneficial effect of postoperative treatment with amoxicillin plus clavulanic acid on the infectious complication rate in patients with mild or moderate acute cholecystitis undergoing emergency cholecystectomy.[1] A decrease of antibiotic use is desirable in view of a reduction of needless medical activities, costs and bacterial resistance. The latter is a growing issue in contemporary medicine and has emerged as one of the eminent public health concerns nowadays.[2]

The subsequent question is whether the single *preoperative* dose of antibiotic prophylaxis is indicated in patients undergoing emergency cholecystectomy for acute calculous cholecystitis. To answer this question we designed a randomized controlled non-inferiority trial (PEANUTS-II trial), the protocol of which is presented in **Chapter 3**. Patients with mild or moderate acute cholecystitis are randomly assigned to receive either a single preoperative dose of cefazoline (2000 mg, IV) or no antibiotic prophylaxis before

emergency cholecystectomy. The primary endpoint is defined as a composite of all infectious complications within 30 days after cholecystectomy. Recruitment commenced in March 2016 and is anticipated to run until March 2019. At present, seven hospitals are participating in the trial and 90 patients have been randomized. If this study demonstrates that omitting antibiotic prophylaxis does not increase the postoperative infection rate, the use of antibiotics for this indication can be dropped as a whole. If so, the role of antibiotic prophylaxis in surgery of the entire upper gastrointestinal tract becomes questionable. A decrease of antibiotic use, on such a scale, may result in a large reduction of needless medical activities and bacterial resistance. Future studies should therefore focus on the effect of antibiotic prophylaxis on postoperative infections in patients undergoing surgery of the upper gastrointestinal tract.

Cholecystectomy is considered the treatment of choice in patients with acute cholecystitis deemed fit enough for surgery.[3-5] It is one of the most frequently performed procedures in surgical practice and nowadays mostly performed laparoscopically. The rationale for cholecystectomy is based on the assumption that the source of infection should immediately be eliminated from the body to prevent clinical deterioration. The actual benefit of surgery in the treatment of acute calculous cholecystitis, however, has never been properly researched. Prospective, let alone randomized studies indicating the superiority of surgical over conservative treatment are lacking. Yet, the decision to perform surgery should be well-considered since cholecystectomy can result in serious morbidity.[6] **Chapter 4** provides a literature review on the short and long-term outcome of conservative (i.e. non-invasive) treatment of acute cholecystitis. Studies reporting on the success rate of conservative treatment during index admission as well as studies reporting on the recurrence rate of gallstone-related disease during long term follow-up (i.e. ≥12 months) after initial non-surgical management were included. Ten randomized controlled trials and 14 non-randomized studies with a total of 1841 patients were included. Conservative treatment during index admission was successful in 87% of patients with acute cholecystitis and in case of mild disease even in 96%. In the long term, 22% of the patients developed recurrent gallstone-related disease. One can conclude that conservative treatment of acute calculous cholecystitis seems to be feasible and safe, especially in patients with mild disease. Just as in case of cholecystitis, also in other acute gastro-intestinal inflammations the benefit of surgery over conservative care is not always clearly demonstrated, leading to treatment algorithms (in select cases) slowly

shifting towards conservative management. In case of uncomplicated acute diverticulitis, previous studies demonstrated that conservative treatment seems feasible;[7,8] surgery should be reserved for cases with significant complications, unresponsive to medical treatment.[9] In acute appendicitis, too, randomized trials showed initial non-surgical management to be safe.[10] A comparable management algorithm for (mild) acute calculous cholecystitis seems plausible.[11] There is, however, insufficient evidence to demonstrate actual superiority of conservative treatment over cholecystectomy for this indication. A large prospective randomized controlled trial with long term follow-up in which conservative treatment is compared with cholecystectomy is sorely needed.

In recent years, several studies aimed to determine the optimal timing of surgery for acute cholecystitis, showing a clear benefit in performing early rather than delayed cholecystectomy.[12] Early cholecystectomy appeared to be associated with lower complication rates, shorter hospital stay, lower costs and higher patient satisfaction. Nevertheless, according to the international guidelines of gallstone disease, delayed cholecystectomy is the preferred treatment in patients with moderate acute cholecystitis while early cholecystectomy should be performed only in patients with mild disease.[5] **Chapter 5** presents the results of a retrospective study on the clinical outcome of emergency cholecystectomy in patients with moderate acute cholecystitis, by comparing the outcome in patients with mild and moderate disease. All consecutive patients who underwent emergency cholecystectomy for acute cholecystitis in a large teaching hospital between January 2002 and January 2015 were included. Between patients with mild (n=270) and moderate acute cholecystitis (n=187) none of the outcome variables significantly differed; the conversion rate, operating time and number and type of perioperative complications as well as the mortality and length of hospital stay were similar. The differentiated approach in timing of cholecystectomy as proposed by the international guidelines seems therefore not justified. Our findings support a revision of these guidelines with respect to performing emergency cholecystectomy in both mild and moderate acute cholecystitis.

Although differentiation between mild and moderate acute cholecystitis obviously has no value in the choice for surgery, this differentiation might otherwise contribute to decisions on post-operative care such as antibiotic treatment or expected recovery time. Perioperative parameters such as empyema or necrosis of the gallbladder could be used, but these criteria have not been investigated yet and should be focus of future research.

Chapter 6 provides an overview of the recent advances in the treatment of acute cholecystitis. Aspects such as timing and approach of cholecystectomy, pros and cons of percutaneous gallbladder drainage and conservative treatment and the effect of antibiotic prophylaxis are addressed.

PART II: Management of high-risk patients with acute calculous cholecystitis

While early cholecystectomy has been firmly established as the procedure of choice for acute cholecystitis in young and fit patients,[13] controversy exists in the surgical management of elderly. In view of the aging population, addressing this controversy becomes a matter of utmost importance. In this era of advanced surgical techniques and improved perioperative care, the willingness to perform emergency operations in elderly continues to increase. **Chapter 7** presents the results of a retrospective study on the feasibility of early cholecystectomy for acute cholecystitis in elderly patients. The perioperative outcome of patients aged 75 or older (n=121) was compared to that in younger patients (n=582). Morbidity was higher in the elderly group (17% vs. 8%, $p<0.004$), which could be attributed to a high incidence of cystic stump leakage; a complication that no longer occurred after changing the technique of ligation of the cystic stump from metal to vascular clips. The cardiopulmonary complication rate (4% vs. 3%, $p=0.35$) as well as mortality (3% vs. 1%, $p=0.07$) did not significantly differ between both groups. Based on these results, one can conclude that early cholecystectomy seems to be a treatment well suited to elderly patients. To reduce the risk of perioperative complications, a carefull selection of patients who may benefit from surgery is required. A large retrospective study of patients who underwent laparoscopic cholecystectomy showed that a prediction of individual outcome based on a patient's individual risk profile and optimization of comorbidities may assist in preventing specific post-operative complications.[14] In addition, anticipation of a complication should be an important incentive to focus on concrete measures to reduce specific complications in patients at risk.

Chapter 8 provides a comprehensive literature review on the clinical outcome of early cholecystectomy in the elderly population. Eight studies with a total of 592 patients aged 70 or older were included. The mean age was 81 years. Nearly half of the patients (44%) had an American Society of Anaesthesiologist score of 3 or higher. Early cholecystectomy was performed laparoscopically in 316 patients (53%) and open in 276

patients (47%). The review demonstrated that early surgical management seems to be a feasible treatment in this patient group, showing a conversion rate of 23%, a perioperative morbidity of 24% and a mortality of 4%. Although increased morbidity and mortality are inextricably linked to any treatment strategy for acute cholecystitis in elderly patients, the perioperative outcome may be improved by several measures. Firstly, elderly patients who might benefit from early cholecystectomy, i.e. in good physical health with few comorbidities, should be carefully selected. Secondly, a thorough preoperative assessment of the individual's health status is required to identify factors associated with increased risks of specific complications and to recommend a management plan that could minimize these risks.[15] Thirdly, the surcical procedure should be performed by an experienced laparoscopic surgeon, as previous studies showed that laparoscopic cholecystectomy is more succesful if carried out by a laparoscopy-oriented surgeon.[16,17] Lastly, specialized postoperative care should be availabel as elderly patients are prone to develop postoperative complications including pulmonary complications, under nutrition, urinary tract infections, ulcers, delirium and functional decline.[15] Education of health care providers in core geriatric principles, risk factors, the incorporation of evidence-based interventions and interdisciplinary communication may contribute to improvement of the postoperative outcome.

In high-risk patients, early cholecystectomy for acute cholecystitis can lead to serious morbidity and mortality due to reduced physiologic reserve.[18-22] Therefore, imaging-guided percutaneous catheter drainage is increasingly being performed as an alternative treatment. This minimally invasive radiological procedure resolves local and systemic inflammation without the risk of surgery. However, the gallbladder remains in situ which may lead to recurrent cholecystitis and other biliary complications.[23,24] The question arises whether early cholecystectomy should therefore be preferred in order to provide a definitive treatment. To determine which treatment strategy is best suited for high risk patients with acute calculous cholecystitis, we conducted a nationwide, randomized controlled, multicenter trial (CHOCOLATE-trial). The results of this trial are presented in **Chapter 9**. High-risk patients with acute calculous cholecystitis were randomly assigned to laparoscopic cholecystectomy or percutaneous catheter drainage. High-risk was defined as an APACHE-II score ≥7. The primary end point was a composite of major complications within 30 days and reintervention, readmission and death within one year. The primary end point occurred in 46 of 68 patients (68%) assigned to percutaneous

drainage and in 10 of 66 patients (15%) assigned to laparoscopic cholecystectomy (risk ratio with laparoscopic cholecystectomy, 0.22; 95% CI 0.12 to 0.41; P<0.001). In the drainage group, 45 patients (66%) required a reintervention as compared with 7 patients (11%) in cholecystectomy group (P<0.001). In addition, readmissions occurred more frequently in the drainage group (62% versus 8%, P<0.001) and the median length of hospital stay was longer (9 days versus 5 days, P<0.001). The rate of death did not significantly differ between the two groups (9% versus 3%, P=0.70). The mean direct medical costs per patient during a follow-up period of one year were €8283 ($9111) for percutaneous drainage €5568 ($6125) for laparoscopic cholecystectomy, with a mean absolute difference of €2715 ($2987) per patient. Thus, laparoscopic cholecystectomy as compared with percutaneous drainage in high-risk patients with acute cholecystitis is the preferred treatment strategy, from both a clinical and economic point of view.

PART III: Surgical treatment of common bile duct stones

Over the past century the management of common bile duct stones has evolved considerably, and endoscopic as well as surgical options are currently available. **Chapter 10** describes the surgical techniques and its complications that are currently available, with the focus on the laparoscopic approach. In patients with common bile duct stones and concomitant gallbladder stones, laparoscopic cholecystectomy can be performed in combination with laparoscopic exploration of the common bile duct. This so called "single-stage" approach can be accomplished through either a transcystic or a transductal approach. A transcystic approach is generally used in case of small stones in small bile ducts. The common bile duct is reached via an opening in the cystic duct and actual extraction is performed with an extraction device (e.g. an atraumatic grasper, a Fogarty balloon catheter or a wire basket) under visual guidance. A transductal approach is preferred in case of large, occluding or multiple common bile duct stones or stones in the proximal ductal system, or in case of small or tortuous cystic ducts. A choledochotomy is made and stones can be extracted by using any of the aforementioned devices. The choledochotomy should be closed primarily using an absorbable suture. Laparoscopic common bile duct exploration can be performed with high efficiency and minimal morbidity and mortality. Yet, it should only be performed by experienced laparoscopic surgeons since laparoscopic common bile duct exploration requires advanced laparoscopic skills. For this reason, the default procedure in many hospitals remains

ERCP, performed either before or after laparoscopic cholecystectomy in separate sessions, a so-called “two-stage” approach. ERCP can also be performed intraoperatively in a rendezvous fashion, which allows easy and fast cannulation and less manipulation.

REFERENCES

1 Regimbeau JM, Fuks D, Pautrat K, Mauvais F, Haccart V, Msika S, et al. Effect of postoperative antibiotic administration on postoperative infection following cholecystectomy for acute calculous cholecystitis: a randomized clinical trial. JAMA 2014;312(2):145-154.

2 World Health Organization. Antimicrobial resistence. Available at: http://www.who.int/mediacentre/factsheets/fs194/en/. Accessed 12 March 2017 .

3 Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, 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. Surgical infections 2010;11(1):79-109.

4 The Dutch guidelines for gallstone disease. Available at: http://www.heelkunde.nl/-uploads/_6/re/_6reZZkgrYUAuCG6uvcN-A/richtlijn_galsteen.pdf. Accessed 12 March 2017.

5 Miura F, Takada T, Strasberg SM, Solomkin JS, Pitt HA, Gouma DJ, et al. TG13 flowchart for the management of acute cholangitis and cholecystitis. Journal of hepato-biliary-pancreatic sciences 2013;20(1):47-54.

6 Cao AM, Eslick GD, Cox MR. Early cholecystectomy is superior to delayed cholecystectomy for acute cholecystitis: a meta-analysis. Journal of Gastrointestinal Surgery 2015;19(5):848-857.

7 Beckham H, Whitlow CB. The medical and nonoperative treatment of diverticulitis. Clinics in colon and rectal surgery 2009;22(03):156-160.

8 Unlu C, Gunadi PM, Gerhards MF, Boermeester MA, Vrouenraets BC. Outpatient treatment for acute uncomplicated diverticulitis. Eur J Gastroenterol Hepatol 2013 Sep;25(9):1038-1043.

9 Bauer VP. Emergency management of diverticulitis. Clinics in colon and rectal surgery 2009;22(03):161-168.

10 Mason RJ. Surgery for appendicitis: is it necessary? Surgical infections 2008;9(4): 481-488.

11 McGillicuddy E, Schuster K, Barre K, Suarez L, Hall M, Kaml G, et al. Non-operative management of acute cholecys-titis in the elderly. Br J Surg 2012;99(9): 1254-1261.

12 Song GM, Bian W, Zeng XT, Zhou JG, Luo YQ, Tian X. Laparoscopic cholecystectomy for acute cholecystitis: early or delayed?: Evidence from a systematic review of discordant meta-analyses. Medicine (Baltimore) 2016 Jun;95(23): 3835.

13 Keus F, Gooszen HG, van Laarhoven CJ. Open, small-incision, or laparoscopic cholecystectomy for patients with symptomatic cholecystolithiasis. An overview of Cochrane Hepato-Biliary Group reviews. The Cochrane Library 2010.

14 Donkervoort S, Kortram K, Dijksman L, Boermeester M, van Ramshorst B, Boerma D. Anticipation of complications after laparoscopic cholecystectomy: prediction of individual outcome. Surg Endosc 2016; 30(12):5388-5394.

15 Optimal Perioperative Management of the Geriatric Patient. Available at: https://www.facs.org/~/media/files/quality%20programs/geriatric/acs%20nsqip%20geriatric%202016%20guidelines.ashx. Accessed 12 March 2017.

16 Boddy A, Bennett J, Ranka S, Rhodes M. Who should perform laparoscopic cholecystectomy? A 10-year audit. Surg Endosc 2007;21(9):1492-1497.

17 Kortram K, Reinders JSK, van Ramshorst B, Wiezer MJ, Go PM, Boerma D. Laparoscopic cholecystectomy for acute cholecystitis should be performed by a laparoscopic surgeon. Surg Endosc 2010; 24(9):2206-2209.

18 Ambe PC, Weber SA, Christ H, Wassenberg D. Primary cholecystectomy is feasible in elderly patients with acute cholecystitis. Aging clinical and experimental research 2015;27(6):921-926.

19 Fukami Y, Kurumiya Y, Mizuno K, Sekoguchi E, Kobayashi S. Cholecystectomy in octogenarians: be careful. Updates in surgery 2014;66(4):265-268.

20 Nikfarjam M, Yeo D, Perini M, Fink MA, Muralidharan V, Starkey G, et al. Outcomes of cholecystectomy for treatment of acute cholecystitis in octogenarians. ANZ J Surg 2014;84(12):943-948.

21 Decker G, Goergen M, Philippart P, Mendes da Costa P. Laparoscopic cholecystectomy for acute cholecystitis in geriatric patients. Acta Chir Belg 2001 Nov-Dec;101(6):294-299.

22 Winbladh A, Gullstrand P, Svanvik J, Sandström P. Systematic review of cholecystostomy as a treatment option in acute cholecystitis. HPB 2009;11(3):183-193.

23 Jang WS, Lim JU, Joo KR, Cha JM, Shin HP, Joo SH. Outcome of conservative percutaneous cholecystostomy in high-risk patients with acute cholecystitis and risk factors leading to surgery. Surg Endosc 2015;29(8):2359-2364.

24 Sanjay P, Mittapalli D, Marioud A, White RD, Ram R, Alijani A. Clinical outcomes of a percutaneous cholecystostomy for acute cholecystitis: a multicentre analysis. HPB 2013;15(7):511-516.

APPENDICES

DUTCH SUMMARY (NEDERLANDSE SAMENVATTING)

Acute galblaasontsteking (acute cholecystitis) is een veel voorkomende aandoening die in meer dan 90% van de gevallen veroorzaakt wordt door galstenen. In westerse landen komen galstenen voor bij circa 1 op de 10 volwassenen; een prevalentie die lineair toeneemt met de leeftijd.[1-4] Indien deze galstenen een obstructie van de galwegen veroorzaken kan dit een ontsteking van de galblaas tot gevolg hebben.

Patiënten met acute cholecystitis worden veelal behandeld middels een laparoscopische cholecystectomie. Ter voorkoming van postoperatieve infecties in het operatiegebied wordt zowel door de nationale als de internationale richtlijn bij deze behandeling perioperatieve antibiotische profylaxe geadviseerd. Het nut hiervan is echter nooit aangetoond. Om het effect van postoperatieve antibiotische profylaxe bij patiënten met acute cholecystitis in kaart te brengen, hebben wij een gerandomiseerde, gecontroleerde, non-inferioriteitsstudie uitgevoerd, de zogeheten PEANUTS-trial. In **hoofdstuk 2** worden de resultaten van deze studie beschreven**.** Honderdvijftig patiënten met milde acute cholecystitis werden gerandomiseerd voor een eenmalige gift antibioticum (2000mg cefazoline) voorafgaand aan de operatie of deze eenmalige gift in combinatie met een verlengde antibiotische kuur (750 mg cefuroxim + 500mg metronidazol, IV, 3 maal daags) gedurende drie dagen na de operatie. In beide groepen kwamen infectieuze complicaties voor bij ca. 4% van de patiënten. Op basis van deze resultaten kan geconcludeerd worden dat postoperatieve antibiotische profylaxe bij patiënten met milde acute cholecystitis naar alle waarschijnlijkheid niet zinvol is. Met het oog op het terugdringen van onnodig antibioticagebruik en de toename van bacteriële resistentie zijn deze bevindingen zeer relevant.[5]

Ook van preoperatieve antibiotische profylaxe bij de chirurgische behandeling van acute cholecystitis is het nut nooit aangetoond. Hiertoe hebben wij een gerandomiseerde, gecontroleerde, non-inferioriteitsstudie opgezet, de zogeheten PEANUTS II-trial. In **hoofdstuk 3** wordt het protocol van deze studie gepresenteerd. Patiënten met milde of matig-ernstige acute cholecystitis worden gerandomiseerd voor een eenmalige gift antibioticum (2000mg cefazoline) voorafgaand aan de operatie of géén antibiotische profylaxe. Als primaire uitkomstmaat geldt het ontstaan van infectieuze complicaties binnen 30 dagen na de operatie. De inclusie van patiënten werd gestart in maart 2016 en zal naar verwachting in 2019 zijn afgerond. Indien ook in deze studie geen verschil tussen beide groepen wordt aangetoond kan men in geval van acute cholecystitis in zijn

geheel afgezien van het gebruik van antibiotische profylaxe. Ook bij andere operaties van de bovenste tractus digestivus kan het nut van antibiotische profylaxe dan in twijfel worden getrokken, hetgeen een enorme afname van onnodig antibioticagebruik tot gevolg kunnen hebben.

Hoewel een laparoscopische cholecystectomie doorgaans met relatief weinig complicaties gepaard gaat, blijft het de vraag of iedere patiënten met acute cholecystitis gebaat is bij een operatie of dat voor sommigen een conservatief (i.e. niet-invasief) beleid meer geschikt is. **Hoofdstuk 4** toont een systematische review van studies naar de effecten van conservatieve behandeling van acute cholecystitis op de korte en lange-termijn (>12 maanden). De meta-analyse betrof 10 gerandomiseerde en 14 niet-gerandomiseerde studies met in totaal 1841 patiënten. Een niet-invasieve behandeling tijdens initiële opname bleek succesvol bij 86% van de patiënten met variërende ernst van cholecystitis, en zelfs bij 96% van de patiënten met milde acute cholecystitis, en ging gepaard met een mortaliteit van slechts 0,5%. In de follow-up periode (gemiddeld drie jaar) ontwikkelde 22% van de patiënten galsteen gerelateerde recidiefklachten. Al met al lijkt een conservatieve aanpak van acute cholecystitis gerechtvaardigd, met name bij patiënten met milde klachten. Om een gedetailleerd beeld van de voor- en nadelen van een conservatief beleid bij verschillende subgroepen van patiënten te krijgen zijn aanvullende prospectieve studies gewenst, waarin met name de duur van herstel en de kans op recidief galsteenlijden de aandacht moeten krijgen.

Laparoscopische cholecystectomie in geval van acute cholecystitis kan ofwel binnen enkele dagen na het ontstaan van de klachten, een zogeheten ‘vroege cholecystectomie’, ofwel na een ‘afkoelingsperiode’ van ten minste zes weken, een ‘uitgestelde cholecystectomie’, uitgevoerd worden. In het laatste geval wordt de patiënt tijdens de initiële opname conservatief behandeld met pijnstilling, zo nodig aangevuld met percutane galblaasdrainage, en pas na het verdwijnen van de acute ziekteverschijnselen geopereerd. Volgens een recente meta-analyse van 15 gerandomiseerde studies zou een vroege cholecystectomie in vergelijking met een uitgestelde procedure leiden tot minder wondinfecties, kortere opnameduur, lagere totale kosten en hogere patiënttevredenheid.[6] Desondanks wordt in de internationale richtlijn geadviseerd de timing van de cholecystectomie af te stemmen op de ernst van de cholecystitis; vroege cholecystectomie bij milde acute cholecystitis en een uitgestelde procedure bij matig-ernstige acute cholecystitis.[7] **Hoofdstuk 5** toont de resultaten van een retrospectieve

studie naar de klinische resultaten van vroege cholecystectomie bij milde en matig-ernstige cholecystitis. Alle patiënten die tussen januari 2002 en januari 2015 een vroege cholecystectomie ondergingen in het St. Antonius Ziekenhuis werden geïncludeerd. Als klinische uitkomstmaten werden conversie ratio, operatieduur, morbiditeit, mortaliteit en opnameduur gehanteerd. Deze bleken bij patiënten met matig-ernstige acute cholecystitis (n = 187) niet significant te verschillen van die bij patiënten met milde acute cholecystitis (n = 270). Een aan de ernst van de cholecystitis gerelateerde timing van cholecystectomie, zoals voorgesteld door de internationale richtlijn, lijkt daarom niet gerechtvaardigd. Een herziening van deze richtlijn met betrekking tot het uitvoeren van een vroege cholecystectomie bij zowel milde als matige-ernstige acute cholecystitis zou op basis van deze studie raadzaam zijn.

Hoofdstuk 6 toont een overzicht van de huidige stand van zaken met betrekking tot de behandeling van acute cholecystitis. Verschillende aspecten komen aan bod, zoals de timing en benadering van een cholecystectomie, de voor- en nadelen van percutane galblaasdrainage, de voor- en nadelen van conservatieve behandeling en het nut van antibiotische profylaxe.

Terwijl de jonge anderszins gezonde patiënt in geval van acute cholecystitis bij voorkeur behandeld wordt middels een vroege cholecystectomie,[8] is het de vraag is of deze behandeling gezien de grotere kans op perioperatieve complicaties en mortaliteit ook de voorkeur geniet bij de oudere patiënt. In deze tijd van steeds geavanceerdere chirurgische technieken en verbeterde perioperatieve zorg is er een toename te zien van de bereidheid om ook bij ouderen vroege chirurgie te verrichten. **Hoofdstuk 7** toont de resultaten van een retrospectieve studie naar deze vroege cholecystectomie bij ouderen over de periode 2002 tot 2016. De klinische uitkomstmaten bij patiënten met een leeftijd van 75 jaar of ouder (n = 121) werden vergeleken met die bij patiënten jonger dan 75 jaar (n = 582). De morbiditeit in de ouderen groep was significant hoger (17% versus 8%, p <0,004); hetgeen voornamelijk was toe te schrijven aan de hoge incidentie cysticus stomp lekkage in deze groep. Na 2013 echter, toen men bij ligatie van de cysticus stomp overging van een metalen op een vasculaire klem, kwam deze complicatie niet meer voor. Het aantal cardiopulmonale complicaties (4% versus 3%, p = 0,35) en de mortaliteit (3% versus 1%, p = 0,07) waren niet significant verschillend tussen beide groepen. Op grond van deze resultaten lijkt een vroege cholecystectomie ook voor de oudere patiënt een geschikte behandeling.

Als aanvulling op deze retrospectieve studie laat **Hoofdstuk 8** de resultaten zien van een systematische review van studies naar vroege cholecystectomie bij ouderen. In acht studies werden in totaal 592 patiënten ouder dan 75 jaar geïncludeerd. De gemiddelde leeftijd was 81 jaar. Bij 47% van de patiënten werd een primaire open cholecystectomie verricht en bij 53% een in opzet laparoscopische procedure. Tijdens de laparoscopische procedure werd bij een kwart van de patiënten alsnog geconverteerd naar een open cholecystectomie. In beide groepen samen deden zich bij 24% van de patiënten complicaties voor en kwam 4% te overlijden. Hoewel de behandeling van oudere patiënten onlosmakelijk is verbonden met een toegenomen kans op complicaties, zijn er opties om de perioperatieve uitkomsten te verbeteren. In de eerste plaats dient een zorgvuldige selectie gemaakt te worden van ouderen die gebaat zijn bij een operatie, te weten patiënten met een relatief goede gezondheid en weinig comorbiditeit. De gezondheidstoestand van iedere patiënt dient dan ook zorgvuldig in kaart gebracht te worden en risicofactoren geïdentificeerd en behandeld.[9] Daarnaast dient de procedure uitgevoerd te worden door een ervaren laparoscopische chirurg om de kans op conversie en complicaties te verkleinen.[10,11] Tenslotte is gespecialiseerde perioperatieve zorg vereist omdat juist ouderen gevoelig zijn voor postoperatieve complicaties zoals pneumonie, ondervoeding, urineweginfectie, ulcera, delirium en functionele achteruitgang.[9]

Bij patiënten met acute cholecystitis en een hoog operatie risico (i.e. ernstige comorbiditeit, hoge leeftijd en/of ernstige cholecystitis) kan een vroege cholecystectomie leiden tot ernstige morbiditeit en toegenomen mortaliteit als gevolg van verminderde fysiologische reserve.[12-16] Een behandeling die bij deze patiëntengroep daarom steeds vaker wordt toegepast is percutane drainage. Hierbij wordt de galblaas onder echo- of CT-geleide via de trans hepatische of trans peritoneale route aangeprikt en gedraineerd. Deze minimaal invasieve procedure wordt uitgevoerd onder lokale anesthesie en voorkomt dus chirurgische complicaties. Echter, omdat de galblaas *in situ* blijft, bestaat er een kans op recidief cholecystitis en andere biliaire complicaties.[17,18] De vraag is of een vroege cholecystectomie derhalve de voorkeur geniet boven percutane drainage. Om te bepalen welke behandelingsstrategie voor hoogrisicopatiënten met acute cholecystitis het meest geschikt is hebben wij een gerandomiseerde, gecontroleerde, multicenter trial uitgevoerd, de zogeheten CHOCOLATE-trial. De resultaten van deze studie worden beschreven in **Hoofdstuk 9**. Hoogrisicopatiënten (APACHE-II score ≥7) met acute cholecystitis werden gerandomiseerd voor vroege cholecystectomie of percutane drainage. De samengestelde primaire uitkomstmaat bestond uit zowel ernstige

complicaties binnen 30 dagen als re-interventie, heropname en dood binnen een jaar, en werd bereikt door 68% van de patiënten in de drainage groep en 15% van de patiënten in de cholecystectomie groep ($p<0.001$). Zowel het aantal re-interventies als het aantal heropnames was significant hoger in de drainage groep en de mediane opname duur significant langer. De mortaliteit daarentegen bleek niet significant te verschillen tussen beide groepen. De gemiddelde kosten per patiënt (over een jaar genomen) bedroegen in de drainage groep € 8283 en in de cholecystectomie groep € 5568, een verschil van € 2715. Derhalve is de conclusie dat vanuit zowel klinisch als economisch oogpunt bij hoog risico patiënten met acute cholecystitis laparoscopische cholecystectomie de voorkeur geniet boven percutane drainage.

De afgelopen decennia heeft de behandeling van choledochusstenen een sterke ontwikkeling doorgemaakt en is het aantal chirurgische en endoscopische methoden sterk toegenomen. **Hoofdstuk 10** biedt inzicht in de diverse chirurgische technieken en de hieraan gerelateerde complicaties. De focus ligt op de laparoscopische benadering. In geval van stenen zowel in de choledochus als in de galblaas kan een zogeheten "single-stage" techniek worden toegepast, waarbij een laparoscopische cholecystectomie en laparoscopische choledochusexploratie in een sessie worden uitgevoerd. In geval van kleine steentjes en/of een nauwe choledochus wordt veelal gekozen voor een transcystische benadering waarbij de extractie van de stenen plaatsvindt via een opening in de ductus cysticus. In geval van grote of obstruerende choledochusstenen of in geval van een kleine of kronkelige ductus cysticus geniet een transductale benadering de voorkeur waarbij de stenen via een choledochotomie verwijderd worden. Voor deze "single-stage" benaderingen zijn echter geavanceerde laparoscopische vaardigheden vereist. In veel ziekenhuizen is de standaard procedure dan ook de "two-stage" benadering, waarbij een endoscopische retrograde cholangiopancreaticografie (ERCP) wordt uitgevoerd voorafgaand aan of volgend op een laparoscopische cholecystectomie. Het is echter ook mogelijk een ERCP en cholecystectomie tegelijkertijd uit te voeren, een zogeheten "rendez-vous" benadering.

REFERENTIES

1 Schirmer BD, Winters KL, Edlich R. Cholelithiasis and cholecystitis. J Long Term Eff Med 2005;15(3).

2 Lirussi F, Nassuato G, Passera D, Toso S, Zalunardo B, Monica F, et al. Gallstone disease in an elderly population: the Silea study. Eur J Gastroenterol Hepatol 1999; 11(5):485-492.

3 Festi D, Dormi A, Capodicasa S, Staniscia T, Attili AF, Loria P, et al. Incidence of gallstone disease in Italy: results from a multicenter, population-based Italian study (the MICOL project). World J Gastroenterol 2008;14(34):5282-5289.

4 Ratner J, Lisbona A, Rosenbloom M, Palayew M, Szabolcsi S, Tupaz T. The prevalence of gallstone disease in very old institutionalized persons. JAMA 1991; 265(7):902-903.

5 World Health Organization. Antimicrobial resistence. Available at: http://www.who.int/mediacentre/factsheets/fs194/en/. Accessed 12 March 2017.

6 Song GM, Bian W, Zeng XT, Zhou JG, Luo YQ, Tian X. Laparoscopic cholecystectomy for acute cholecystitis: early or delayed?: Evidence from a systematic review of discordant meta-analyses. Medicine (Baltimore) 2016 Jun;95(23): e3835.

7 Miura F, Takada T, Strasberg SM, Solomkin JS, Pitt HA, Gouma DJ, et al. TG13 flowchart for the management of acute cholangitis and cholecystitis. Journal of hepato-biliary-pancreatic sciences 2013;20(1):47-54.

8 Keus F, Gooszen HG, van Laarhoven CJ. Open, small-incision, or laparoscopic cholecystectomy for patients with symptomatic cholecystolithiasis. An overview of Cochrane Hepato-Biliary Group reviews. The Cochrane Library 2010.

9 Optimal Perioperative Management of the Geriatric Patient. Available at: https://www.facs.org/~/media/files/quality%20programs/geriatric/acs%20nsqip%20geriatric%202016%20guidelines.ashx. Accessed 12 March 2017

10 Boddy A, Bennett J, Ranka S, Rhodes M. Who should perform laparoscopic cholecystectomy? A 10-year audit. Surg Endosc 2007;21(9):1492-1497.

11 Kortram K, Reinders JSK, van Ramshorst B, Wiezer MJ, Go PM, Boerma D. Laparoscopic cholecystectomy for acute cholecystitis should be performed by a laparoscopic surgeon. Surg Endosc 2010; 24(9):2206-2209.

12 Ambe PC, Weber SA, Christ H, Wassenberg D. Primary cholecystectomy is feasible in elderly patients with acute cholecystitis. Aging clinical and experimental research 2015;27(6):921-926.

13 Fukami Y, Kurumiya Y, Mizuno K, Sekoguchi E, Kobayashi S. Cholecystectomy in octogenarians: be careful. Updates in surgery 2014;66(4):265-268.

14 Nikfarjam M, Yeo D, Perini M, Fink MA, Muralidharan V, Starkey G, et al. Outcomes of cholecystectomy for treatment of acute cholecystitis in octogenarians. ANZ J Surg 2014;84(12):943-948.

15 Decker G, Goergen M, Philippart P, Mendes da Costa P. Laparoscopic chole-

cystectomy for acute cholecystitis in geriatric patients. Acta Chir Belg 2001 Nov-Dec;101(6):294-299.

16 Winbladh A, Gullstrand P, Svanvik J, Sandström P. Systematic review of cholecystostomy as a treatment option in acute cholecystitis. HPB 2009;11(3):183-193.

17 Jang WS, Lim JU, Joo KR, Cha JM, Shin HP, Joo SH. Outcome of conservative percutaneous cholecystostomy in high-risk patients with acute cholecystitis and risk factors leading to surgery. Surg Endosc 2015;29(8):2359-2364.

18 Sanjay P, Mittapalli D, Marioud A, White RD, Ram R, Alijani A. Clinical outcomes of a percutaneous cholecystostomy for acute cholecystitis: a multicentre analysis. HPB 2013;15(7):511-516.

REVIEW COMMITTEE

Prof. dr. H.A.H. Kaasjager
Professor of Internal Medicine
Department of Internal Medicine, University Medical Center Utrecht
The Netherlands

Prof. dr. L.P.H. Leenen
Professor of Surgery
Department of Surgery, University Medical Center Utrecht
The Netherlands

Prof. dr. B.L.A.M. Weusten
Professor of Gastroenterology
Department of Gastroenterology, University Medical Center Utrecht
The Netherlands

Prof. dr. M.J.M. Bonten
Professor of Medical Microbiology
Department of Medical Microbiology, University Medical Center Utrecht
The Netherlands

Prof. dr. H.J. Bonjer
Professor of Surgery
Department of Surgery, VU University Medical Center Amsterdam
The Netherlands

AUTHORS AND AFFILIATIONS

St. Antonius Hospital, Nieuwegein
Department of Surgery
D. Boerma
H.C. van Santvoort
B. van Ramshorst
J.E. Oor

Department of Radiology
T.L. Bollen

Department of Clinical Pharmacology
C.A.J. Knibbe

Department of Clinical Epidemiology
J.C. Kelder

Department of Medical Microbiology
B. Vlaminckx

Department of Internal Medicine
W.J.W. Bos

Medical student
M.M. Blessing

Academic Medical Center, Amsterdam
Department of Surgery
M.H.G. Besselink
D.J. Gouma

Catharina Hospital, Eindhoven
Department of Surgery
G.A.P. Nieuwenhuijzen
J.E.H. Ponten

Gelre Hospital, Apeldoorn
Department of Surgery
P. van Duijvendijk

Onze Lieve Vrouwe Gasthuis, Amsterdam
Department of Surgery
S.C. Donkervoort

University Medical Center Utrecht, Utrecht
Department of Surgery
H.C. van Santvoort

Tergooi Hospital, Hilversum
Department of Surgery
A.A.W van Geloven

Gelderse Vallei Hospital, Ede
Department of Surgery
P.M. Kruyt

Reinier de Graaff Hospital, Delft
Department of Surgery
D. Roos

Diakonessenhuis, Utrecht
Department of Surgery
A. Pronk

VU university medical center, Amsterdam
Department of Surgery
D.L. van der Peet

Erasmus University Medical Center, Rotterdam
Department of Surgery
K. Kortram

Radboud University Medical Center, Nijmegen
Department of Surgery
P.R. de Reuver
V.N.N. Kornmann

Amphia Hospital, Breda
Department of Surgery
R.M. Crolla

ACKNOWLEDGEMENTS (DANKDWOORD)

Graag wil ik iedereen bedanken die heeft bijgedragen aan de totstandkoming van dit proefschrift. De volgende personen in het bijzonder:

- Prof. dr. M.R. Vriens, promotor. Beste Menno, dank voor uw interesse, tijd en energie en voor de leerzame periode in het UMCU.

- Dr. D. Boerma, copromotor, baas, vriend en af toe een beetje mijn moeder. Lieve Djamila, ontzettend bedankt voor jouw tijd en energie; mijn voorspoedige promotie heb ik aan jou te danken. Je bent een ontzettend leuk mens met een geweldig gevoel voor humor. Waren er maar meer zoals jij (niet te veel want dan kan jij niet meer de hele tijd eerste worden).

- Dr. H.C. van Santvoort, copromotor. Beste Hjalmar, dank voor je waardevolle bijdrage aan dit proefschrift. Jouw enthousiasme en toewijding voor de wetenschap zijn ongeëvenaard en jouw perfectionisme is zeer noemenswaardig (daar kan ik nog wel een puntje aan zuigen!).

- Prof. dr. H.A.H. Kaasjager, prof. dr. L.P.H. Leenen, prof. dr. B.L.A.M. Weusten, prof. dr. M.J.M. Bonten, prof. dr. H.J. Bonjer en dr. P.R. de Reuver. Beste leden van de beoordelings- en oppositiecommissie, hartelijk dank voor de kritische beoordeling van mijn proefschrift.

- Vief en Q, mijn lieve paranimfjes. Niet alleen zijn jullie geweldige paranimfjes (duizend maal dank hiervoor), vooral zijn jullie fantastische vriendinnen. Ik ben dol op jullie!

- De staf, assistenten, onderzoekers, studenten en secretaresses van het St. Antonius Ziekenhuis. Dank voor de mooie tijd in ’t Antonnetje.

- De artsen die betrokken zijn geweest bij de multicentrische studies en ook alle patiënten die geheel belangeloos hebben deelgenomen aan de wetenschappelijke onderzoeken. Dank!

- Mijn geweldige vrienden. Wat bof ik met jullie!

- Mijn schoonfamilie. Fijn dat de deur altijd voor me open staat.

- Mijn lieve zusje Mie en grote broer Loek. Fijn dat jullie er altijd voor me zijn. En El natuurlijk!

- Papichulo, de liefste papa van de wereld. Met jou is het leven een feest.

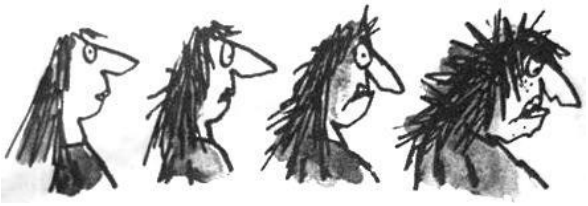
- Moekelicious, de liefste mama van de wereld en de motor van ons gezin. Tot diep in de nacht heb jij al mijn artikelen nagekeken, wat ben jij een doorzetter. Duizend maal dank voor jouw onmisbare hulp (ik vind dat jij ook een beetje gepromoveerd bent).

- Hansiepansie. Met jou kan ik de wereld aan.

CURRICULUM VITAE

Charlotte Susan Loozen werd geboren op 3 februari 1988 te Haarlem. In 2006 behaalde ze haar VWO diploma aan het Eerste Christelijk Lyceum te Haarlem. Na een tussenjaar startte ze in 2007 met de studie geneeskunde aan de Universiteit van Utrecht, waar zij in 2014 het artsenexamen met goed gevolg aflegde. Als arts-assistent chirurgie heeft zij haar carrière vervolgd in het St. Antonius Ziekenhuis te Nieuwegein, gevolgd door promotie-onderzoek naar de behandeling van acute galblaasontsteking onder supervisie van Djamila Boerma. Zij werkte kortdurend als art-assistent chirurgie in het Universiteit Medisch Centrum Utrecht en begon op 1 juli 2017 aan de opleiding tot algemeen chirurg aan de Vrije Universiteit Amsterdam.

In topsport en als fanatiek bergbeklimmer heeft Charlotte zich ontwikkeld tot een gedreven en daadkrachtige teamplayer en benut zij haar doorzettingsvermogen, stressbestendigheid, besluitvaardigheid en optimisme. Ze woont in Amsterdam samen met Hans Claassen, die haar volledig de baas is.



If a person has ugly thoughts, it begins to show on the face.
And when that person has ugly thoughts every day, every week,
every year, the face gets uglier and uglier until it gets so ugly
you can hardly bear to look at it.

A person who has good thoughts cannot ever be ugly.
You can have a wonky nose and a crooked mouth and a double chin
and stick-out teeth, but if you have good thoughts they will shine out
of your face like sunbeams and you will always look lovely.

- Roald Dahl-