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# **ANTIBIOTIC PROPHYLAXIS AND INFECTIOUS COMPLICATIONS IN SURGERY FOR ACUTE CHOLECYSTITIS**

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# **Antibiotic Prophylaxis and Infectious Complications in Surgery for Acute Cholecystitis**

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*To my family*

*Creativity is Intelligence Having Fun*

*Albert Einstein*

# ABSTRACT

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The prevalence of gallstone disease in the world is 10-20%. Almost 20% of those with gallstone disease develop a complication during their lifetime. Acute cholecystitis (AC) is a common complication of gallstones, that is routinely managed with cholecystectomy. Technical developments have made it possible to use a minimally invasive laparoscopic technique for removing the gallbladder and stones. The postoperative complication rate, although seen after only a minority of procedures, is important due to the large number of cholecystectomies performed annually. The complication rate is lower in healthy patients and when the procedure is performed electively. The infectious complication rate may, however, reach 17% if surgery is performed for mild to moderately severe AC. Use of antibiotic prophylaxis (AP) has been firmly established as routine practice despite the lack of international guideline recommendations. There are many studies on low-risk patients showing minor or no impact of preoperative antibiotic prophylaxis (PAP) on postoperative infectious complications (PIC). Prior to this thesis, the benefit of AP in acute laparoscopic cholecystectomy (Lap-C) had not been studied.

The aim of Study I was to explore the impact of AP on PIC in AC. In Study II the use of AP in Sweden was plotted at three different levels; county, hospital and surgeon. Study III aimed at exploring the impact of comorbidity on the risk for PIC. Study IV was a randomised controlled trial assessing the effectiveness of AP in reducing PIC.

For the population-based cohort studies (I – III), we used Swedish Registry for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (GallRiks) and the National patient register (NPR) as sources of data. Study IV was conducted as a double-blinded randomised study between 2009 and 2017.

Study I showed that there was no benefit of AP on PIC in acute cholecystectomy due to AC, even when adjusting for the most relevant confounders. Study II showed that AP usage differed between hospitals and surgeons, but not between counties. The difference was not related to the degree of inflammation or procedure difficulty. Study III explored patient-related risk factors. The risk for surgical site infection was increased in patients with connective tissue disease, diabetes, chronic kidney disease, cirrhosis and obesity. There was also a significantly higher risk for septicæmia in patients with chronic kidney disease or cirrhosis. In Study IV, there was no difference in the rate of PIC and bactibilia between the group receiving AP and those receiving placebo. Raised CRP and operation method were significantly associated with PIC.

PIC is multifactorial and single dose AP preoperatively has no more than an additive effect on PIC. Patient-related risk factors should, however, be taken into consideration when deciding on AP. International guidelines based on well-designed studies are urgently needed so that the decision to administer AP during acute cholecystectomy for AC becomes more stringent and uniform.

# LIST OF SCIENTIFIC PAPERS

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- I. Outcomes of antibiotic prophylaxis in acute cholecystectomy in a population-based gallstone surgery registry.**  
Jaafar, G., Persson, G., Svennblad, B., & Sandblom, G.  
British Journal of Surgery, (2014). 101(2), 69-73. doi:10.1002/bjs.9369
- II. Disparities in the regional, hospital and individual levels of antibiotic use in gallstone surgery in Sweden.**  
Jaafar, G., Darkahi, B., Lindhagen, L., Persson, G., & Sandblom, G. BMC Surgery, (2017). 17, 7. doi:10.1186/s12893-017-0312-0
- III. Patient-Related Risk Factors for Postoperative Infection After Cholecystectomy.**  
Jaafar, G., Hammarqvist, F., Enochsson, L., & Sandblom, G.  
World Journal of Surgery, (2017). 41(9), 2240-2244. doi:10.1007/s00268-017-4029-0
- IV. Antibiotic prophylaxis in acute cholecystectomy revisited: results of a double-blind randomised controlled trial**  
Jaafar, G., Sandblom, G., Lundell, L., Hammarqvist, F.  
Manuscript



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## LIST OF ABBREVIATIONS

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AC	Acute Cholecystitis
ACC	Acute Calculous Cholecystitis
AP	Antibiotic Prophylaxis
ASA	American Society of Anaesthesiologists
AUS	Abdominal Ultrasonography
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CRP	C-Reactive Protein
EAES	The European Association of Endoscopic Surgery
ESWL	Extracorporeal Shoch Wave Lithotripsy
GallRiks	Swedish Registry for Gallstone Surgery and ERCP
ICD	International Classification of Diseases
IK	Infektiösa komplikationer
Lap-C	Laparoscopic Cholecystectomy
NICE	The National Institute for Health and Care Excellence
NNT	Number needed to treat
NPR	National Patient Register
OR	Odds Ratio
PAP	Preoperative Antibiotic Prophylaxis
PC	Percutaneous Cholecystostomy
PIC	Postoperative infectious complication
RCT	Randomised Controlled Trial
RUQ	Right upper Quadrant
SAGES	The Society of American Gastrointestinal and Endoscopic Surgery
SIGN	The Scottish Intercollegiate Guideline Network
SSI	Surgical Site Infectious
STRAMA	The Swedish Strategic Programme for the Rational Use of Antimicrobial Agents

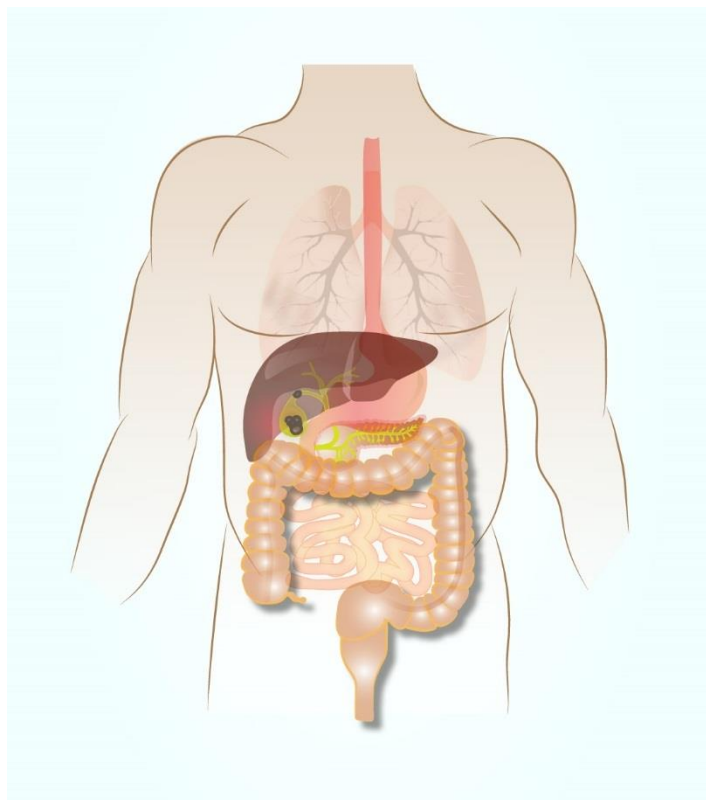
TG07	Tokyo Guideline 2007
TG13	Tokyo Guideline 2013
TG18	Tokyo Guideline 2018
TPN	Total Parenteral Nutrition
WBC	White Blood Cells
WSES	The World Society of Emergency Surgery

# 1 INTRODUCTION

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## 1.1 HISTORICAL BACKGROUND

The first surgical management of gallbladder disease was accidentally undertaken when Jean-Louis Petit (1674-1750), a Parisian surgeon, in 1743 incised an abdominal wall lesion that turned out to be the inflamed gallbladder firmly adherent to the abdominal wall (1). He thus became the first to describe a cholecystostomy. In 1867 Dr J. Bobbs performed surgery on a patient for a mass presumed to originate from the ovary, which however turned out to be an enlarged stone-filled gallbladder. Cholecystostomy was later performed by Sims, Kocher and Tait in the succeeding decade. It was not until 1882, however, that Langenbuch, a German surgeon, performed the first cholecystectomy at Lazarus Hospital in Kiel, Germany. The procedure was successfully performed on a 43-year-old patient with chronic cholecystitis, biliary colic and morphine addiction. By 1897, he had performed 100 cholecystectomies with a mortality rate of about 20%. In 1985, almost one century later, technical developments made it possible for Erich Mühe, also from Kiel, to perform the first laparoscopic cholecystectomy (Lap-C) (2).



**Figure 1:** Overview image of trunk anatomy. Illustration by FB Scientific Art Design, Fuad Bahram.

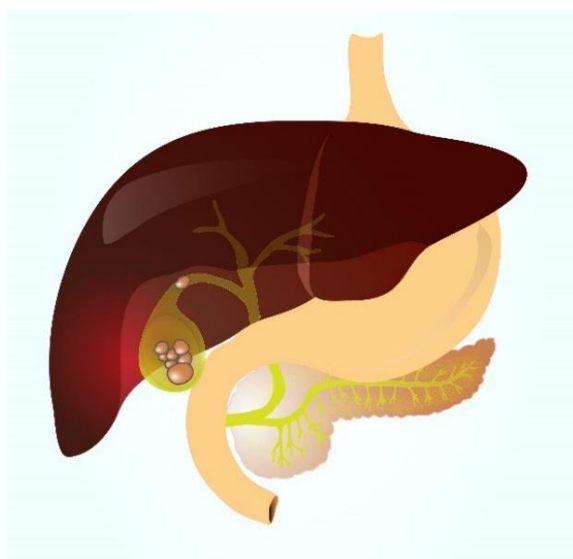
## 1.2 PREVALENCE

Gallstone disease has afflicted humans since long time, and gallstone have been found at autopsy on Egyptian (3) and Chinese mummies (4).

The overall prevalence of gallstones worldwide is 10-20%, and about 10 % in the Western world (5). The formation of gallstone disease is multifactorial as witnessed by prevalence figures that vary between different ethnical populations as well as between countries. It is inordinately high amongst American natives and lowest in black Africans (6, 7). More than 80 % of people with gallstones are asymptomatic and their disease clinically silent (5, 7). The cumulative rate of biliary complication in asymptomatic stone disease is about 3% over 10 years, while 1-3% of those with symptomatic gallstone disease develop acute cholecystitis (AC) each year following diagnosis (5, 6). In Scandinavia, 50% of those eventually treated for gallstones developed their disease by the age of 50 (6).

## 1.3 PATHOGENESIS

The three principal factors involved in the formation of cholesterol gallstone are cholesterol supersaturation, nucleation and hypomotility of the gallbladder (6). There are two main types of gallstones; cholesterol gallstones, containing more than 50% cholesterol (75-80% of gallstones in the Western world), and pigment stones. Pigment stones may further be divided into black (10-15%), and brown (5-10%) that contain 30% cholesterol. Bacterial colonisation is involved in the formation of pigment gallstones (3) and black gallstones are the result of increased production of unconjugated bilirubin that forms the stone (6). Ethnicity plays an important role in stone formation; cholesterol gallstones being more common in developed countries in the Western world, while brown pigment stones are more common in Asia (7).



**Figure 2:** Gallstone in the gallbladder and bile duct anatomy. Illustration by FB Scientific Art Design, Fuad Bahram.

Risk factors for gallstone formation are many, some being modifiable:

### **1.3.1 Age**

Age is a well-known risk factor, which may be explained by the fact that cholesterol secretion into the bile increases with age.

### **1.3.2 Gender**

The prevalence of gallstone disease differs between younger men and women but this difference declines in the elderly (7, 8). In general, gallstones are approximately twice as common in women as in men. In many studies, the prevalence has been found to be as much as three times higher in women. However, after the fifth decade the prevalence differs little between men and women, which may be explained by the fact that the oestrogen levels in women decrease (6). In Europe, the rate is 18.8% for women and 9.5% for men (6). In the USA, the corresponding rates are 16.6% and 8.6% (7). Changes in prevalence with age in women is probably related to the influence of female hormones. Oestrogen increases cholesterol secretion and decreases bile salt secretion, while progestin decreases bile salt secretion and lessens gallbladder emptying (7).

### **1.3.3 Obesity**

Genetic predisposition to gallstone disease is not fully understood, but there is undoubtedly a strong genetic influence (6).

### **1.3.4 Total parenteral nutrition (TPN) and rapid weight loss**

TPN is associated with acalculous cholecystitis, cholelithiasis and cholecystitis. The pathogenesis behind the association between total parenteral nutrition and gallstones may be gallbladder hypomotility with bile stasis due to prolonged periods without enteral nutrition (6). Biliary sludge has been seen in patients after 5-10 days who did not receive enteral nutrition on the intensive care unit (7). The sludge usually dissolves within 4 weeks of TPN discontinuation (7). Similar pattern has been seen in pregnancy and in rapid weight loss. Rapid weight loss is associated with gallstone formation in 30-71%, the association has been seen in persons with weight loss  $\geq 1.5$  kg/ week (7). The assumed pathogenesis is a change in cholesterol metabolism and increase of cholesterol concentration in the bile that promotes stone formation (9).

### **1.3.5 Pregnancy**

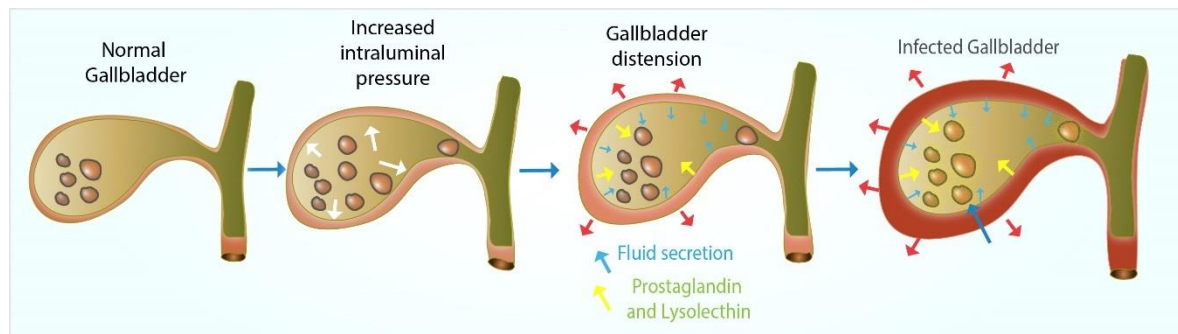
Gallstone formation in pregnant women is caused by increased oestrogen levels, increased cholesterol secretion, and decreased motility of the gallbladder due to increased progesterone levels (6). The stone usually dissolve after delivery (7).

### 1.3.6 Other risk factors

Drugs, liver disease, Crohn's disease, cystic fibrosis, chronic kidney disease, sickle cell disease, chronic haemolysis, spinal cord injury, increased cholesterol intake, dyslipidaemia and insulin-resistant diabetes may all promote gallstone formation (3, 6, 7, 10).

## 1.4 GALLSTONE DISEASES COMPLICATIONS

Cholecystitis is one of the most common complications of gallstone disease. AC is most often caused by gallstones, i.e. acute calculous cholecystitis (ACC). Biliary duct obstruction due to an impacted gallstone with associated bile stasis is the initial step in the development of AC. Increased and sustained intraluminal pressure in the gallbladder impairs mucosal blood flow and leads to ischaemia. Chemical mediators such as Lysolecithin are released within the stagnant bile, causing ischaemic damage to the mucosa. This leads to chemical cholecystitis with accumulation of inflammatory infiltration and oedema of the gallbladder wall. Once inflammation of the gallbladder begins, further inflammatory mediators are released; the most important being prostaglandin, which is involved in gallbladder contraction and fluid absorption. Secondary bacterial infection of the bile may subsequently occur in patients with ACC (Fig 3) (5, 11).



**Figure 3:** Pathogenesis of acute calculous cholecystitis. Illustration by FB Scientific Art Design, Fuad Bahram.

AC is a common clinical problem accounting for up to 5% of visits to the emergency department (11), and 9% or the third major cause of hospital admissions (11, 12).

Almost 30% of patients who do not undergo surgery after ACC suffer a new event (biliary colic, bile duct obstruction or pancreatitis) within a year (8).

## 1.5 DIAGNOSTIC CRITERIA

Diagnostic criteria commonly used are the Tokyo Guidelines 13 (TG13) criteria; a revised form of the TG07 diagnostic criteria. They include the following:

- A. Local signs of inflammation (Murphy's sign / Right Upper Quadrant [RUQ] mass/pain/tenderness).
- B. Systemic signs of inflammation (fever, elevated C-Reactive Peptide [CRP], elevated White Blood Cell count [WBC]).
- C. Imaging findings characteristic of AC.

According to the TG13, AC should be suspected if at least 1 item in A + 1 item in B are positive. The AC diagnosis is definite if 1 item in A, 1 item in B, and C are positive. This definition has a sensitivity of 91.2% and a specificity of 96.9 % (13). There are, however, studies showing a sensitivity of only 53% in the diagnosis of AC (14). A detailed medical history, careful clinical examination, laboratory test results and imaging may indicate AC more accurately (8).

### 1.5.1 Clinical indicators

There is no single clinical or laboratory finding with sufficient diagnostic accuracy to confirm or exclude AC (8). Since Murphy's sign was described as a sign of cholecystitis in 1903, it has been widely recognised as part of the clinical examination, but it has low sensitivity albeit a high specificity (13). RUQ pain and tenderness are more frequent in patients with AC than are Murphy's sign and a RUQ mass (14).

### 1.5.2 Radiologic imaging

Abdominal ultrasonography (AUS) is the investigation of choice and primary imaging technique for ACC (5, 8) even though it only has a sensitivity of 81% and a specificity of 83% in detecting cholecystitis (15). The reason is its low cost, availability, lack of invasiveness and high accuracy regarding stones in the gallbladder (8). Stones and inflammatory changes in the gallbladder wall on AUS or during surgery are criteria for diagnosing ACC. The TG18 criteria for ACC are: thickening of the gallbladder wall ( $\geq 4$  mm); enlargement of the gallbladder (long axis  $\geq 8$  cm, short axis  $\geq 4$  cm); gallstones or retained debris; pericholecystic fluid accumulation; linear shadows in the fatty tissue around the gallbladder (15); and direct tenderness when the probe is pushed against the gallbladder (sonographic Murphy's sign) (13).

Computer tomography has a relatively low sensitivity and specificity when diagnosing ACC. There is insufficient data available to support magnetic resonance imaging (MRI), which has the same sensitivity and specificity as AUS. Although cholescintigraphy (hepatobiliary iminodiacetic acid scan) has a sensitivity of 95% and specificity 90%, its availability, the time required to perform the test, and exposure to ionizing radiation limit its use (8).

## **1.6 GRADING AND SEVERITY OF CHOLECYSTITIS**

In 2007, severity assessment criteria for AC were presented in Tokyo Guidelines 2007 (TG07). AC was graded from I to III, where Grade I is cholecystitis without any organ dysfunction and mild disease of the gallbladder. Grade II is moderate AC, where the degree of acute inflammation is likely to be associated with increased difficulty in performing cholecystectomy. Grade III is defined as AC associated with organ dysfunction (Table 1) (13).

Several studies have validated TG13 severity grading and concluded that it has a high predictive value for 30-day mortality, length of hospital stay, conversion rate and medical costs. Even bile duct injury and postoperative pathological findings of gangrenous and emphysematous cholecystitis are significantly higher in higher grade cases (15).

However, the TG13 classification of AC does not include the risk stratification scores most adopted, lacks clinical validation, and has no prognostic value regarding surgical risk, and does not improve outcome (8).

**Grade I (mild) acute cholecystitis**

Does not meet the criteria of “Grade III” or “Grade III” acute cholecystitis. Grade I can also be defined as acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure.

**Grade II (moderate) acute cholecystitis** associated with any one of the following conditions:

1. Elevated white blood cell count ( $>18,000/\text{mm}^3$ ).
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) acute cholecystitis** associated with dysfunction of any one of the following organs/systems:

1. Cardiovascular dysfunction: Hypotension requiring treatment.
2. Neurological dysfunction: Decreased level of consciousness.
3. Respiratory dysfunction:  $\text{PaO}_2/\text{FiO}_2$ .
4. Renal dysfunction: Oliguria, creatinine  $>2.0$  mg/dl.
5. Hepatic dysfunction: PT-INR (1.5).
6. Haematological dysfunction: Platelet count/ $100,000/\text{mm}^3$ .

**Table 1:** Severity grading of AC according to TG13 (13).

## 1.7 MANAGEMENT

Management of AC has evolved over time, from the treatment of inflammation with antibiotics and elective open cholecystectomy after 4-6 weeks, to early open cholecystectomy, and finally to Lap-C. Lap-C was initially recommended for elective surgery, but there has recently been a trend towards acute Lap-C (11).

Several studies have shown that surgery is superior to observation. In a population-based longitudinal study of patients managed with a conservative approach and followed for 7 years in Canada, almost 30% had a gallstone-related event within a year most of these being in the

18-34 age-group (8). An RCT study in UK found that symptomatic but uncomplicated cholecystitis managed conservatively was associated with a higher rate of complications (14% compared to 2% with intervention) (8). Cholecystectomy for Grade I AC is considered a safe low-risk procedure (13). In a review from 2008, cholecystectomy for Grade III cholecystitis was not associated with an increase in local postoperative complications despite a three times higher conversion rate. Based on these findings, the authors concluded that severe cholecystitis is an acceptable indication for Lap-C (16). Surgery compared to conservative treatment in the management of high-risk patients has not been so well investigated (11).

Percutaneous cholecystostomy (PC), i.e. gallbladder drainage with decompression and removal of infected bile and pus, is a potential alternative to cholecystectomy in high-risk patients. This enables conversion of a septic patient with cholecystitis into a non-septic condition. It has a low procedure-related mortality rate (0.36%) though the 30-day mortality is high (15.4%) (8) up to 36% in other studies (17). Of patients with severe AC undergoing PC during the acute admission, 60-80% did not undergo cholecystectomy at a later stage (11). PC had no beneficial effect on surgical outcomes such as duration of surgery, hospital stay, and mortality rate (18).

Surgical removal of gallstones in ACC is not routine. However, in 2013 Young et al published 316 consecutive laparoscopic gallbladder-preserving cholelithotomy procedures, where the recurrence rate was 15%. Since the gallbladder is dysfunctional in the acute setting, this is not an alternative for treating ACC (8).

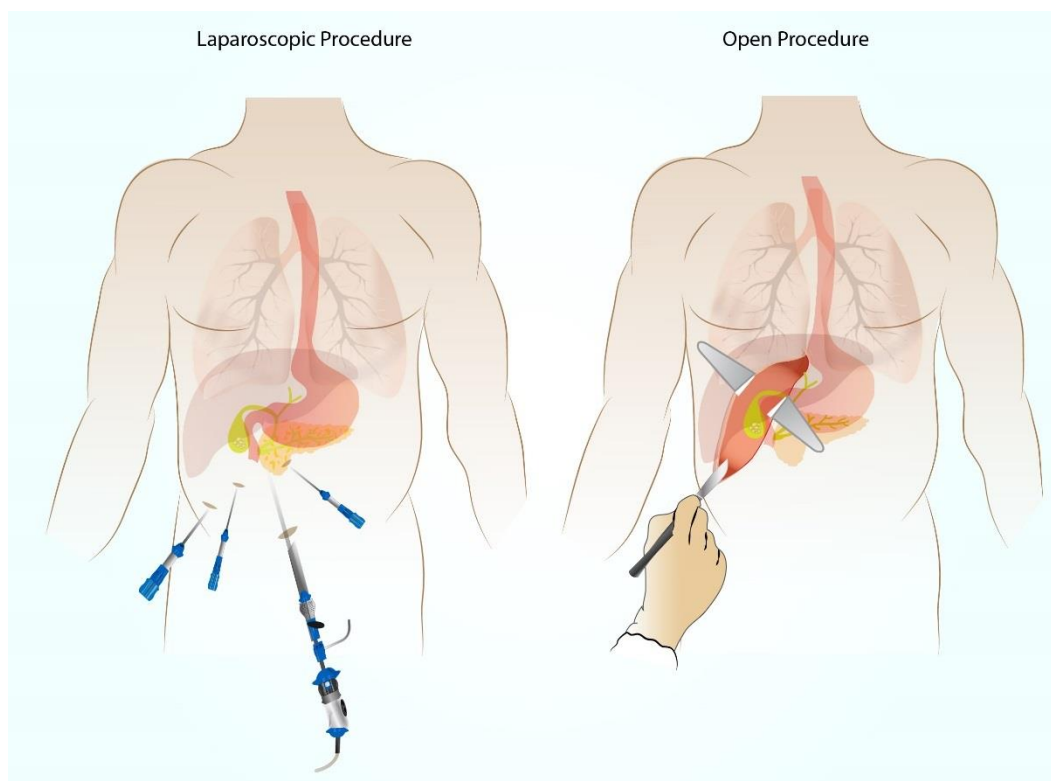
Initial management, including fasting, intravenous fluid and antibiotics, has gained consensus, though not supported by well-designed studies. This approach has been accepted worldwide and is recognised by the Tokyo Guidelines 2018 (TG18) (18). Even the Surgical Infection Society and the Infectious Diseases Society of America recommend intravenous antibiotic treatment (18). Despite the high rate of ACC, this recommendation had not been tested scientifically before (12).

The role of ursodeoxycholic acid in the treatment of cholecystitis was studied in a large randomised, double-blind, placebo-controlled trial in patients waiting for elective cholecystectomy for biliary colic, and found to be ineffective (19). It has been shown to significantly decrease the risk for cholelithiasis after sleeve gastrectomy in patient with morbid obesity (20). Other non-surgical methods such as extra-corporeal shock wave lithotripsy (ESWL) in non-inflamed gallbladder disease, have been tested. The rate of recurrence after ESWL was 30 to 50 % after a 5-year follow-up (8).

## 1.8 SURGICAL APPROACH (LAPAROSCOPIC OR OPEN SURGERY)

The majority of cholecystectomies for ACC (71-95.8 %) begin with a laparoscopic approach. This includes a large number of procedures converted to an open procedure due to technical or anatomical difficulties (Fig 4) (18).

Two randomised studies and one population-based cohort study have been published, demonstrating that Lap-C is associated with faster recovery, shorter hospital stay, and lower mortality and morbidity rates compared to open cholecystectomy (21, 22). This also applies to the elderly population (23). The TG13 recommended that Lap-C be limited to the mildest forms of AC (21). In 2018 this recommendation was modified to state that Grades I–III cholecystitis are eligible for Lap-C depending on the patient's Charlson Comorbidity Index (CCI) score and American Society of Anaesthesiologists physical status classification (ASA) (18). Contrary to TG13, the WSES and EAES recommend Lap-C even for severe cholecystitis, based on the results of a meta-analysis (21). However, the TG 18 do not use POSSUM and APACHE II, which are superior to ASA in risk prediction (8). In cases where Lap-C is not possible, TG18 recommend a conservative approach including PC in Grades II–III cholecystitis (18).



**Figure 4:** Laparoscopic versus open cholecystectomy.. Illustration by FB Scientific Art Design, Fuad Bahram.

In a few poorly designed RCTs on heterogeneous study groups, Lap-C has been shown to result in shorter duration of surgery, lower overall incidence of postoperative complications, lower in-hospital morbidity and mortality, fewer infectious complications, and shorter hospital stay compared to open cholecystectomy (24, 25). Lap-C is the method of choice even in high-risk patients with cirrhosis Child Grades A and B (8, 26, 27). The same applies for those aged 80 years and over (8, 21) and pregnant women, but not in cases where there is absolute contraindication to anaesthesia or septic shock (8).

Robot-assisted cholecystectomy has been tried in experiment procedures, with a similar complication rate and duration of surgery as Lap-C (28).

## 1.9 TIMING

Despite the relative frequency of ACC, historically there has always been controversy about the timing of surgery (8). The initial “golden” 72-hour period after admission has been proposed as an appropriate window in which to perform Lap-C. After that, the risk for complications and conversion rate to open procedure increase (29).

A population-based study showed no significant association between preoperative symptom duration and 30-day mortality, but an association with longer operation time and higher conversion rate to open cholecystectomy. Based on these results, the European Association of Endoscopic Surgery (EAES) recommends Lap-C as soon as possible after the onset of symptoms of AC (21).

A meta-analysis of case-control studies including over 40,000 patients showed that the mortality rate (0.57%) was lower after early Lap-C than after delayed (72 hours-7 days and >7 days or >4 weeks and <4 weeks). The overall complication rate was 8% in the early Lap-C groups and 11.5% in the delayed groups, where differences were significant comparing <72 with >72 hours or < 7 days with < 4 weeks, but not significant when comparing <72 hours with >4 weeks or <7 days with >4 weeks. The risk for bile duct injury was significantly lower in operations performed <7 days compared to >4 weeks, almost reached significance comparing <7 days with <4 weeks and <72 with >72 hours, but was not significant when comparing <72 hours with >4 weeks. Wound infection and conversion rates were significantly lower and length of hospital stay significantly shorter in the early group compared to the delayed group. The authors recommended early Lap-C even if more than 72 hours have passed, and stated that this should be standard care in the management of AC. Even from the point of view of bile duct injury and postoperative bile leakage, Lap-C should be performed after 72 hours since it is not associated with increased risk. A weakness of this meta-analysis is that selection bias, i.e. straightforward procedures in the early Lap-C groups and more complicated in the delayed groups, could not be ruled out (29).

Several randomised controlled trials and meta-analyses have shown advantages of early cholecystectomy in terms of total hospital stay, complications and conversion rates (21).

In a meta-analysis of 15 RCTs comparing early (72 hours-1 week) with delayed (at least > 6 weeks) cholecystectomy, early surgery resulted in shorter hospital stay and lower overall cost. There was no difference in mortality rate, complication rate or bile duct injury rate. However, tissues were seen to become progressively more scarred after repeated episodes of inflammation, making surgery more difficult (18).

The World Society of Emergency Surgery (WSES) recommends early cholecystectomy if the onset of the symptoms is less than 10 days prior to admission, since the complication or conversion rates are not higher and the total hospital stay is shorter. If patients with symptoms > 10 days develop peritonitis or sepsis, emergency surgical intervention may become necessary. Otherwise, cholecystectomy delayed for 45 days is preferable (8).

## **1.10 MICROBIAL PATTERN**

The inflammatory process in cholecystitis is initially sterile. However, bactibilia develops in 9-72 % of cases (8, 12). In studies from the last two decades it ranges from 7.7% to 15.8% (30). *Escherichia coli*, *Enterobacter*, *Klebsiella* and *Enterococcus* species are the most commonly identified organisms in patients with AC (11).

Intra-abdominal microbiological cultures obtained from 306 patients with severe cholecystitis and sepsis showed that 7.8 % had resistant bacteria. Almost ten per cent of gram-negative strains and 4.6% of gram-positive strains were found to be resistant. Presence of resistant bacteria was associated with nosocomial infection, inadequate antimicrobial therapy and recent antimicrobial therapy (31).

The TG18 recommend that bile should be obtained for culture at the beginning of all procedures performed for AC Grades II and III (Level 1 recommendation) (30). Bactibilia was found not to be a predictive risk factor for the development of wound infection; it is, however, associated with postoperative mortality and morbidity (32).

There is a higher probability of finding positive bile cultures in AC with a common bile duct stone than in chronic cholecystitis without a common bile duct stone. In a study on 84 patients undergoing elective cholecystectomy, no positive bile culture was found in any of the gallbladders with a normal wall or in those with cholesterosis (33).

## **1.11 POSTOPERATIVE COMPLICATIONS**

The overall postoperative complication rate after planned cholecystectomy ranges from 1 % to 11 %. However, the rate is higher after AC; reaching 20 % in some hospitals (34). The postoperative infectious complication rate (PIC) during admission is approximately 11% (32).

Risk factor for postoperative complications:

### **1.11.1 Severity grade of inflammation**

The mortality rate of patients with cholecystitis is approximately 1%; 1.1% with Grade I and 5.4% with Grades II-III (35).

The risk for more serious complications (higher than Grade II on the Clavien-Dindo postoperative complication scale) is higher in Grade III cholecystitis (15).

### **1.11.2 Comorbidity**

The TG18 identify neurological and respiratory dysfunction and coexistence of jaundice as negative predictive factors in Grade III AC, with a statistically significant increase in 30-day postoperative mortality rate (18). Diabetes is another risk factor that increases the mortality risk with an adjusted odds ratio (OR) of 1.79. Furthermore, delayed surgery in patients with diabetes is associated with a significantly higher risk for developing surgical site infection (SSI) and a longer hospital stay (8). Cardiovascular event and renal failure were associated with adjusted ORs of 2.5 and 3.9, respectively (8), but according to TG18 renal and cardiovascular dysfunction are not negative predictive factors (18).

Cirrhosis remains the major risk factor for surgery. In a population-based study using data from the Swedish Register for Gallstone Surgery and endoscopic retrograde cholangiopancreatography (GallRiks) between 2006 and 2011, the postoperative complication rate in cirrhotic patients was 16.9% compared to 9.2% in non-cirrhotic patients (36). Lap-C in patients with liver cirrhosis is associated with significantly longer operation time, increased blood loss, increased conversion rate, longer hospital stay and increased overall morbidity and mortality rates compared to non-cirrhotic (8).

### **1.11.3 Age**

Age older than 80 years, even patients with ASA I-II, has been shown to be associated with a significantly higher mortality rate (30 % compared to 5.5 % for age group 65-79 years and 1% for age group 50-64 years). With higher ASA Classes (III and IV) or urgent cholecystectomy, the mortality rates increase to 76 %, 25.6 % and 29 % respectively (8).

## **1.12 ANTIBIOTIC TREATMENT**

There is substantial evidence that the selective use of antibiotic prophylaxis (AP) in high-risk surgical procedures reduces PIC and decreases the overall use of antibiotics, which in turn reduces the risk of resistance. There is, however, no scientific basis for using AP in gallstone surgery if there are no specific patient or procedure risk factors. What is meant by “postoperative infectious complication” needs to be defined more clearly and registration of this outcome should be done after sufficiently long follow-up if we are to develop better evidence-based routines (37).

WSES favours antibiotic treatment in all case of ACC, even though the recurrence rate is high (8). Antibiotic resistance is one of the greatest threats to global health and it is related to longer hospital stays, higher costs and increase in mortality (38). Inappropriate antibiotic use increases medical costs. Furthermore, long-term antibiotic misuse leads to increase in the isolation of drug-resistant bacteria, difficulty in treating infectious diseases, and the spread of multiple-resistant bacteria within hospitals (39). Overuse or inappropriate antibiotic use not only increases bacterial resistance and makes treatment more difficult; it also severely threatens medical quality and safety (39). Careful choice of antibiotics, good timing of administration, proper supplementary antimicrobial treatment, and a high pathogen detection rate enhance the chances of successful treatment, and thus reduce the use of unnecessary antibiotics. Furthermore, this reduces SSI and the development of bacterial resistance (39).

A randomised study comparing intravenous antibiotic treatment with placebo in mild ACC according to the TG grading system at index admission and treated by elective Lap-C, showed that there was no significant difference in the length of hospital stay, readmission, positive bile culture or postoperative complication rate (bleeding or need for ERCP) (12).

The use of antibiotics varies greatly between clinicians, indicating a lack of evidence-based guidelines. Many clinicians advocate routine administration of antibiotics to all patients diagnosed with AC, whereas others restrict antibiotic treatment to patients likely to develop sepsis based on clinical, laboratory, and imaging findings (8).

Because of the development of bactibilia in up to two-thirds of AC cases, it is still recommended that antibiotics covering gram-negative bacteria and anaerobes are routinely administered to all patients diagnosed with AC, and continued until clinical resolution or cholecystectomy (11), despite the fact that there is no correlation between bactibilia and overall outcome (17).

### **1.12.1 Preoperative antibiotic prophylaxis (PAP)**

The Janusinfo recommendation is to give 1-2 doses AP immediately prior to acute cholecystectomy and a second dose if the duration of surgery exceeds 3 hours, and no AP in elective cholecystectomy. The choice of the antibiotic is trimethoprim-sulfamethoxazole 10 ml iv, or doxycycline 200 mg iv or cefuroxime 1,5 g iv, or cefotaxime 1 g iv. In the case of Type 1 allergy to penicillin or cephalosporin, clindamycin 600 mg intravenous may be given (40).

Based on TG18 recommendations, mild cholecystitis (Grade I) should not be treated, or treated with a first-generation cephalosporin (oral or iv) without any further explanation. Moderate cholecystitis (Grade II) should be treated with a wider-spectrum penicillin or second-generation cephalosporin, and for severe cholecystitis (Grade III) a third or fourth-generation cephalosporin, or a carbapenem, plus metronidazole should be used (30). The TG18 recommend antimicrobial prophylaxis based on the results of a study from 2007 (41), which was consensus- and in vitro activity-based, not RCT studies (30).

Many studies and meta-analyses have reported no benefit of AP in elective laparoscopic cholecystectomy (42).

It has been suggested that AP should be given to patients with a high risk of having bactibilia, i.e. in those aged >60 years, and those with fever, leucocytosis or hyperbilirubinemia (advanced cholecystitis and/ cholangitis) (32).

### **1.12.2 Postoperative antibiotic prophylaxis**

It was not until the late 1980's that surgeons began to accept the surgical procedure per se to be the most critical factor in predicting SSI. In 1985, Haley and colleagues investigated factors related to SSI, and confirmed the great impact of surgical performance. Single-dose AP is now recommended in clean surgical procedures where foreign body material is used and in clean-contaminated procedures. If the procedure lasts more than 2-3 hours, the dose is repeated (43).

Two RCTs on postoperative antibiotic treatment in Grades I and II cholecystitis showed that placebo is not inferior to treatment (44, 45). In another two RCTs on placebo versus postoperative antibiotic treatment showed no difference in PIC or other morbidity rates (46, 47).

The TG18 recommends discontinuation antimicrobial therapy within 24 hours after cholecystectomy performed for community-acquired Grades I and II cholecystitis. If perforation, emphysematous changes, or necrosis of the gallbladder are encountered during surgery, antibiotic treatment over 4-7 days is recommended. In cholecystitis Grade III, antibiotics should be given 4-7 days after the source of infection has been controlled, and if bacteraemia with gram-positive cocci (*Enterococcus* spp., *Streptococcus* spp.) is found, then antibiotics should be given a minimum duration of 2 weeks (30). In a prospective study, it was seen that surgeons commonly prolong postoperative antibiotic treatment in the elderly and if bile spillage occurs (32).

On the other hand, the WSES does not advocate postoperative antibiotic treatment in uncomplicated ACC (Grades I and II). In complicated cases, the antimicrobial regimen depends on the pathogens assumed to be involved and the risk of major resistance patterns. If used, antibiotics must have good bile penetration (bile/serum concentration ratio >1) e.g. piperacillin/tazobactam with penetration efficiency of 4.8, or ciprofloxacin or a penicillin >5.

According to the WSES recommendation, there are 5 lines of treatment in community-acquired ACC:

- A. Beta-lactam inhibitor combination-based regimens - amoxicillin/clavulanate in the stable patient and piperacillin/tazobactam in the unstable patient;
- B. Cephalosporin-based regimens - third and fourth generation cephalosporin in combination with metronidazole (in stable patients);

- C. Carbapenem-based regimens - ertapenem in stable patients and imipenem/cilastatin (Tienam), meropenem or doripenem in unstable patients;
- D. Fluoroquinolone-based regimens (in cases of stable patients with allergy to beta-lactams) - ciprofloxacin or levofloxacin in combination with metronidazole, or moxifloxacin.
- E. Tigecycline in the stable patient with risk for ESBL.

In hospital-acquired infections:

- A. Tigecycline + piperacillin/tazobactam (in stable patients);
- B. Imipenem/cilastatin +/- teicoplanin (unstable patients only);
- C. Meropenem +/- teicoplanin (unstable patients only);
- D. Doripenem +/- teicoplanin (unstable patients only) (8).



## 2 BACKGROUND

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Gallstone disease together with secondary gallstone-related complications are one of the most common reasons for surgery worldwide. In Sweden, around 13,000 patients undergo gallbladder surgery each year (48, 49), and in the UK, 70,000 procedures are performed annually (50). The procedure is usually performed with no major risk for the patient, though there are minor postoperative complications and a general mortality rate < 1% (51). However, the high volume of the procedure renders it one of the most important causes of PIC and prescription of antibiotics in surgical practice.

Of all cholecystectomies performed and registered in GallRiks during 2016, 37 % were emergency procedures. Cholecystectomy was most often performed for bile colic (71%). The second most common cause, however, was acute inflammation (26%) of the gallbladder due to gallstone obstruction of the bile duct (34). In NY, the indication for Lap-C is quite the opposite, with ACC around 73 % and biliary colic 5 %; the remainder having other indications (52).

In various hospitals in Sweden, the overall postoperative complication rate after planned cholecystectomy ranges from 1 % to 11 %. However, the rate is higher after acute cholecystectomy; reaching 20 % in some hospitals (34). Although the risk for postoperative complications after acute cholecystectomy is higher, including an infectious complication rate of 3-17 % (8, 53), the role of AP in Lap-C for AC has not been fully evaluated.

Antibiotic prophylaxis in elective surgery has been studied in several trials and many meta-analyses. Results have shown no or only minor benefit regarding PIC (50, 54-57). In a meta-analysis by Pasquali based on 19 RCTs with a total of 5,259 patients, where perioperative AP was defined as antibiotics given preoperatively and/or postoperatively, only a minor benefit without significance from AP was seen. The rate of SSI was 2.4% and 3.2% (P=0.21) in the antibiotic group and non-antibiotic group, respectively. Nor did the risk for nosocomial infection differ significantly between the groups, with rates of 4.2% and 7.2% (P=0.13) in the antibiotic and non-antibiotic groups, respectively. The authors concluded that antibiotic administration before Lap-C in patients with biliary colic and low to moderate risk cholecystitis is not to be recommended (50). Unfortunately, this analysis included studies on both elective (n=17) and acute (n=2) procedures. Furthermore, one of the studies on elective procedures included patients with history of inflammation. The meta-analysis also included a trial where three doses of antibiotics were given to all patients with mild to moderate AC. Another meta-analysis (58) showed that AP during elective Lap-C is safe and effective in reducing SSI, global infections and hospital stay. This meta-analysis included 21 RCT trials covering 5207 procedures, where only two studies showed an OR in favour of prophylactic antibiotics; a study from Nepal 1999, where 93 % were female and age range between 18-74 years (59) and one by Matsui including 1037 procedures showing the highest influence on outcome (60).

A study by Matsui and co-workers is so far the only study to show benefit of antibiotic treatment in elective Lap-C. It was conducted as a RCT in Japan 2009-2013, with a total 1037

participants. Patients in the study were randomised between antibiotic treatment with 3 doses of a first-generation cephalosporin, starting at the time of skin incision, and no antibiotics in the other arm. They showed a significantly reduced postoperative infectious complication rate; SSI 0.8% vs. 3.7%, distant infection; 0.4% vs. 3.1%, and overall infection; 1.2% vs. 6.7% for antibiotic vs. non-antibiotic groups, respectively. The study did, however, have some weaknesses. Allocation was not blinded to the surgeon, and it was unclear whether it was blinded to the patients and staff. It was also unclear how soon the procedure was scheduled after the latest episode of AC. No information was given about inflammation status before or during the operation. The patients were treated with a drain if spill of bile occurred, despite the lack of evidence supporting insertion of a sub-hepatic drain after elective surgery to prevent intra-abdominal abscess. Routine urinary catheterisation was used, and the patients stayed in hospital for approximately 4 days postoperatively, which could indicate that these were not low-risk Lap-C procedures. The majority of the postoperative infectious complications were SSI and urinary tract infections. Patients were given antibiotics on postoperative Days 1 or 2 if they had fever of unknown origin (60). These issues make it hard to compare this study with those on elective procedures on low-risk patients as performed in the majority of units in the Western world, where most procedures are done as day case surgery, with no drain and no urinary catheter. However, the Number Needed to Treat (NNT) to prevent SSI in this study was 34, which leads to the conclusion that the use of AP in low-risk procedures is questionable. This was even more pronounced in another study on the benefit of AP in preventing superficial SSI after elective surgery, where the NNT was too high (45) for AP to be of worthwhile clinical benefit to the patient (56).

Nevertheless, 20-80% of patients undergoing cholecystectomy with low to moderate risk for SSI receive AP in mixed cohorts of planned and acute cholecystectomies (50, 61). A similar pattern is seen in the UK and Ireland, where use of antibiotic prophylaxis in routine elective Lap-C still varies between surgeons four years after national guidelines on AP in routine Lap-C were published. Thirty-six per cent of surgeons (78 % consultants) still give single-dose AP before routine Lap-C even if no risk factors are present. Should a perioperative complication occur, e.g. bile spillage or presence of gallbladder empyema, then treatment varies greatly between surgeons from no treatment at all to one dose, 3 doses, 5 days or > 5 days antibiotics (61). Current guidelines diverge in their recommendations on AP. The World Society of Emergency Surgery (WSES) does not recommend postoperative AP in uncomplicated cholecystitis, but that it should be given in complicated cases (8). The Scottish Intercollegiate Guideline Network (SIGN) and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), on the other hand, recommend that AP be reserved for high-risk patients only (61). Other guidelines recommend AP for open surgery and high risk Lap-C but not for low risk Lap-C (acute Lap-C not mentioned) (62). The latest Tokyo Guidelines recommend AP or no AP during cholecystectomy for Grade I cholecystitis without providing any further criteria when AP is indicated (30).

The procedure and actual inflammation status of the patient are highly predictive of the risk for postoperative complication. Patient-related risk factors should be taken into account when deciding on AP (51) especially age >65 years, comorbidity and male gender. SIGN (2008)

and SAGES (2010) recommend reservation of AP for high-risk patients and procedures only, and that AP should be avoided in low-risk patients. They define high-risk patients as: >60 years old, history of diabetes, acute symptoms of biliary colic within 30 days before surgery, jaundice, AC or cholangitis, immunosuppression and pregnant women. High-risk procedures are defined as: intraoperative cholangiography, conversion to laparotomy, insertion of prosthetic devices and intraoperative bile spillage (61). Spillage of bile, however, is encountered in almost 25% of elective Lap-Cs but has not been found to predict PIC. A single dose of cephalosporin did not affect occurrence of infection after bile spill either (63). Not even Valvular heart disease or valve replacement, which appears to be the comorbidity that most surgeons still pay attention to and consider being an indication for AP in cholecystectomy, is an unequivocal indication for AP. There is no evidence supporting the use of AP in these situations to prevent infective endocarditis according to the National Institute for Health and Care Excellence (NICE) guidelines from 2008 (61).



### 3 AIMS OF THE THESIS

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#### **Overall aim**

To assess the role of antibiotic prophylaxis in preventing postoperative infectious complications after acute cholecystectomy for acute calculous cholecystitis.

#### **Specific aims**

##### **Paper I**

To explore the impact of antibiotic prophylaxis on postoperative infectious complication after acute cholecystectomy in a population-based setting.

##### **Paper II**

To investigate differences in use of antibiotic prophylaxis in cholecystectomy between regions, hospitals and surgeons.

##### **Paper III**

To explore the clinical impact of patient- and procedure-related risk factors on the occurrence of postoperative infectious complications.

##### **Paper IV**

To determine the effect of preoperative antibiotic prophylaxis, given prior to acute cholecystectomy in mild to moderate acute cholecystitis, on the occurrence of postoperative infectious complication.



## **4 DATA SOURCES USED IN THE THESIS (I-III)**

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### **4.1 SWEDISH REGISTRY FOR GALLSTONE SURGERY AND ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (GALLRIKS)**

GallRiks is a nationwide register that was started in 2005. Six months after its start, 26 units were registered in GallRiks, and by the end of 2016, 83 hospitals were affiliated. As with other patient registers, the primary purpose of GallRiks is to assure quality of care and patient safety, as well as to provide a database for clinical research. It is approved by the Swedish National Board of Health and Welfare and the Swedish Surgical Society (that also appoints the members of the GallRiks Board). Since 2009, GallRiks has 85 % coverage of all laparoscopic and open cholecystectomies, and all endoscopic interventions of the bile ducts performed in Sweden.

The register uses a web-based form (see appendix for the form). The surgeon or endoscopist who performs the procedure registers all relevant data intra- or postoperatively. Each affiliated unit has a coordinator who registers postoperative complications, including infections, 30 days and 6 months after procedures. In cases where data are missing, the coordinator bids the surgeon responsible to complete the form properly. The director of each unit affiliated is responsible for ensuring that every cholecystectomy and endoscopic retrograde cholangiopancreatography has been registered by the end of the year. The medical records are reviewed by the coordinators to check that all postoperative complications are registered.

Annual validation of data in GallRiks between 2007 and 2011, based on comparison with the medical records, showed continual improvement reaching 73% completeness by the end of 2011. Erroneous data on one or more of the 43 variables validated were found in only 17% of registrations at the end of the period (48). The coverage today is 90% and 97% of data match the medical records ([www.GallRiks.se](http://www.GallRiks.se)) based on the annual validation program where selected hospitals are visited to check the accuracy of data.

### **4.2 NATIONAL PATIENT REGISTER (NPR)**

The National Patient Register (NPR) was started in the 1960's when the National Board of Health and Welfare in Sweden began collecting data on inpatients discharged from public hospitals. Since 1987, the NPR has had national coverage, and since 2001 the register has also included all hospital outpatient visits. The primary healthcare system is not covered. Variables registered in the NPR include patient data, geographical data, administrative data and medical data. Under-reporting of inpatient data has been estimated to <1 %. Every Swedish citizen has a unique personal identity number, and this makes it possible to track patients over time. Data on non-residents, asylum seekers and new-borns, however, may be missing. All inpatient diagnoses are registered according to the International Classification of

Diseases (ICD) codes (64). The surgeon responsible for the discharge of a patient after surgery registers all diagnosis codes. NPR is regularly validated, showing that 99% of all discharges are registered with all relevant diagnoses coded according to the ICD. Degree of correctness ranges from 85 to 95% (65).

## 5 PAPER I

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This was a study on a population-based cohort of all acute cholecystectomies performed in Sweden between January 2006 and December 2010. Data were retrieved from GallRiks. The inclusion criteria were: patients undergoing acute cholecystectomy before discharge after emergent admission; indication for the surgery being gallstone-related disease or acalculous cholecystitis; and surgery performed at a unit where at least 50 procedures had been performed during the study period. A total of 13911 patients were included. Confounding variables extracted from GallRiks were: age; gender; indication for surgery; ASA class; surgical approach; duration of surgery; accidental gallbladder perforation; and AP. AP was defined as antibiotic treatment lasting up to one day, or antibiotic treatment lasting more than one day given in repeated doses before, during and after the procedure. PIC within 30 days after surgery, as registered by the local coordinator at each hospital, were also retrieved from GallRiks to define the two outcomes measures:

PIC included conditions requiring antibiotic treatment, i.e. PIC related to the procedure or nosocomial infection. Intra-abdominal abscess included abscesses diagnosed in the postoperative period using imaging diagnostics, regardless of whether requiring percutaneous drainage or not.

### **Statistical analyses**

$\chi^2$  test was used to analyse associations between clinical and surgical variables and use of AP. Univariate and multivariate logistic regression analyses were performed, where AP was treated as a variable together with other covariables (age, gender, indication for surgery, ASA class, surgical approach, duration of surgery, and accidental gallbladder perforation) in a stepwise inclusion model. Subgroup analyses were performed for patients with perioperative AC, jaundice and accidental gallbladder perforation. Odds ratio was presented with 95% confidence interval, where ( $p < 0.05$ ) was considered statistically significant. R version 2.15.3 was used for statistical analyses.

### **Results**

Altogether, 13,911 procedures were included in the study. AP was given to 68.6 % whereas 31.4 % did not get antibiotics. The subgroup of patients with AC included 8,205 procedures, the subgroup with obstructive jaundice included 2,786 procedures, and the group of accidental gallbladder perforation included 3,938 patients. The subgroup of patients with obstructive jaundice group also included those with other complications related to common bile duct stones such as pancreatitis and cholangitis.

Baseline data are presented in Table 2. Age was distributed as follows: <40 years (30.4%); 41-60 years (34.3%); and >60 years (35.3%). There were 39.3 % men and 60.7 % women. Indication for surgery was either complicated, i.e. cholecystitis, pancreatitis or obstructive

jaundice or acalculous cholecystitis (73.2%), or uncomplicated, i.e. biliary colic (26.8%). Altogether 51.2% were ASA class 1 (and 48.8% were class 2 or more Surgical approach was either open (i.e. open cholecystectomy, laparoscopic converted to open cholecystectomy, subtotal cholecystectomy and mini-laparotomy (46.6%), or laparoscopic cholecystectomy (53.4%). Duration of surgery was <90 minutes in (39.2%) or >90 minutes in (60.8%) of the cases. Gallbladder perforation occurred in 28.6%. The total PIC rate was 7.6 %, including 1.5 % abdominal abscesses and 6.1 % PIC. Comparing the group of patients who received AP with those who did not, the adjusted OR was 0.93 (95% confidence interval [CI] 0.79-1.10) for PIC and 0.88 for intra-abdominal abscess (95% confidence interval [CI] 0.64-1.21).

Variable	All patients (n = 13,911)	No antibiotic prophylaxis (n = 4,362)	Antibiotic prophylaxis (n = 9,549)	P†
Age (years)				< 0.001
≤ 40	4,216 (30.3)	2,055 (47.3)	2,161 (22.7)	
41–60	4,754 (34.2)	1,478 (34.0)	3,276 (34.4)	
> 60	4,890 (35.2)	808 (18.6)	4,082 (42.9)	
Unknown	51 (0.4)	21	30	
Gender (M: F)	5,468: 8,443	1,217: 3145	4,251: 5,298	< 0.001
Indication for cholecystectomy				< 0.001
Uncomplicated	3,732 (26.8)	2,063 (47.3)	1,669 (17.5)	
Complicated*	10,179 (73.2)	2,299 (52.7)	7,880 (82.5)	
ASA class				< 0.001
I	7,125 (51.2)	2,791 (64.0)	4,334 (45.4)	
> I	6,786 (48.8)	1,571 (36.0)	5,215 (54.6)	
Surgical approach				< 0.001
Open	5,175(37.2)	7,15(16.4)	4,460 (46.7)	
Laparoscopic	8,736(62.8)	3,647 (83.6)	5,089(53.3)	
Duration of surgery (min)				< 0.001
< 90	5,456 (39.2)	2,451 (56.2)	3,005 (31.5)	
≥ 90	8,450 (60.7)	1,909 (43.8)	6,541 (68.5)	
Unknown	5 (< 0.1)	2	3	
Gallbladder perforation				< 0.001
No	9,827 (70.6)	3,415 (79.0)	6,412 (67.9)	
Yes	3,938 (28.3)	909 (21.0)	3,029 (32.1)	
Unknown	146 (1.0)	38	108	
Postop. infection requiring antibiotics				< 0.001
No	12,837 (92.3)	4,095 (93.9)	8,742 (91.6)	
Yes	1,070 (7.7)	265 (6.1)	805 (8.4)	
Unknown	4 (< 0.1)	2	2	
Abscess				0.007
No	13,638 (98.0)	42,97 (98.5)	9,341 (97.8)	
Yes	273 (2.0)	65 (1.5)	208 (2.2)	

Values in parentheses are percentages. \*Pancreatitis, obstructive jaundice, cholecystitis and acalculous cholecystitis. †  $\chi^2$  test used

**Table 2:** Baseline data.

In the subgroup of patients with AC (n=8,205), 96.3 % had ACC and 3.7% acalculous cholecystitis. The total PIC rate in this group was 10.7%, with PIC 8.5% and abdominal abscess 2.2%. Comparing the group who received AP with those who did not, the adjusted OR was 0.84 (95% confidence interval [CI] 0.67-1.06) for PIC and 0.72 for intra-abdominal abscess (95% confidence interval [CI] 0.47-1.1).

In the subgroup of patients with obstructive jaundice (n= 2,786), the total PIC rate was 11 %, with PIC 9.1 % and intra-abdominal abscess 1.9 %. Comparing the group who received AP with those who did not, the adjusted OR was 0.75 (CI 0.54-1.05) for PIC and 0.69 (CI 0.34-1.4) for intra-abdominal abscess.

In the subgroup of patients with accidental gallbladder perforation, regardless of indication for surgery (n=3938), the total PIC rate was, 9.7 %, rate of complications requiring antibiotics 7.7% and intra-abdominal abscess 2.0%. When comparing the group of patients who received AP with those who did not, the adjusted OR was 1.09 (95% confidence interval [CI] 0.78-1.5) for PIC and 0.93 (95% confidence interval [CI] 0.50-1.71) for intra-abdominal abscess.

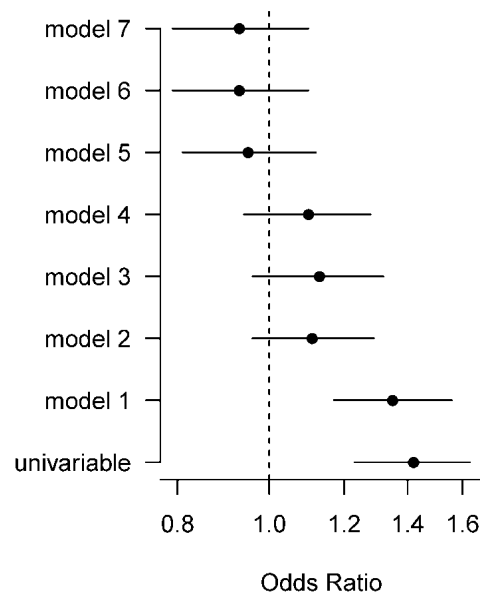
Univariate and multivariate logistic regression ORs regarding outcomes, for patients in the whole group as well as for those in the subgroups, are presented in Table 3.

The multivariate analysis of impact of AP (Figs 5 and 6) on outcomes were added stepwise to the univariate OR, starting with gender in Model 1, gender + age in Model 2, and thereafter adding indication for cholecystectomy, ASA class, surgical approach, duration of surgery, and finally accidental gallbladder perforation in Model 7. The OR decreased for each covariate added, but never reached the level of statistical significance. The final OR was 0.93 (CI 0.79-1.10) for PIC and 0.88 (CI 0.64-1.21) for intra-abdominal abscess.

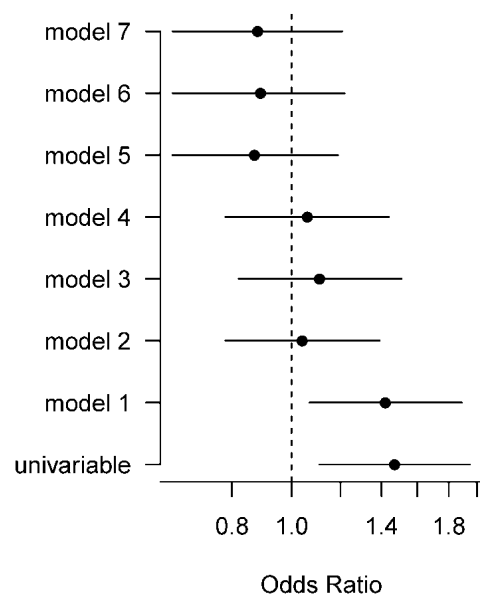
	Analysis†	n	Odds ratio
All patients			
Postop. infection requiring antibiotics	Univariate	13,907	1.42 (1.23, 1.64)
	Adjusted	13,707	0.93 (0.79, 1.10)
Abscess	Univariate	13,911	1.47 (1.11, 1.95)
	Adjusted	13,711	0.88 (0.64, 1.21)
Cholecystitis subgroup			
Postop. infection requiring antibiotics	Univariate	8,203	1.25 (1.01, 1.55)
	Adjusted	8,090	0.84 (0.67, 1.06)
Abscess	Univariate	8,205	1.13 (0.76, 1.69)
	Adjusted	8,092	0.72 (0.47, 1.11)
Obstructive jaundice subgroup*			
Postop. infection requiring antibiotics	Univariate	2,785	1.19 (0.88, 1.62)
	Adjusted	2,735	0.75 (0.54, 1.05)
Abscess	Univariate	2,786	1.17 (0.61, 2.24)
	Adjusted	2,736	0.69 (0.34, 1.4)
Gallbladder perforation subgroup			
Postop. infection requiring antibiotics	Univariate	3,937	1.43 (1.05, 1.94)
	Adjusted	3,923	1.09 (0.78, 1.52)
Abscess	Univariate	3,938	1.19 (0.68, 2.06)
	Adjusted	3,924	0.93 (0.50, 1.71)

Values in parentheses are 95 per cent confidence intervals. \*Surgery with jaundice as indication and/or common bile duct stone diagnosed at peroperative cholangiography. †Results are shown for the final adjusted model (Model 7). An odds ratio of less than 1 favours antibiotic prophylaxis.

**Table 3:** Logistic regression analyses of patients undergoing cholecystectomy for acute gallstone disease.



**Figure 5:** Multivariate analyses of impact of antibiotic prophylaxis on development of postoperative infectious complication necessitating antibiotic treatment. OR with 95 % confidence intervals. OR less than 1 favours antibiotic prophylaxis.



**Figure 6:** Multivariate analyses of impact of antibiotic prophylaxis on development of abscess. OR with 95 % confidence intervals. OR less than 1 favours antibiotic prophylaxis.



## 6 PAPER II

All cholecystectomies registered in GallRiks between 2005 and 2015 (n=113,209) constituted the base for this cohort study. Covariate variables retrieved from GallRiks were: age ( $\leq 40$  years, 41-60 years and  $\geq 60$  years); gender; ASA class (1 or  $\geq 2$ ); indication for surgery (uncomplicated versus complicated); approach (laparoscopic including laparoscopic cholecystectomy, mini-incision cholecystectomy and open for other approaches); duration of the procedure ( $< 90$  minutes or  $\geq 90$  minutes); accidental gallbladder perforation; urgency status (acute or planned); year of surgery; and AP (including both treatment lasting  $\leq 24$  hours and that continued  $> 24$  hours).

The exclusion criteria were: Hospitals and surgeons with less than 25 cholecystectomies registered during the study period; patients with data missing on any of the variables; data missing on the surgeon responsible; exploration of the common bile duct without concomitant cholecystectomy; indication for surgery other than gallstone-related; emergency procedure on patients with impaired vital function; duration of the procedure unknown or registered as  $> 24$  hours (assumed to be erroneous).

The numbers of patients excluded are presented in Table 4. There were no data on type of antibiotic given in GallRiks, only the duration.

Criterion	Number remaining patients
Original data	113,209
Antibiotics treatment known	110,301
Surgeon known	109,681
ASA class known	109,664
Removed: indication "undergoing other surgery"	109,196
Removed: operation method "undergoing common bile duct exploration"	109,108
Duration of surgery $\leq 24$ hours known	109,083
Age known	108,841
Gender known	108,839
Gallbladder perforation known	108,502
Urgency status known	107,925
Removed: institution with fewer than 25 patients	99,101

**Table 4:** Assembly of the study cohort.

The study was approved by the Stockholm Ethics Review Committee. All participants gave informed consent to inclusion. The study was conducted in accordance with the Helsinki Declaration.

The outcome was use of AP at different healthcare levels; region, hospital and surgeon.

## Statistical analyses

The R version 2.14.1 (2011-12-22) and WinBugs 1.4 were used for the statistical analyses.

Funnel plots were applied to create a graphical presentation of the region's, hospital's and surgeon's use of antibiotics outside the confidence intervals. Regions, hospitals or surgeons deviating from the general population by more than could be expected, i.e. outside 95% CI; if there had been an underlying uniform approach and random variation at each level (66). The funnel plots were used to study grouping factors, i.e. region, hospital and surgeon. In plain funnel plots, each indicator is equal to the proportion of the patients that received antibiotics (y axis), and on the x is the total number treated at the units (region, hospital and surgeon) (Figs 7-9). The 95% confidence intervals were defined as  $\theta_0 \pm 1.96 \times \sqrt{p_0(1-p_0)/n}$ , where  $p_0$  is the proportion of patients receiving antibiotics in the whole population and n is the number of patients undergoing surgery in the region, hospital, or by the surgeon.

In the regression funnel plots, the indicators were derived from a regression model after adjusting for covariates (age, gender, ASA class, indication for surgery, approach, duration of the procedure, accidental gallbladder perforation, and urgency status) using Bayesian multilevel regression model (Figs 10-12). The regression funnel plots enabled identification of specific differences at a certain level (e.g. region) beyond those that could be explained by differences at other levels (hospital/surgeon). This implies that if a hospital deviates from the total population, it remains within the confidence intervals in the multilevel regression funnel plots if it does not deviate extremely from the other units in the same region. In other words, the hospital's variation and value outside the 95% confidence interval in the regression funnel plot, cannot be explain by a routine at the region level. The statistical basis of this study had been described in detail previously (66).

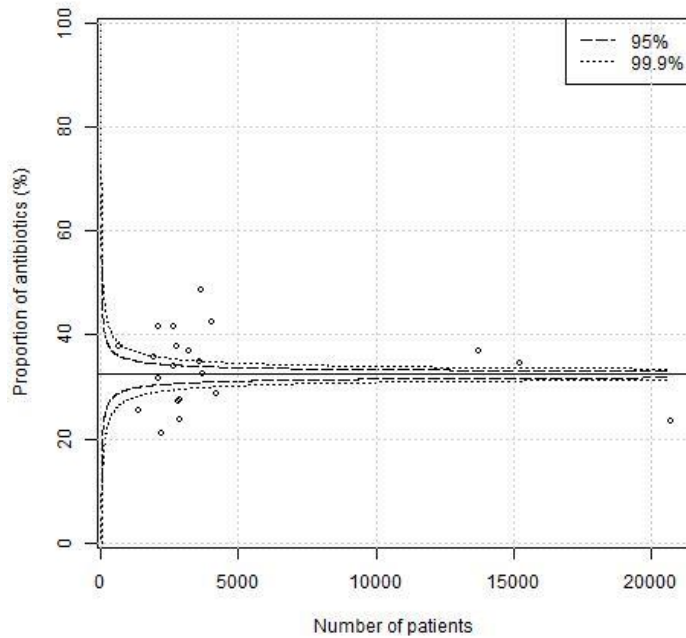
Funnel plots are used to illustrate credibility intervals, i.e. the Bayesian analogy to confidence intervals. The main difference is the use of fixed boundaries and estimated parameters as the random variable, and not *vice versa*.

Indicators outside the 99.9% confidence interval were considered highly clinically relevant.

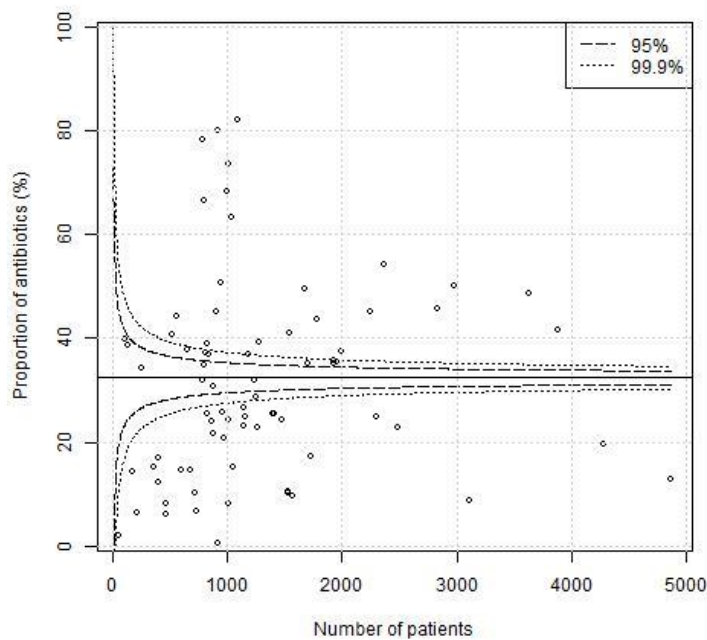
## Results

A total of 113,209 patients were included in the study. Patients excluded (14,108) are presented in Table 4. A complete case-analysis was performed for the study group of 99,101 subjects. The baseline data for each covariate are given in Table 5. The number of patients 2005-2006 was relatively small (6,477), these two years were therefore pooled together in order to gain more balanced categories. The covariate effect on the choice of AP in a fixed effect is shown in Table 6. All covariates were associated with the decision to give AP, and this increased slightly for each year. The factor having the greatest impact was open surgical approach, with an OR of 4.87 (CI 4.56-5.16).

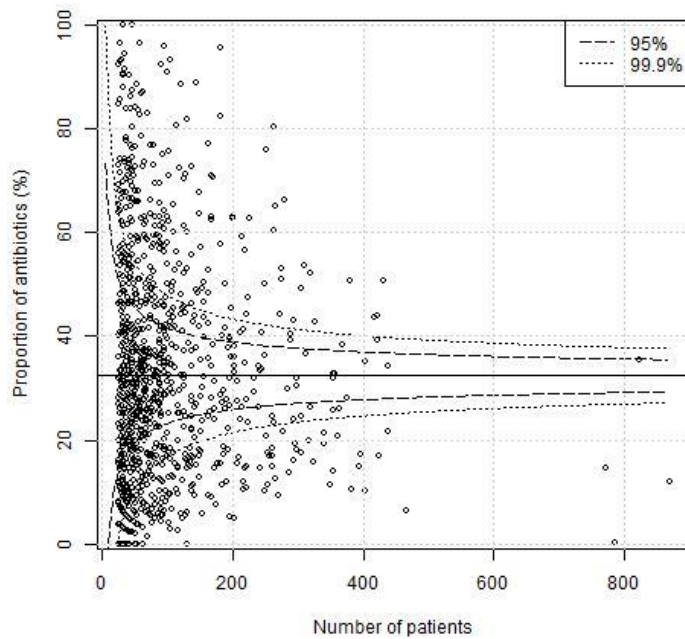
The funnel plots for AP proportions, without adjustment for confounders or level (region, hospital and surgeon) are shown in Figs 7-9. There were 15/21 (71%) outside the 99.9% confidence interval at region level, 61/76 (80%) at the hospital level and 400/1038 (39%) at the surgeon level. Large deviations were observed at each level.



**Figure 7.** Plain funnel plot for regions. Outliers: 15/21 (71%)

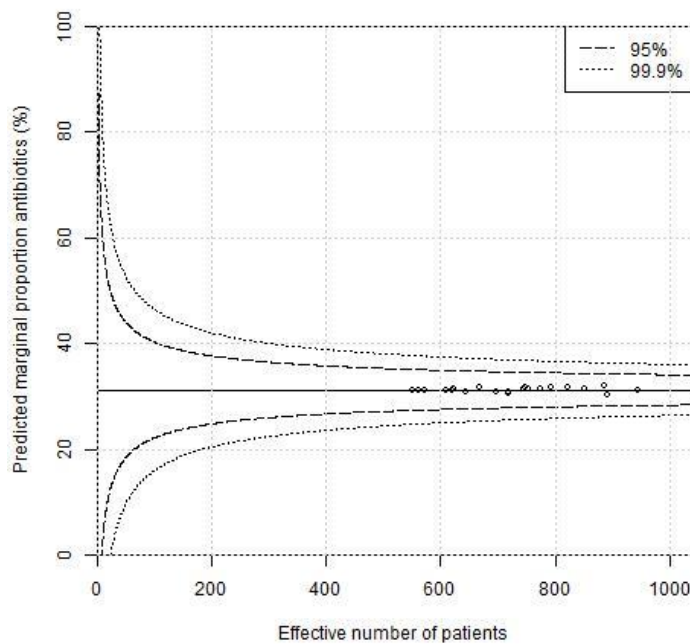


**Figure 8.** Plain funnel plot for hospitals. Outliers: 61/76 (80%)

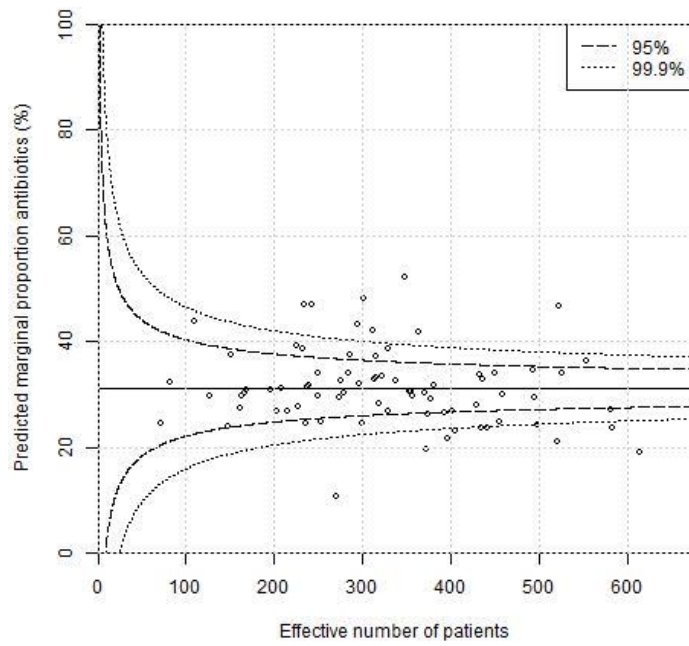


**Figure 9.** Plain funnel plot for Surgeons. Outliers: 400/1038 (39%)

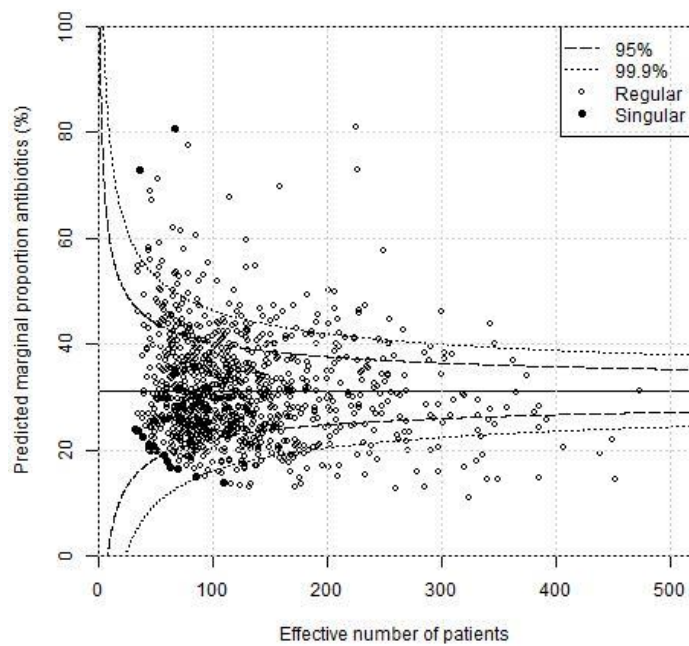
The regression funnel plots with adjustment for confounding covariates and levels are shown in Figs 10-12. There was no deviation outside the 95% confidence interval at the region level, but there were 18/76 (24%) and 128/1038 (12%) indicators outside the 99.9% confidence interval at hospital and surgeon levels, respectively.



**Figure 10.** Covariate-adjusted multilevel funnel plot for regions. Outliers: 0/21 (0%)



**Figure 11.** Covariate-adjusted multilevel funnel plot for hospitals. Outliers: 18/76 (24%)



**Figure 12.** Covariate-adjusted multilevel funnel plot for surgeons. Outliers: 128/1038 (12%)

Variable	No antibiotic N =66995	Antibiotic given N=32106	Combined N=99,101
Age:			
≤40	23,114 (77.5%)	6,720 (22.5%)	29,834
41-60	27,621 (70.3%)	11,671 (29.7%)	39,292
>60	16,260 (54.2%)	13,715 (45.8%)	29,975
Gender:			
Male	18,775 (57.1%)	14,081 (42.9%)	32,856
Female	48,220 (72.8%)	18,025(27.2%)	66,245
ASA class:			
1	38,134 (74.8%)	12,854 (25.2%)	50,988
>1	28,861 (60.0%)	19,252 (40.0%)	48,113
Indication:			
Uncomplicated	49,722 (84.2%)	9,331 (15.8%)	59,053
Complicated	17,273 (43.1%)	22,775 (56.9%)	40,048
Surgical technique:			
Laparoscopic	63,791 (73.9%)	22,534 (26.1%)	86,325
Open	3,204 (25.1%)	9,572 (74.9%)	12,776
Duration of surgery (min):			
<90	41,010 (81.4%)	9,386 (18.6%)	50,396
≥90	25,985 (53.4%)	22,720 (46.6%)	48,705
Gallbladder perforation:			
No	50,878 (73.5%)	18,329 (26.5%)	69,207
Yes	16,117 (53.9%)	13,777(46.1%)	29,894
Urgency:			
Elective	56,475 (82.4%)	12,093 (17.6%)	68,568
Emergency	10,520 (34.5%)	20,013 (65.5%)	30,533
Year:			
2005-2006	3,938 (60.8%)	2,539 (39.2%)	6,477
2007-2015	63,057 (68.1%)	29,567(31.9)	92,624

**Table 5:** Baseline data of the study group.

Variable	Reference	Level	Odds ratio	95% CI
Age (years)	≤ 40	41-60	1.43	(1.36, 1.50)
		>60	1.93	(1.83, 2.04)
Gender	Male	Female	0.79	(0.76, 0.82)
Year	2005/2006	2007	1.22	(1.13, 1.32)
		2008	1.17	(1.08, 1.25)
		2009	1.04	(0.97, 1.11)
		2010	0.93	(0.87, 0.99)
ASA class	1	≥2	1.29	(1.24, 1.35)
Surgical approach	Laparoscopic	Open	4.87	(4.56, 5.16)
Duration of surgery (min)	<90	≥90	2.65	(2.53, 2.76)
Indication	Uncomplicated	Complicated	2.70	(2.59, 2.82)
Gallbladder perforation	No	Yes	2.48	(2.37, 2.58)

**Table 6:** Estimates and credibility intervals for the fixed effects.

## 7 PAPER III

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The study population for this cohort was obtained from GallRiks and NPR.

Data on all cholecystectomies registered in GallRiks between 2006 and 2014 were retrieved. The procedure and relevant patient-related risk factors obtained from GallRiks were: age (<70 or  $\geq 70$  years old); gender; ASA class (1 or  $\geq 2$ ); indication for surgery (uncomplicated (bile colic) or complicated (gallstone-related complications); surgical approach (laparoscopic or open, including conversion from laparoscopic to open surgery and mini-laparotomy); duration of surgery (<120 minutes or  $\geq 120$  minutes); antibiotic treatment (including continuous treatment and single-dose prophylaxis); and accidental gallbladder perforation.

The covariant variables obtained from IPR were: history of connective tissue disease (ICD codes M05-06, M 31.5, M32-M34, M35.1, M35.3 and M36.6); diabetes mellitus (ICD codes E10-E14); chronic kidney disease (ICD codes N03.2-N03.7, N05.2-N05.7, N18, N19, I12.0, I13.1, Z49.0-Z49.2, Z94.0, Z99.2); liver cirrhosis (ICD codes K70.3, K71.7, K74, I85); immunodeficiency (ICD codes D80-D89); and obesity (ICD code E86). Only diagnoses registered before the date of surgery were used.

In the present study, a PIC was defined as a complication registered in GallRiks and/or NPR. PIC were registered in GallRiks 30 days after the procedure, based on patient records, and relevant patient diagnoses were obtained from the NPR, including outcome diagnoses (ICD codes T81.4 = infection after surgical or medical procedure, K 83.0 = cholangitis, and A40 and A41= septicemia).

A cross-checking between NPR and GallRiks was performed for outcome and comorbidity diagnoses.

Outcomes were *surgical site infection SSI* including PIC necessitating antibiotic treatment or percutaneous drainage and *septicemia*, including diagnoses of cholangitis and or septicemia.

The study was approved by the Regional Research Ethics Committee in Stockholm, Sweden. All data were imported retrospectively and processed without entering patient records.

### Statistical analysis

Univariate and multivariate logistic regression analyses were used to analyse patients and procedure-related risk factors for SSI and septicemia. Odds ratio (OR) with 95% confidence interval was conducted and a  $p$  value <0.05 was considered significant.

### Results

In total, 94,557 cholecystectomy procedures registered in GallRiks between 2006 and 2014 were included.

SSI or infection requiring antibiotics was registered in 4,835 (5.2%) of the procedures in GallRiks. Wound infections within 30 days postoperatively were registered after 1,532 (1.6%) of the procedures. Any infection, i.e. wound infection and/or septicaemia, were registered in the NPR after 2016 of the procedures. SSI or infection requiring antibiotics was registered in both GallRiks and the NPR in 1,136 of the procedures.

There were only 63 procedures in which sepsis and/or septic cholangitis within 30 days postoperatively was registered in GallRiks as well as in the NPR. Septicaemia was registered in the NPR following 538 procedures (0.6%). Postoperative septic cholangitis was registered following 175 procedures (0.2%) in GallRiks.

The outcome of the simple logistic regression analysis is presented in Table 7. OR for the outcome SSI was statistically significant, with 95% confidence intervals for all confounders and comorbidities except immunodeficiency. The OR for septicaemia was statistically significant for all variables except accidental gallbladder perforation, immunodeficiency and obesity (Table 7).

The multivariate logistic regression analyses were performed with adjustment for the confounders retrieved from GallRiks (age, gender, ASA class, indication for surgery, surgical approach, duration of surgery, antibiotic treatment and accidental gallbladder perforations, Table 8). For the outcome SSI, the adjusted OR was significantly higher for connective tissue disease (OR 1.40, CI 1.21-1.63), complicated (OR 1.44, CI 1.21-1.71) and uncomplicated diabetes (OR 1.39, CI 1.26-1.53), chronic kidney disease (OR 1.79, CI 1.46-2.19), cirrhosis (OR 1.76, CI 1.27-2.45) and obesity (OR 1.63, CI 1.48-1.80) but not for immunodeficiency (OR 0.86, CI 0.58-1.28). The adjusted OR for the second outcome, septicaemia was statistically significant for chronic kidney disease (OR 5.02, CI 3.02-8.34) and cirrhosis (OR 3.07, CI 2.12-4.43) only.

Variable	Surgical site infection					Septicaemia				
	Simple logistic regression analyses for SSI					Simple logistic regression analyses for septicaemia				
	N	%	p-value	Odds Ratio	CI	N	%	p-value	Odds Ratio	CI
Age,>70 years vs <70 years	1,375/12,725	10.8	<0.001	2.41	2.25-2.57	232/12,725	1.8	<0.001	3.52	3.00-4.14
Gender, male vs female	2,255/31,068	7.3	<0.001	1.55	1.47-1.64	341/31,068	1.1	<0.001	2.19	1.88-2.55
ASA >1 vs 1	3,493/45,385	7.7	<0.001	2.19	2.06-2.32	501/45,385	1.1	<0.001	3.42	2.86-4.09
Indication for surgery, gallstone pain or complication of gallstone disease	3,216/39,876	8.1	<0.001	2.21	2.09-2.34	514/39,876	1.3	<0.001	4.84	4.03-5.82
Open approach, including conversion from laparoscopic to open or laparoscopic	1,868/13,450	13.9	<0.001	3.71	3.49-3.93	309/13,450	2.3	<0.001	5.71	4.88-6.67
Op. time >120 min	1,985/22,711	8.7	<0.001	1.99	1.88-2.11	301/22,711	1.3	<0.001	2.76	2.36-3.22

Antibiotic treatment	2,632/31,025	8.5	<0.001	2.13	2.02-2.25	438/31,025	1.4	<0.001	4.32	3.66-5.10
Accidental gallbladder perforation	1,868/27,490	6.8	<0.001	1.36	1.29-1.45	201/27,490	0.7	0.226	1.11	0.94-1.31
Connective tissue disease	216/2,035	10.6	<0.001	2.04	1.77-2.36	38/2,035	1.9	<0.001	2.81	2.02-3.91
Complicated diabetes	166/1,269	13.1	<0.001	2.59	2.19-3.05	27/1,269	2.1	<0.001	3.18	2.15-4.69
Uncomplicated diabetes	608/ 5,283	11.5	<0.001	2.35	2.15-2.57	97/ 5,283	1.8	<0.001	2.94	2.37-3.66
Chronic kidney disease	123/788	15.6	<0.001	3.17	2.61-3.85	33/ 788	4.2	<0.001	6.48	4.54-9.27
Cirrhosis	44/ 345	12.8	<0.001	2.48	1.80-3.40	17/ 345	4.9	<0.001	7.53	4.60-12.34
Immunodeficiency	28/ 489	5.7	0.904	1.02	0.70-1.50	4/ 489	0.8	0.752	1.17	0.44-3.15
Obesity	507/ 6,173	8.2	<0.001	1.56	1.42-1.72	46/ 6,173	0.7	0.653	1.07	0.79-1.45

**Table 7:** Univariate logistic regression analyses for SSI and septicaemia with covariates indicated.

Conditions	Multivariate logistic analyses for SSI			Multivariate logistic analyses for septicaemia		
	p-value	Odds Ratio	CI	p-value	Odds Ratio	CI
Connective tissue disease	<0.001	1.40	1.21-1.63	0.004	1.66	1.17-2.34
Complicated diabetes	<0.001	1.44	1.20-1.71	0.158	1.35	0.89-2.03
Uncomplicated diabetes	<0.001	1.39	1.26-1.53	0.023	1.31	1.04-1.66
Chronic kidney disease	<0.001	1.79	1.46-2.19	<0.001	3.07	2.12-4.43
Cirrhosis	0.001	1.76	1.27-2.45	<0.001	5.02	3.02-8.34
Immunodeficiency	0.468	0.86	0.58-1.28	0.916	1.06	0.39-2.85
Obesity	<0.001	1.63	1.48-1.80	0.261	1.20	0.88-1.64

**Table 8:** Multivariate logistic regression analysis for patient-related risk factors after adjustment for other confounders.



## 8 PAPER IV

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The study was designed as single-centre double-blinded randomised controlled prospective study. Patients diagnosed with ACC (Grades I and II according to TG18) at Karolinska Hospital between January 2009 and May 2017 participated in the study if they fulfilled the eligibility criteria. The patients were randomised to 4 g of piperacillin/ tazobactam PAP three times daily until surgery, or equivalent volumes of saline.

Eligibility criteria were: age > 18 years; clinical, biochemical and radiological signs of ACC; symptom duration <5 days; and intention to perform cholecystectomy before discharge.

Exclusion criteria were: signs of organ failure; ongoing sepsis; pregnancy; common bile duct obstruction; had taken antibiotics in the last 24 hours; contraindication to surgery; and allergy to piperacillin/ tazobactam.

Written consent was obtained from all participants after receiving verbal and written information about the study from a physician at the emergency care unit. Randomisation between the two parallel arms was made and the result kept in a sealed envelope. The nurses at the emergency care unit, clinicians, surgeons, researchers and the patients were all blinded to the allocation. The drip set was covered by an opaque bag to maintain blinding, and the infusion was administered by a research nurse. From the day of inclusion, vital parameters and blood samples, including CRP and WBC, were documented daily until two days after surgery or discharge from the hospital, in order to monitor the inflammatory status of the patient. The infusion was repeated 3 times a day if necessary because of delay to surgery due to OR availability (79% received one dose only prior to surgery).

Using a long needle, bile was aspirated from the gallbladder fundus at the start of the procedure, and, whenever possible, via the cystic duct prior to cholangiography, and sent for culture. In cases where the surgeon performing the procedure found it necessary to interrupt blinding and give intraoperative antibiotics or continue antibiotic treatment postoperatively, patients remained in the same allocation group for an intention-to-treat analysis.

The patients were followed up 30 days after the procedure by abstracting data from the medical records and interviewing the patient at a follow-up visit or by telephone.

The outcomes were: PIC requiring antibiotic treatment within 30 days postoperatively (PIC defined as SSI, intra-abdominal abscess, sepsis, cholangitis or nosocomial infection such as urinary tract infection and pneumonia); postoperative signs of infection without primary focus (signs of gallbladder infection, i.e. empyema or necrotic gallbladder, seen perioperatively were also included in this endpoint).

Secondary outcomes were bactibilia and infection marker response (raised CRP, WBC or body temperature).

This study was approved by the Local Ethics Review Board in Stockholm (2008/1135-31). The study is registered at [clinicaltrials.gov](https://clinicaltrials.gov) (NCT02619149).

### **Statistical analyses**

The hypothesis was that placebo was not inferior to PAP in preventing postoperative infection after acute cholecystectomy.

The correlation between positive bile culture and rise in infection markers indicating PIC was also analysed.

Variation between groups regarding known risk factors (age, gender, duration of symptoms, comorbidity, method of approach) and their effect on PIC was analysed.

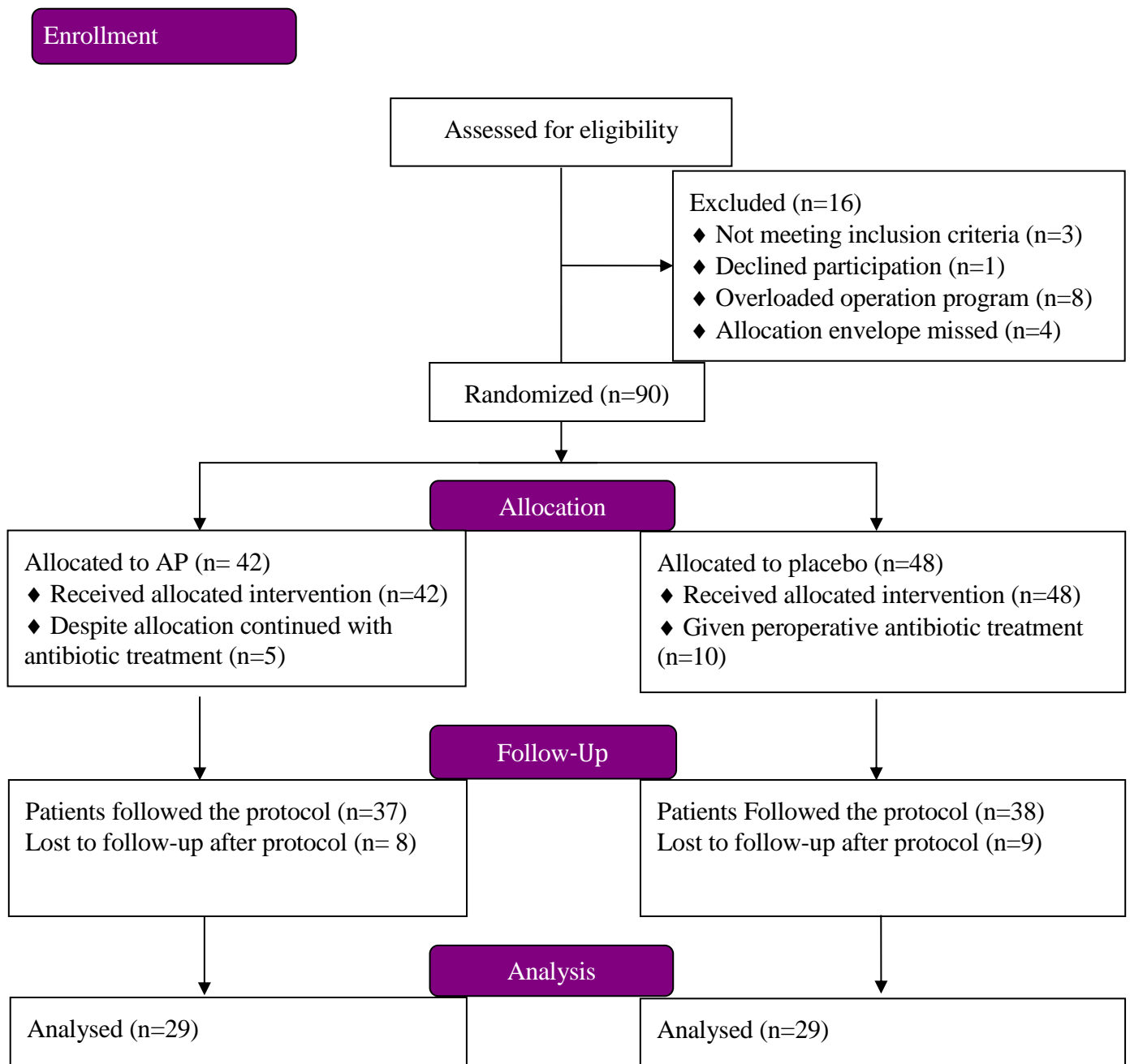
A per-protocol analysis was made, i.e. excluding patients where blinding was interrupted during the operation, and patients where no follow-up interview was made.

A sample size of 77 patients was needed to have a power of 80% to reduce the rate of PIC from 25% to 10% in order to detect a clinically and statistically significant difference at the  $p < 0.05$  level (one-sided test).

Chi-square and T-test were used to determine differences between the groups regarding categorical variables, and Mann Whitney U-test was used to analyse parametric data.

### **Results**

The total number of patients included in the study was 106. A flow chart of the study group is presented in Fig 13. After the initial drop-out, 90 patients were randomly allocated to one of two groups; 42 patients were randomised to the antibiotic group and 48 to the placebo group. These groups constituted the intention-to-treat cohort. The surgeon decided to interrupt blinding for five patients in the antibiotic group and 10 patients in the placebo group. The 10 patients in the placebo group that did not follow the protocol received antibiotic treatment intraoperatively and this was continued postoperatively due to severe wound contamination. The 5 patients in the antibiotic group that did not follow the protocol continued antibiotic treatment postoperatively for the same reason. There were 8 and 9 patients lost to follow-up in the antibiotic and placebo groups, respectively. The remaining 78 patients (29 in each group) formed the per-protocol group.



**Figure 13:** Flow diagram.

There was no variation in known risk factors between the two groups (Table 9). The PIC rate was lower in the antibiotic group than the placebo group (19% versus 29%), but there was no statistically significant difference ( $p= 0.193$ ). In the per-protocol analyses the PIC rate was 10% in each group.

Variables	Intention-to-treat analysis n 90			Per-protocol Analysis (allocation and follow-up) n 58		
	Antibiotic (%) 42 (47)	Placebo (%) 48 (53)	p-value	Antibiotic 29 (50)	Placebo 29 (50)	p-value
Gender, Men (%)	18 (43)	23 (48)	0.675	13 (45)	11 (38)	0.395
Women	24 (57)	25 (52)		16 (55)	18 (62)	
Age (IQR)	48.5 (24)	49 (25)	0.768	55 (20)	45 (20)	0.194
BMI (median) (IQR)	27 (7)	28 (6)	0.874	28 (9)	27 (5)	0.428
Previous gallstone symptom (%)	13 (31)	11 (30)	0.476	10 (34)	6 (21)	0.379
No Comorbidity (%)	13 (31)	21 (44)	0.277	8 (28)	14 (48)	0.175
Symptom duration (median) (IQR)	4 (3)	4 (2)	0.653	4 (3)	4 (1)	0.178
Op-method (%)			0.487			0.838
Laparoscopic	37 (88)	38 (79)		26 (90)	25 (86)	
Open	1 (2)	3 (6)		1 (3)	2 (7)	
Converted	4 (10)	7 (15)		2 (7)	2 (7)	
Temp inclusion day (IQR)	37 (21)	37 (1)	0.810	37 (2)	37 (2)	0.433
CRP inclusion day median (IQR)	57 (121)	81 (129)	0.140	46 (129)	76 (79)	0.409
LPK inclusion day (median)(IQR)	10 (5)	12 (7)	0.105	9 (6)	10.5 (8)	0.600
Temp day 2 (median) (IQR)	37 (2)	37(0.5)	0.398	37 (2)	37 (1)	0.893
CRP day 2 (median) (IQR)	760 (175)	80 (118)	0.650	56 (151)	70 (52)	0.844
LPK day 2 (median) (IQR)	10 (7)	11 (5)	0.536	8 (8)	10 (4)	0.545
Antibiotic treatment start postop (%)	5 (12)	10 (21)	0.396	--	--	
Postop complication (%)	8 (19)	14 (29)	0.193	3 (10)	3(10)	0.665

**Table 9:** characteristics of study population.

The conversion rate was the only variable that differed in patients with PIC, with a higher conversion rate from Lap-C to open in the group with PIC (27% compared to 7 % in the non-event group). The comorbidity rate was also high in the PIC group (77 % versus 57% in the non-event group), but the difference was not statistically significant (Table 10). CRP levels were significantly higher on the day of allocation and the day following in patients with PIC.

The total number procedures where bile was sent for culture was 48. In some of the cultures more than one bacterial species was found. Altogether 18 cultures were positive and 30 negative. The predominant agent was gram-negative bacteria (n=11), followed by gram-positive (n=10). The number of PICs in the antibiotic group (6) was almost significantly higher, than in placebo group (3) ( $p= 0.054$ ). In the group with a positive culture, 67% (n=12) did not develop PIC (Table 11).

Variables	Intension-to-treat analysis (90)			Per-Protocol analysis (58)		
	Non-event (%) 68 (76)	Event (%) 22 (24)	p-value	Non-event (%) 52 (90)	Event (%) 6 (10)	p-value
Men (%)	32 (47)	9 (41)	0.633	22 (42)	2 (33)	1.000
Age (IQR)	47,5 (24)	58 (25)	0.081	49 (22)	59 (26)	0.301
BMI (IQR)	27.4 (6.5)	27.7 (6.3)	0.936	28 (7)	28 (6)	0.861
Symptom duration (IQR)	4 (2)	4 (3)	0.400	4 (2)	5 (4)	0.388
No Comorbidity (%)	29 (43)	5 (23)	0.075 (1s)	21(40)	1(17)	0.253 (1s)
Operation method (%)			0.017*			0.335
laparoscopic	61 (90)	14 (64)		46 (88)	5 (83)	
open	2 (3)	2 (9)		2 (4)	1 (17)	
converted	5 (7)	6 (27)		4 (8)	0 (0)	
Temp allocation day (IQR)	37 (2)	37 (1)	0.513	37(1)	37(1)	0.409
CRP allocation day (IQR)	57 (121)	124 (118)	0.008*	57(94)	131 (123)	0.102
LPK allocation day (IQR)	10 (7)	12 (5)	0.258	9 (8)	11 (3)	0.564
Temp day 1 (IQR)	37 (2)	37 (1)	0.560	37(2)	36 (2)	0.278
CRP day 1 (IQR)	64 (87)	206.5 (164)	0.004*	58 (63)	113(152)	0.163
LPK day 1 (IQR)	8.5 (5)	11 (5)	0.053	8 (5)	10 (5)	0.096
Nr allocated to AP (%)	34 (50)	8 (36)	0.193 (1s)	26 (50)	3 (50)	0.665 (1s)

**Table 10:** Postoperative infectious complications.

	Culture (n=48)		P-Value (1s)
	Positive (n=18, 37.5%)	Negative (n=30,62.5%)	
Randomised			0.076
Antibiotic	13 (72)	14 (47)	
Placebo	5 (28)	16 (53)	
Postoperative infectious complications			0.054
Non-event	12 (67)	27 (90)	
Event	6 (33)	3 (10)	

**Table 11:** Bile culture results.

## 9 DISCUSSION

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The studies in the thesis have shown that there are great disparities in routines regarding AP in patients operated for gallstone disease. Whereas the risk for serious infectious complication may be reduced in selected high-risk patients, there is no need for the routine use of AP in gallstone surgery. Any decision to use AP must be weighed against the side-effects associated with uncritical widespread use of antibiotics.

There is evidence that AP is beneficial during high-risk and contaminated procedures. This was confirmed in Study III. Gallstone surgery has generally been considered a contaminated procedure due to presumed bactibilia. Most elective surgery after a cholecystitis or episode of bile colic reveals no sign of inflammation or infection. The majority of studies performed, have not shown any benefit of AP in reducing PIC rates in elective cases. Studies on bile sampled intraoperatively using standardised methods have not shown a clear relationship between positive bile culture and the risk for PIC. Accordingly, the value of AP in surgery for mild to moderate cholecystitis should be questioned. There are reasons to believe that proper preoperative skin preparation and good surgical technique avoiding gallbladder perforation, is more effective in preventing surgical site infection than AP.

There are still no generally accepted evidence-based guidelines on when to give AP. Furthermore, there is no consensus on whether to give a single dose, 3 doses or 5 doses. This is probably the reason behind the lack conformity between hospitals and between surgeons in Sweden regarding the use of prophylaxis, as seen in Study II. The results were adjusted for all relevant confounders that could possibly explain any difference in routines, but the difference remained statistically significant. There is a clear overuse of antibiotics in many situations, which may fuel the increase in antibiotic resistance. Even if the level antimicrobial drug resistance in Sweden is low, it is steadily increasing (67). Uncertainty, variation and overuse of AP exposes the patients to risk without scientifically proven benefit.

The disparities shown in Study II probably reflect local and personal traditions. Over time such traditions may give a delusive feeling of following principles that are assumed to be established and based on evidence.

The National Institute for Health and Care Excellence (NICE) aims at improving health and social care through evidence-based guidelines. NICE guidelines regarding prevention and treatment of SSI around skin incisions include evidence-based advice that may suitably be applied in the perioperative period (68). Although 11 years have passed since these guidelines were published, they are seldom adhered to by the surgeon despite the evidence in their favour (69). In one of the largest hospitals in Italy, adherence to international guidelines on AP regarding, duration, timing and type of antibiotic was only 48%. Prophylaxis was used in 73% of procedures despite this not being recommended in current guidelines (70). It is the

responsibility of each hospital and surgeon to adhere to the evidence based international guidelines.

It is the professional responsibility of every physician to limit the use of antimicrobial treatment, and to follow guidelines when prescribing them. This is an important part of all stewardship programmes and is necessary if we are to maximise clinical outcome and minimise the emergence of antimicrobial resistance (71).

A Cochrane review published 2017 assessed the effectiveness of antibiotic stewardship interventions in hospital healthcare, and evaluated the impact of these interventions on compliance with antibiotic policy and reduction in duration of antibiotic treatment (72). The report suggested that stewardship interventions could be effective, particularly in terms of feedback to prescribers, in reducing length of hospital stay without endangering safety, duration of antibiotic treatment and excessive antibiotic prescribing to hospital inpatients.

There is evidence that hospital-based programmes aimed at stricter routines for antibiotic use, may optimise the treatment of infections as well as reduce adverse events associated with antibiotic use (71). A Cochrane review of 89 studies showed that interventions to reduce antimicrobial prescription to inpatients may reduce drug-resistance and hospital-acquired infections and improve clinical outcome (73).

The implementation of an effective antimicrobial stewardship programme, based on antimicrobial use and resistance patterns, may prevent antimicrobial resistance development and reduce the number of cases of *Clostridium difficile* diarrhea (74-76).

In view of the continuing emergence of antibiotic resistance, developing new drugs that are based on the same pharmacological principles as drugs that are already established is not a sustainable strategy in the long run, particularly as antibiotics are difficult and costly to develop (77). At present there are no antibiotics in the pipeline that are effective against the most drug-resistant gram-negative organisms (78), and totally resistant *Neisseria gonorrhoea* is a typical example.

Continual feedback, increased awareness of the surgeon, and repeated surveys may improve compliance to antimicrobial stewardship interventions (79). Furthermore, if antimicrobial stewardship is to be more convincing for practitioners, it needs to be widely understood that it is crucial for patient safety (77).

STRAMA (Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance) was started in Sweden 1994 in order to provide surveillance of antibiotic use and resistance, to implement rational routines for use of antibiotics and provide us with new knowledge (67). The goals of STRAMA are to preserve the effectiveness of currently available antibiotics, to work for better basic hygiene precautions, and encourage more appropriate choice, dosage, and length of antibiotic treatments in Sweden (80).

STRAMA has indeed played an important role in the reduction of antibiotic use in Sweden

(67, 79), but even so there is still considerable room for improvement as seen in the results of Study II regarding antibiotic usage.

In Study III, we undertook unadjusted and adjusted analyses in order to assess patient-related factors that may have had an impact on the SSI and septicaemia. The multivariate analyses included age >70 years, ASA class  $\geq 2$ , indication for surgery (gallstone complication versus no complication), open surgery, duration of surgery >120 minutes and intraoperative antibiotics. These factors must be taken into consideration together with procedure-related risk factors when deciding on PAP. This study was based on a cohort from GallRiks, and we found a moderate impact of comorbidity on SSI and septicaemia. The comorbidities found to have the greatest impact were chronic kidney disease and cirrhosis when adjusting for other confounders (age, gender, ASA, indication for surgery, operation approach and time, antibiotic treatment and accidental gallbladder perforation). The risk for SSI was found to increase four- and five-fold in patients with these conditions respectively. The planning of any procedure in a patient with either of these risk factors should aim at minimising other factors that may affect outcome. Postoperative care with resources for monitoring and frequent controls may reduce perioperative risks, as may AP, good surgical technique and experienced surgeons. Another study focusing on patient-related risk factors, including diabetes, obesity, smoking, malnutrition, steroid use, and immunosuppression showed a significant association between these factors and PIC (69).

Obesity is a major health problem in many countries and an independent risk factor for SSI (81-83). This has also been confirmed in a recent study (84).

Hyperglycaemia has been reported to increase the risk for SSI (85). Although we did not have any data on glucose levels in Study III, we did find an association between history of diabetes and the risk for SSI and septicaemia.

The high OR for each comorbidity investigated suggests that AP should be considered in high-risk patients, even when risk factors related to the procedure *per se* are not anticipated.

Smoking, nutrition status and grade of cholecystitis are also important confounders that we, unfortunately, were not able to adjust for based on data from the registers.

Results from an RCT study including 166 patients did not show any reason to give AP to prevent SSI and abscess simply because bile spillage occurs during routine elective cholecystectomy (86). The subgroup analyses in Study I regarding accidental gallbladder perforation during cholecystectomy did not show significant decrease in OR for PIC and abscess, not even when adjusting for all relevant confounders. Bile spillage, conversion to open surgery and ASA class >2 have been shown in a large prospective study, to be independent risk factors for SSI (87). In that study, patients received at least 1 dose of a second-generation cephalosporin, both acute and elective cholecystectomies were included, and no information was given about bile spillage.

NICE recommendations regarding SSI prevention is giving AP in clean surgery (i.e. no inflammation and without interference with sterile circumstances where respiratory, and where alimentary or genitourinary tracts are not entered) only in case of replacement of a prosthesis or implant, and to all clean-contaminated and contaminated procedures. Contaminated surgery includes acute cholecystectomy where there is mild degree non-purulent inflammation of the gallbladder (Grade I) (68).

The same advice is given in other guidelines, recommending AP in AC even when it is mild or moderate. These recommendations are probably based on safety assumptions and lack of scientific evidence against benefit from AP (TG18). To our knowledge, there is still no published study on randomised AP in acute cholecystectomy regarding the effect on PIC.

Study I was a cohort study based on a database of 13,911 cholecystectomies registered between January 2006 and December 2010 in Sweden. The study showed no significant association between AP and PIC. Association between AP and PIC was adjusted for cofounders by stepwise inclusion. The OR decreased with each covariate added, but did not reach statistical significance. Subgroup analysis for AC, obstructive jaundice and gallbladder perforation also resulted in an OR that remained insignificant, even when adjusting for the cofounders. The population Study I is of the largest yet published. Although the coverage of GallRiks is high, it is not 100%. Missing data and misclassification might have led to selection bias. The fact that only one randomised study has shown benefit of AP was one of the reasons for performing Study IV.

Many studies and meta-analyses have reported no benefit of AP in elective laparoscopic cholecystectomy. Matsui performed a review of all RCTs included in 7 meta-analyses and calculated the pooled risk ratio and found that AP significantly reduces the risk for postoperative infection (42). In this review, they excluded 11 meta-analyses because of irrelevant content. The remaining studies all had RR overlapping 1 apart from their own study.

On the other hand, four RCTs have recently been presented on the effects of postoperative AP versus placebo on the postoperative infection rate after acute cholecystectomy for mild to moderate cholecystitis. In all of these studies the patients received PAP ( $\geq 1$  dose). Postoperative complications ranged from (5.7 – 17%) (45-47, 88) and continued postoperative, AP gave no benefit compared to placebo. Based on the experience from these studies, the next step would be to conduct a RCT study with only preoperative AP or placebo. A few randomised trials comparing antibiotic with placebo in surgery for cholecystitis have been published. These studies were performed before the era of Lap-C, and although they showed some benefit from AP, the validity of these studies today is limited (89, 90). Conducting a similar trial today is difficult because of the complexity of the current healthcare system and is probably why there has not been a recent RCT study on AP in acute cholecystectomy. Study IV was a single-centre double-blinded randomised study conducted between 2009 and 2017.

The study showed, albeit without power sufficient to detect any minor reduction, no great impact on PIC rate and we concluded that the routine use of AP is questionable. The study population included Grades I and II cholecystitis according to the Tokyo guidelines, i.e. a group with a high risk for PIC. However, the latest Tokyo guidelines, 2018, recommend antibiotic treatment with type and duration depending on the severity of cholecystitis (30). The guidelines state that mild cholecystitis could be treated without AP, but give no clear criteria for patients requiring antibiotic treatment. Postoperative complications are multifactorial and AP does not provide the benefit expected. Bactibilia does not seem to be of predictive value for PIC (positive cultures were more frequent in the non-event group than in group with PIC), but CRP and method of approach had a significant impact on PIC in Study IV. Further studies with higher power are needed to confirm these results.

When deciding on AP during acute cholecystectomy, patient- as well as procedure-related risk factors should be considered. These include severity of gallbladder inflammation, duration of symptoms, comorbidity, blood markers of infection and contamination level during the operation. Only then can we improve patient outcome and minimise the adverse effects of antibiotic treatment, both for the patient and society.



## 10 CONCLUSIONS

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- I. Antibiotic prophylaxis has no significant impact on postoperative infectious complication rate in acute cholecystectomy.
- II. There is a disparity in routines regarding antibiotic prophylaxis during surgery for gallstone disease in Sweden. This is apparent at hospital and surgeon levels, but not at the county level.
- III. Patient-related risk factors have an impact on surgical site infection and septicemia after surgery for acute cholecystitis. These factors should be taken into consideration when deciding on antibiotic prophylaxis.
- IV. Antibiotic prophylaxis does not have a significant impact on the risk for postoperative infectious complication and bactibilia in acute cholecystitis.



## 11 POPULÄRVETENSKAPLIG SAMMANFATTNING

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Gallstenar förekommer hos 10–20% av befolkningen. Av dessa utvecklar 20 % komplikationer i form av gallstensanfall, kolecystit (gallblåsinflammation), kolangit (gallgångs infektion) eller pankreatit (bukspottskörtelinflammation) någon gång under livet. Standardbehandlingen för patienter med gallsten och kolecystit, pankreatit eller gallstenskolik är att operera bort gallblåsan med dess innehåll av stenar med hjälp av laparoskopi (titthålsteknik), så kallad laparoskopisk kolecystektomi. Den första laparoskopiska kolecystektomin utfördes 1985 av den tyske kirurgen Mühe. Idag utförs upp till 95% av kolecystektomier laparoskopiskt, i de flesta fall utan betydande risker. Komplikationsrisken är som lägst på friska individer vars operation görs elektivt (planerad i lugnt skede) medan den ökar med graden av inflammation i gallblåsan, patientrelaterade riskfaktorer och andra operationsrelaterade riskfaktorer.

Infektiösa komplikationer (IK) drabbar upp till 17% hos patienter med låg till moderat grad av kolecystit när de opereras akut. Längre har man trott att en dos av antibiotika som ges innan operationen (antibiotikaproylax, AP) minskar risk för IK efter kolecystektomi. Denna princip har etablerat sig i dagens rutiner. Risken för IK är betydligt lägre vid planerade operationer, där studier har visat att antibiotikaproylax inte har någon plats hos patienter med låg risk vid planerad kirurgi. Detta är dock inte studerat i situationer när operationen utförs i ett skede där man har inflammation och kanske infektion i gallblåsan. Vissa riskfaktorer som skulle kunna påverka IK risken är välkända och välstuderade. Riktlinjer på många håll är dock att man ordinerar antibiotikaproylax vid alla akuta laparoskopiska kolecystektomier. Många rekommendationer är baserade på konsensus och inte på kliniska väl genomförda studier. Detta leder till överanvändning och felanvändning av antibiotika över hela världen med ökad risk för selektion av bakterier som är resistenta och spridning av dessa i en snabbare takt.

Multiresistenta bakterier sprider sig allt mer i hela världen, särskilt där förskrivning av antibiotika är frikostig. Sverige har haft en låg nivå av multiresistenta bakterier sedan länge, även om den dock ökat långsamt. Idag har vi ett mycket begränsat urval av antibiotika som är effektiva och det finns inga nya antibiotika som förväntas komma i bruk inom den närmaste framtiden. Vi måste därför i våra rutiner begränsa användningen av de antibiotika som finns tillgängliga idag.

I delarbete ett har vi hämtat information om patienter som genomgått akuta kolecystektomier mellan januari 2006 och december 2010 från det svenska kvalitetsregistret GallRiks med täckning upp till 85% av alla utförda kolecystektomier i Sverige. Totalt 13 911 patienter inkluderades i analysen, där AP gavs i 68,6% av ingreppen. Analyserna visade ingen skillnad mellan gruppen som fick AP jämfört med de som inte fick AP vad gäller IK när man tar hänsyn till de kända riskfaktorerna.

I det andra delarbetet studerade vi alla de 113 209 patienter som genomgått kolecystektomi registrerade i GallRiks mellan 2005–2015. Där såg man att rutiner för AP användning varierar signifikant mellan sjukhusen och kirurger men inte mellan landstingen i Sverige. Variationen berodde inte på typ av operation eller svårighetsgraden, utan lokala och personliga rutiner som påverkade valet.

Vi undersökte också om patientrelaterade riskfaktorer påverkar risken för IK i tredje delarbetet. Information hämtades från GallRiks och matchades med Nationella patientregistret för de totalt 94 557 patienter som var registrerade mellan 2006–2016. När resultatet korrigerades för riskfaktorer som var relaterade till proceduren, fann vi att bindvävssjukdom, diabetes, njursvikt, skrumplever och övervikt var sjukdomar som påverkade risken för lokala infektioner efter operationen. Vi fann också att risken för blodförgiftningar och kolangit ökade och att patienter med njursvikt och skrumplever hade en tre respektive fem gånger ökad risk. En mindre riskökning sågs även hos de med bindvävssjukdom och diabetes.

I det fjärde delarbetet, som var en dubbelblind randomiserad studie, ingick patienter med låg och mild kolecystit vilka randomiserades mellan att få antibiotika eller placebo (infusionslösning utan verksamt substans) utan att varken patient, kirurg eller sjuksköterska visste vad patienten fick. Vi följde upp patienterna 30 dagar efter operationen för att registrera IK och återhämtningen. Incidensen av IK var något högre hos patienter som inte fick AP men resultatet var inte signifikant. Positiva odlingar från gallan i gallblåsan skiljde sig inte heller mellan grupperna. CRP (blodprov som stiger vid infektioner) var högre hos de som hade IK. Andelen operationen oftast konverterades till öppen teknik var fler hos patienter med IK.

Sammanfattningsvis fann vi att AP inte har den förväntade och önskvärda effekten på IK hos patienter som opereras akut för kolecystit. Risken att få IK beror på många faktorer och patientens egna risker måste beaktas vid bedömning av risk för IK. Riktlinjer som är vetenskapligt välgrundade krävs för en enhetlig och tydlig regim för AP vid akuta laparoskopiska kolecystektomier.

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# 14 APPENDIX

Description ENG	Allowed value ENG	Help text ENG
Patient data		
Personal identification number (incl. sex and age)	maxNrOfCharacters = 30 allowedSigns = aAbBcCdDeEfFgGhHijJkKlLmMnNoOpPqQrRsStTuUvVwWxXyYzZaÄö Ö-1234567890	
Name (given)	maxNrOfCharacters = 60 allowedSigns = aAbBcCdDeEfFg GhHijJkKlLmMnNoOp PqQrRsStTuUvVwWxXy YzZaÄöÖ ñÑëË-ü ÜäÄ´./., 1234567890	
Surname	maxNrOfCharacters = 60 allowedSigns = aAbBcCdDeEfFg GhHijJkKlLmMnNoOp PqQrRsStTuUvVwWxXy YzZaÄöÖ ñÑëË-ü ÜäÄ´./., 1234567890	
Date of birth	YYYY-MM-DD Min = startofcentury Max = today WarningMin = WarningMax =	
Gender	0=Unknown 1=Male 2=Female	
Date of surgery		
Surgical unit		
In patient or day care? (intention)	1=In patient care 2=Day care	Is the intention that the patient will be discharged on the day of surgery or stay in hospital? Day care is defined as discharge on the day of surgery.
Acute or elective surgery	1=Elective 2=Acute admission (treatment performed during the same episode) 3=Life threatening condition	Acute admission = treatment performed during the same episode when admitted from the emergency department. Acute operation for clinical reasons, for example frequent recurrence of gallstone seizures or cholecystitis. Life-threatening is defined as a clinical condition which requires acute operation within 12 hours, for example progressing peritonitis in cholecystitis, cholangitis or pancreatitis.
Date of admission		
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	YYYY-MM-DD Min = Max = treatdate WarningMin = WarningMax =	
ASA 1-5	1=1 (Healthy) 2=2 (Mild systemic disease) 3=3 (Severe systemic disease) 4=4 (Life threatening disease) 5=5 (Moribund)	1 - A normal healthy patient 2 - A patient with mild systemic disease 3 - A patient with severe systemic disease 4 - A patient with severe systemic disease that is a constant threat to life 5 - A moribund patient who is not expected to survive without the operation
Previously operated in upper abdomen?	1=No 2=Billroth-2/Roux-en-Y 3=Liver resection/transplantation 4=Pancreatic resection 5=Other operation/anatomic anomaly	Operations, previous conditions or anomalies making treatment more difficult
If other - please describe	maxNrOfCharacters = 150 allowedSigns = &%aAbBcCdDeEfFg GhHijJkKlLmMnNoOp PqQrRsStTuUvVwWxXy YzZaÄöÖ ñÑëË-ü ÜäÄ´./., 1234567890	Short description
Preoperative diagnostic evaluation of bile ducts?	1=No 2=MRCP 3=CT-cholangiography 4=Endoscopic ultrasound	Investigations of bile ducts performed preoperatively. If more than one - note the one that was most clarifying.
What was the finding?	1=Normal 2=Anomaly 3=Bile duct stone/stones 4=Stenosis/malignancy 5=Bile duct stone and malignancy 6=Other	Note the most important finding.
Any preoperative measure taken?	1=None 2=Stones have been removed 3=Endoluminal stent	
Is the patient pregnant?	1=No 2=Yes 0=Not known	
Gestational age (weeks)		

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	## Min=5 Max=45 WarningMin= WarningMax= evAllowedOnPag evAllowedInTable	Note the number of weeks of gestation.
Weight (kg)	#### Min = 10 Max = 300 WarningMin = 25 WarningMax = 150	Patient bodyweight in kg.
Length (cm)	#### Min = 50 Max = 250 WarningMin = 100 WarningMax = 210	Patient length in cm.
BMI (Body Mass Index)		System calculates BMI
Indication for surgery	1=Gallstone seizures / Biliary colic 2=Gallstone complications 5=Cholecystitis without stone (Acalculous cholecystitis!) 6=Suspect malignancy/polyps 3=Cholecystectomy secondary, to other major operation 4=Other	Note the main reason for cholecystectomy. If the reason is gallstone complications more than one alternative will be available in the following. Secondary to other major operation should be chosen for example in pancreaticoduodenectomy with cholecystectomy.
Cholecystitis (ongoing)	1=No 2=Yes	Clinical evaluation based on status, fever och laboratory findings.
Pancreatitis (ongoing)	1=No 2=Yes	Clinical evaluation based on status, fever och laboratory findings.
Bile duct obstruction/stone (ongoing)	1=No 2=Yes	Jaundice/bilirubin >50 micromole/L and/or known bile duct stone
Cholecystitis (past)	1=No 2=Yes	Previously diagnosed acute cholecystitis.
Pancreatitis (past)	1=No 2=Yes	Previously diagnosed acute pancreatitis.
If so - date of pancreatitis		

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	YYYY-MM-DD Min = Max = today WarningMin = WarningMax =	
Bile duct obstruction/stone (past)	1=No 2=Yes	Previous jaundice/bilirubin > 50micromol/L and/or bile duct stone
Surgical method	1=Laparoscopic cholecystectomy 2=Laparoscopy but converted to open approach 3=Open cholecystectomy 4="Minicholecystectomy" (< 8cm skin incision) 5=Open bile duct exploration (when previous cholecystectomy) 6=Other surgery (=subtotal cholecystectomy)	Other surgery is used for subtotal cholecystectomy when part of the gallbladder wall is deliberately left in place.
Reason for conversion	1=Unclear anatomy 2=Adhesions 3=Severe cholecystitis 4=Bile duct stones 7=Too wide or short cystic duct 5=Difficult bleeding 8=Susp. of bile duct injury 6=Other complication	Main reason for conversion is noted. If bleeding or other complication is noted this is also registered in the part of peroperative complications.
Mode of access (laparoscopy)	1=Open - at or caudal navel 2=Other mode of access 3=Closed with Veress needle	Method of establishing pneumoperitoneum in laparoscopy
If other - what mode	maxNrOfCharacters = 150 allowedSigns = &%aAbBcCdDeEffG GhIiJjKkLlMmNnOoPp QqRrSsTtUuVvWwXxYy ZzAaAaO ñÑÊË-ü ÜäÄ` /.. 1234567890	Please describe the technique used
Mode of gallbladder mobilization	1=Start at cystic duct and upward 2=Start at fundus and downward 3=No dissection started before conversion	Approach for dissection of the gallbladder during laparoscopy - starts up at fundus or at cystic duct? The approach used after conversion to open surgery is not applicable.
Antibiotics	1=No 2=Prophylaxis (intended <= 24 hours) 3=Therapy (ongoing or started, intended > 24 hours)	Prophylaxis = duration intended less than 24 hours. Therapy is intended for more than 24 hours.
Systemic thromboprophylaxis	1=No 2=Yes	Any form of systemic thromboprophylaxis including infusion of dextran.
Surgeon		The surgeon performing the main part of the procedure,

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	1=No 2=Yes, but complete cleanup. 3=Yes, complete cleanup uncertain.	Peroperative accidental perforation of the gallbladder with leakage of stones in abdomen? If no stones are suspected to be left in the abdomen complete cleanup is chosen.
Other surgery concomitantly	maxNrOfCharacters = 10 allowedSigns = aAbBcCdDeEfFg GhHijJkKlLmMnNoOp PqQrRsStTuUvVwWxXy YzZaAaÄö ñÑêË-ü ÜäÅ` /., 1234567890	Other surgery performed concomitantly that can inflict on postoperative recovery.
Registration of advanced methods	1=No 2=Yes	For example SPA (Single port access), peroperative ultrasound
Peroperative ultrasound	1=No 2=Yes	Ultrasound of for example the bile ducts during surgery
Results of ultrasound	1=Normal 2=Stone in bile duct 3=Susp. malignancy 4=Other	Results of ultrasound
If else please explain	maxNrOfCharacters = 150 allowedSigns = &%aAbBcCdDeEfFg GhHijJkKlLmMnNoOp PqQrRsStTuUvVwWxXy YzZaAaÄö ñÑêË-ü ÜäÅ` /., 1234567890	
Type of port used (intention/at start)	1=SPA (Single Port Access) 2=Other	The type or number of ports that was intended to be used to complete the cholecystectomy.
SPA success?	1=Cholecystectomy completed with SPA 2=SPA + one extra port 3=SPA + two extra ports 4=SPA converted to regular laparoscopy 5=SPA converted to open surgery	How successful was SPA?
Cause of conversion	1=Difficulties with the equipment 2=Difficulties with vision/safety 3=Difficulties due to bleeding 4=Other problems - please describe	The most important reason for conversion
If other problems please explain	maxNrOfCharacters = 150 allowedSigns = &%aAbBcCdDeEfFg GhHijJkKlLmMnNoOp PqQrRsStTuUvVwWxXy YzZaAaÄö ñÑêË-ü ÜäÅ` /., 1234567890	
Time - start of surgery (hh:mm)		

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	HH:MM Min = Max = WarningMin = WarningMax =	Time for start of surgery - "knife in patient"
Time - end of surgery (hh:mm)	HH:MM Min = Max = WarningMin = WarningMax =	Time for end of surgery - "suture complete". If peroperative ERCP is performed the time for this is subtracted and noted in the ERCP protocol
Operating time	#### Min = 0 Max = 600 WarningMin = 25 WarningMax = 210 evAllowedInTable	System calculates.
Perioperative complications	1=No 2=Yes	Yes - if gut is perforated, bleeding needing intervention, bile duct injuries or other complications is noted that significantly affects the course of the operation.
Perforated bowel	1=No 2=Yes	Perforation of any part of the gastrointestinal tract
Bleeding requiring intervention	1=No 2=Yes	
Bile duct injury (incl anatomical position and measure taken)	1=No 2=Bile duct injury < 1/3 of the circumference. 3=Bile duct injury > 1/3 of the circumference. 4=Resection of substantial portion of the circumference. 5=Resection of all of the bile duct circumference.	Bile duct injury < 1/3 and > 1/3 of the circumference are used for injuries with no tissue loss such as cuts with scissors, diathermia or crush injury. Resection of the bile duct circumference can be either partly or comprising all of the circumference. The extent of the resection is noted below on the figure.
Anatomical position (mark on figure)	src = images/rutad5.jpg height = 360 width = 276 usemap = #COMMONMAP_GALLMAPREDUCED	Please plot the position and extent of injury in the figure.
Measures taken		

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	maxNrOfCharacters = 150 allowedSigns = &%aAbBcCdDeEfGhHijJkKlMmNnOoPpQrRsStTuUvVwWxXyYzZaAaöÖñÑëË-üÜäÄ`./,. 1234567890	Please describe shortly how the injury was managed during the procedure for example conversion and biliary reconstruction, suture over a T-tube placement etc.
Other complication	maxNrOfCharacters = 150 allowedSigns = &%aAbBcCdDeEfGhHijJkKlMmNnOoPpQrRsStTuUvVwWxXyYzZaAaöÖñÑëË-üÜäÄ`./,. 1234567890 evAllowedOnPag evAllowedInTable	Please describe what.
Follow up 30 days		
Follow-up date	YYYY-MM-DD Min = treatdate Max = today WarningMin = WarningMax =	Follow-up can be done at the earliest after 30 days. (System controls this)
Date of discharge	YYYY-MM-DD Min = treatdate Max = today WarningMin = WarningMax =	When did the patient leave the department (date).
Main final diagnosis	maxNrOfCharacters = 10 allowedSigns = aAbBcCdDeEfGhHijJkKlMmNnOoPpQrRsStTuUvVwWxXyYzZaAaöÖñÑëË-üÜäÄ`./,. 1234567890	Main diagnosis (according to medical record)
Other diagnosis if any	maxNrOfCharacters = 10 allowedSigns = aAbBcCdDeEfGhHijJkKlMmNnOoPpQrRsStTuUvVwWxXyYzZaAaöÖñÑëË-üÜäÄ`./,. 1234567890	Secondary diagnosis (according to medical record)
Deceased date		
Cause of death?	1=Procedure related complication 2=Other complication such as cardiovascular etc. 4=Other cause of death 3=Unknown cause of death	The patient is deceased. What was the cause of death?
PAD (Pathological Anatomical Diagnosis)		

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	0=Normal gallbladder 1=Cholesterosis 2=Chronic cholecystitis 3=Acute cholecystitis 4=Mixed acute and chronic cholecystitis 5=Adenoma 6=Cancer 7=Information missing 8=Other benign findings	Results from PAD of the gallbladder
Complications discovered postoperatively		
	0=Information unavailable 2=Yes 1=No	Any complication needing intervention.
Bleeding requiring intervention	1=No 2=Yes	Bleeding requiring transfusion and/or reoperation
Abscess	1=No 2=Yes	Infection requiring treatment, for example antibiotics. Register type of treatment below!
Pancreatitis	1=No 2=Yes	
Severity of the pancreatitis	1=Minor/medium 2=Severe (requiring intensive care)	Minor/medium=No intensive care needed Severe=Intensive care was used
Perforation	1=No 2=Yes	Perforation of gut
Cholangitis	1=No 2=Yes	Sepsis originating from the bile ducts. Sepsis origination from bile ducts
Thrombosis/Embolism	1=No 2=Yes	
Other postoperative complication	maxNrOfCharacters = 150 allowedSigns = &%aAbBcCdDeEfGhHijJkKlMmNnOoPpQrRsStTuUvVwWxXyYzZaAaöÖñÑëË-üÜäÄ`./,. 1234567890	
Biliary leakage (incl anatomical position where appropriate)	1=No 2=Yes	Intraabdominal bile collection requiring intervention. Bile collection requiring treatment
Cause of leakage		

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	1=Cystic duct 2=Gallbladder bed 3=Bile duct injury < 1/3 of the circumference. 4=Bile duct injury > 1/3 of the circumference. 4=Resection of substantial portion of the circumference. 5=Resection of all of the bile duct circumference. 7=Leakage after T-tube removal 8=Unknown cause	Bile duct injury < 1/3 and > 1/3 of the circumference are used for injuries with no tissue loss such as cuts with scissors, diathermia or crush injury. Resection of the bile duct circumference can be either partly or comprising all of the circumference. The extent of the resection is noted below on the figure.
<b>Anatomical position (mark on figure)</b>	src = images/rutad8.jpg height = 360 width = 276 usemap = #COMMONMAP_GALLMAP	Please mark the position and extent of injury on the figure.
<b>Biliary obstruction (incl cause)</b>	1=No 2=Yes	Jaundice requiring intervention
<b>Cause of biliary obstruction</b>	1=Bile duct stone retained 2=Ligature/clip over bile duct. 3=Stricture. 5=Hemobilia/blood clot 4=Unknown cause	
<b>Anatomical position (mark on figure)</b>	src = images/rutad5.jpg height = 360 width = 276 usemap = #COMMONMAP_GALLMAPREDUCED	Please mark the position and extent of injury on the figure.
<b>Measures taken for complications</b>		
<b>Reoperation</b>		
<b>Biliary reconstruction</b>	0=No 1=Ligature of bile duct (JKB96) 2=Suture of bile duct (JKB40) 3=Hepatico-jejunostomy (JKD20, JKD30) 4=Other reconstruction (JKD96) 5=Exploration and drainage (JAH00, JWC00, JWB00) 6=Bleeding control and evacuation of clots (JWE00, JWD00) 7=Other	The complication demanded reoperation for reconstruction, hemostasis, drainage etc
<b>Other reoperation</b>	maxNrOfCharacters = 150 allowedSigns = &%aAbBcCdDeEfFg GhIiJjKkLlMmNnOoPpQqRrSsTtUuVvWwXxYy ZzAaAaöÖ ñNëE-ü Ü&A^` /.. 1234567890	
<b>Referral to other hospital</b>	1=No 2=Yes	Patient referred to other hospital
<b>Percutaneous drainage</b>	1=No 2=Yes	Percutaneous drainage applied as treatment for the complication
<b>Antibiotic treatment</b>		
	1=No 2=Yes	The complication was treated with antibiotics
<b>Transfusion</b>	1=No 2=Yes	Bleeding requiring transfusion.
<b>ERC (endoscopic retrograde cholangiography)</b>	1=No 2=Yes	ERC was used to treat the complication

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