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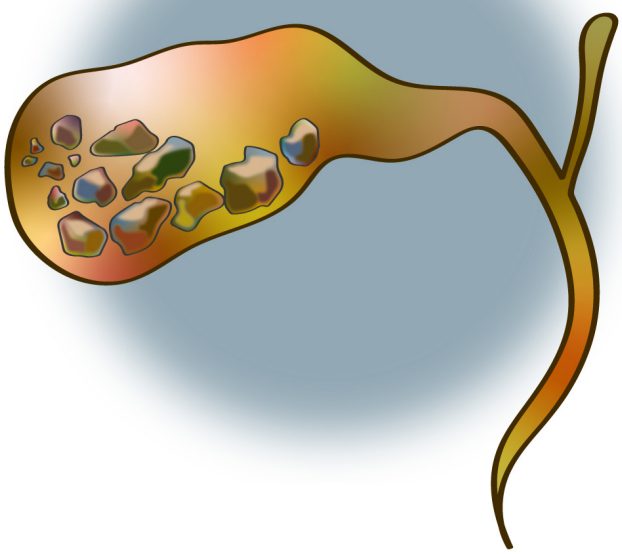
Mangement of acute cholecystitis. Surgery, drainage and gallbladder aspiration.



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MANAGEMENT OF ACUTE CHOLECYSTITS. SURGERY, DRAINAGE AND GALLBLADDER ASPIRATION

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By

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To my family and in loving memory of my father

Popular science summary of the thesis

Acute inflammation of the gallbladder is a common condition among the general population. It occurs when a gallstone gets stuck in the neck of the gallbladder. This causes a high pressure in the gallbladder and leads to inflammation. Approximately 10-20 % of the population in western countries have gallstones and 20% of these get symptoms from their gallstones. Of those that have symptoms approximately 1-3 % develop complications including inflammation of the gallbladder. The treatment of choice for gallbladder inflammation is emergency surgery where the gallbladder is removed. However, some patients afflicted by this condition have a higher risk for anesthesia and surgery where performing an emergency surgery can lead to high risk for morbidity or mortality. In those cases, when a patient is not chosen for emergency surgery other conservative treatment options are given such as pain medication, fasting, antibiotics or decompression of the gallbladder with a drainage. Studies on treatment of acute inflammation of the gallbladder in patients not suitable for emergency surgery due to high age or high co-morbidity are few and many questions remains unanswered. The aim of this thesis is to improve the care of frail and old patients with high co-morbidity who suffers from acute gallbladder inflammation.

In the first paper we studied 1649 patients treated for acute inflammation of the gallbladder in Stockholm County in the years 2003 and 2008. We found that less than 50% are treated with acute surgery even as this is the treatment of choice. We saw that emergency surgery is a relatively safe treatment and found no difference in complications if surgery is performed in the acute setting or as a delayed surgery when the inflammation subsides. We found that 17.8 % of patients treated conservatively get a recurrence of the disease. Emergency surgery should be the treatment of choice at least for the younger and healthier patients.

In paper two the same patient population was studied but we focused on those treated with a drainage of the gallbladder. We found that drainage is a treatment given to patients that are older, frailer and have a higher co-morbidity. This treatment was proven as a safe option to emergency surgery in this frail group but leads to longer hospital stay.

For paper three data was collected from the Swedish quality register for gallbladder surgery, GallRiks. GallRiks has a high coverage of all gallbladder surgeries performed in the country and information on outcome after surgery. We studied 8532 patients treated in the acute setting conservatively for their gallbladder inflammation and who later performed an elective surgery. The aim was to study when the ideal time is to perform an elective surgery after the inflammation subsides. We found that safety increases if surgery is performed after 30 days.

In paper four we studied a new treatment option for those patients not chosen for emergency surgery where the gallbladder is punctured and drained of its content, but no drainage tube is left in place. This treatment was given to 25 patients and all patients improved in their condition and could be discharged from the hospital after approximately 3 days. We found this treatment to be a safe option to drainage, but it needs further evaluation in larger studies.

In the last paper, five we studied how to best handle a gallbladder drainage after it is put in place. Outcome after drainage is studied but there are few studies on how to handle the drainage. We reviewed 241 patients treated with drainage between the years 2016 and 2021 and found that removal of these drains within one week seems safe and performing radiology before removal does not affect the outcome.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Akut gallblåseinflammation är en vanligt förekommande sjukdom bland befolkningen som kan uppkomma då en sten fastnar i gallblåsehalsen och orsakar tryckstegring i gallblåsan som i sin tur leder till inflammation och smärta. Man beräknar att ca 10-20 % av befolkningen i västvärlden har gallstenar där 20 % av dessa får symptom och ca 1-3% av de med symptom drabbas av komplikation så som gallblåseinflammation. Standardbehandling vid gallblåseinflammation är akut operation där man tar bort gallblåsan. Många gånger drabbas dock patienter som har en påtagligt ökad risk för sövning och kirurgiska ingrepp där operation kan leda till betydande morbiditet och mortalitet. I de fall man väljer att inte operera en patient akut erbjuds alternativa behandlingsformer som smärtlindring, fasta, antibiotika eller avlastning av gallblåsan med dränage. Studier kring behandling av akut cholecystit hos patienter som inte är lämpliga att genomgå akut operation pga ålder eller samsjuklighet är begränsande och många frågor är obesvarade. Syftet med denna avhandling är att förbättra vården för sköra och gamla patienter med hög samsjuklighet som drabbas av akut gallblåseinflammation.

I delarbete ett granskade vi 1649 patienter som har vårdats i Stockholms län för akut gallblåseinflammation under åren 2003 och 2008. Vi fann att mindre än 50% av patienterna erbjöds akut operation vid gallblåseinflammation trots att denna behandlingsform anses vara standardbehandling. Vi såg att akut operation var ett säkert alternativ och fann inga skillnader för komplikation om patienter behandlades med akut operation eller senarelagd operation. Vi såg att 17,8% av patienterna får återfall av gallblåseinflammation ifall de behandlas med konservativ strategi. Akut operation bör väljas primärt som behandling i de fall där patienterna är yngre och friskare.

I delarbete två fokuserade vi på de patienter i Stockholms Län som behandlades med galldrän. Studiepopulationen var samma som för delarbete ett. Vi kunde se att behandling med galldrän erbjuds ffa till äldre, skörare och multisjuka patienter. Denna behandling visade sig vara ett säkert alternativ till akut operation för denna sköra patientgrupp men leder till påtagligt längre sjukvårdtid.

Till delarbete tre har vi hämtat data från det svenska kvalitetsregistret för gallstenskirurgi, GallRiks som har en väldigt hög täckning av registrerade gallblåseoperationer och utfall efter dessa. Vi granskade 8532 patienter som i det akuta skedet av sin gallblåseinflammation behandlats konservativt dvs utan operation och senare genomfört en elektiv operation av sin gallblåsa när inflammationen läkt ut. Syftet var att se när det var mest fördelaktigt att genomföra en elektiv operation efter en tidigare genomgången gallblåsinflammation. Vi kunde se att säkerheten vid operationen stiger om denna genomförs minst 30 dagar efter utskrivning.

I delarbete fyra undersökte vi en ny behandlingsmetod för de patienter som inte opereras akut som innebär att gallblåsan punkteras och töms på sitt innehåll utan att man lämnar kvar en slang för dränering. 25 patienter erhöll denna behandling och alla patienter förbättrades i sin sjukdom och kunde i snitt skrivas ut efter ca 3 dagar från sjukhuset. Vi fann denna behandling vara ett säkert alternativ till galldrän men metoden bör utvärderas i större studier.

I delarbete fem studerade vi hur man bäst hanterar galldrän när det väl har satts. Utfall efter behandling av galldrän har studerats i flera studier men däremot hur man skall hantera själva dränet är inte lika studerat. Vi granskade journaler för 241 patienter som behandlats med galldrän mellan åren 2016 och 2021 och fann att det verkar säkert att avlägsna drän tidigt dvs inom en vecka och det ser inte ut som att genomförande av röntgenundersökning innan drändragning verkar påverka utfallet.

Abstract

Background

Early laparoscopic cholecystectomy is considered the standard of care for patients admitted with acute cholecystitis. Nevertheless, a large proportion of patients admitted for acute cholecystitis are managed without acute surgery. The reasons for not opting on acute surgery include lack of resources, severe comorbidity, frailty, protracted history prior to admission or non-compliance with guidelines due to local routines. Even if early cholecystectomy remains the firsthand alternative for patients with acute cholecystitis, safe and effective management is needed in case this routine is not followed.

Methods

For study one and two we retrospectively reviewed medical records of 1649 patients treated for acute cholecystitis in Stockholm County in the years 2003 and 2008. The aim was to study management and outcome after different treatment strategies. The primary focus for study one was to compare acute cholecystectomy with delayed surgery and for study two focus was on those treated with percutaneous cholecystostomy (PC).

For study three we used the Swedish Registry for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (GallRiks) as well as the National patient register (NPR) to study the outcome after elective cholecystectomy for those patients treated initially conservatively for acute cholecystitis. The impact of time after discharge from hospital to elective surgery with focus on intra- and postoperative complications, bile duct injuries and leakage, operating time and surgeries completed laparoscopically was analyzed.

Study four was a prospective safety feasibility pilot study of percutaneous gallbladder aspiration, (PGBA) as treatment of patients not suitable for emergency surgery. We performed PGBA on 25 high-risk patients.

Study five was a retrospective review of 241 patients treated with cholecystostomy to evaluate maintenance of the cholecystostomy once in place. We studied when it is safe to remove a drainage and whether retrograde cholangiography adds to safety.

Results

In study one and two we found that during the year 2003 42.9% and the year 2008 47.4% of patients were treated with acute cholecystectomy. Those receiving acute surgery tend to be younger and healthier. When adjusting for age, gender, severity of the inflammation, maximal white blood cell count and CRP we found no difference in complication rate between early and delayed surgery but in early surgery the operating time was shorter albeit with higher blood loss and delayed surgery had a lower conversion rate to open surgery. Between these groups there was no significant difference in intra- or and postoperative complication rates. In study two we found that patients treated with cholecystostomy tend to be older with higher co-morbidity and treatment with cholecystostomy for this group was a safe option with lower complication rate than for those treated with acute surgery, although with a longer hospital stay.

In study three 8532 patients were divided into six different time intervals from discharge after acute cholecystitis to elective cholecystectomy. We found a reduction in the risk for cystic duct leakage and perioperative complications if surgery was performed more than 30 days after discharge and if surgery was performed more than one year after discharge there was an increased risk for bile duct injury.

Study four was based on 25 high-risk patients treated with PGBA, showing that the procedure was successful in all patients, although one patient needed two aspirations. We registered one minor complication that did not require any intervention. Median hospital stay was 3 days (IQR 2-4 days). Recurrence rate of cholecystitis was 28%.

In study five, 241 patients with a median age of 77 years, 82.6% with Tokyo grade 2 and 14.1 % grade 3 cholecystitis treated with cholecystostomy were included. Complications related to cholecystostomy Clavien-Dindo ≥ 2 were found in 19.5%. Recurrence rate following treatment with cholecystostomy was 12%. We found no significant difference in outcome if the drainage was removed based on clinical judgment or cholangiography finding. Time to drain removal did not have any impact on the complication rate either Management of the cholecystostomy had no impact on recurrence rate.

Discussion

Although early cholecystectomy is considered the treatment of choice for acute cholecystitis, it is routinely applied. Rescue strategies should be evaluated for this patient group. PC seems to be a safe option for those with high risk for emergency surgery.

We found that safety of cholecystectomy increases if performed more than 30 days after discharge after a conservatively treated cholecystitis. PGBA seems to be a safe treatment option in high-risk patients, although it should be evaluated in larger studies. A cholecystostomy can be safely removed early and performing a cholangiography does not seem to change the outcome.

List of scientific papers

I. **Early versus delayed surgery for acute cholecystitis as an applied treatment strategy when assessed in population-based cohort.**
E Pieniowski, A Popowicz, L Lundell, P Gerber, U Gustafsson, H Sinabulya, K Sjödahl, A Tsekrekos, G Sandblom
Digestive Surgery 2014;31:169-176

II. **Cholecystostomy as bridge to surgery and as definitive treatment or acute cholecystectomy in patients with acute cholecystits**
A Popowicz, L Lundell, P Gerber, U Gustafsson, E Pieniowski, H Sinabulya, K Sjödahl, A Tsekrekos, G Sandblom
Gastroenterology Research and Practice 2016: 3672416

III. **Timing of elective cholecystectomy after acute cholecystits: a population-based register study**
A Popowicz, L Enochsson, G Sandblom
World Journal of Surgery 2023 Jan;47(1):152-161

IV. **Percutaneous gallbladder aspiration (PGBA) as alternative management in high-risk patients with acute cholecystitis**
A Popowicz, A Babiker, F Hammarqvist, G Sandblom

V. **Clinical management, safety and timing for removal of percutaneous cholecystostomy for acute cholecystitis. A single center cohort study**
A Popowicz, H Enhager, F Hammarqvist, G Sandblom

Contents

List of abbreviations

AC	Acute cholecystitis
AAC	Acute acalculous cholecystitis
ASA	American Society of Anesthesiologists
BMI	Body mass index
CBD	Common bile duct
CCI	Charlson co morbidity index
CDCA	chenodeoxycholic acid
CI	Confidence interval
CRP	C-reactive protein
CT	Computerized tomography
DC	Delayed open cholecystectomy
DLC	Delayed laparoscopic cholecystectomy
EC	Early cholecystectomy
ELC	Early laparoscopic cholecystectomy
ESWL	Extracorporeal shockwave lithotripsy
GallRiks	Swedish Registry for Gallstone and Endoscopic Retrograde Cholangiopancreatography
HDL	High-density lipoprotein
IQR	Interquartile range
MRI	Magnetic resonance imaging
NPR	National Patient Register
PC	Percutaneous cholecystostomy
PGBA	Percutaneous gallbladder aspiration
TG	Tokyo Guidelines

UDCA	ursodeoxycholic acid
VAS	Visual Analog Scale
WBC	White blood cell count

1 Introduction

Gallstone disease and complications secondary to gallstones constitute the most common diseases of the gastrointestinal tract and laparoscopic cholecystectomy is today considered a routine operation worldwide. In Sweden approximately 13000 cholecystectomies are performed each year (1). Complications, including minor and major ones, occur in approximately 2-11 % of surgeries performed in the elective setting (2, 3) and are reported as high as 30% for complicated gallstone disease and emergency surgery (4). Approximately 7% of laparoscopic cholecystectomies are converted to open surgery due to failure to visualize the "critical view of safety" of Calot's triangle and/or severe adhesions (5). Bile duct injuries are the most feared complication of cholecystectomy and incidence of bile duct injuries and bile leakage are 1,5% of all cholecystectomies performed with a higher risk for those performed in the acute setting (6). Mortality rates are reported to be 0.15% for all cholecystectomies (7).

This thesis presents the results of five studies performed to improve healthcare for those patients with acute cholecystitis that are frail, old and have a high co-morbidity. As there are many studies proving the advantages of early laparoscopic cholecystectomy in the clinical setting, we are often faced with situations that do not fit the standard protocol. How do we treat our patients that face a high risk for anesthesia and poor outcome after surgery or those that do not fit into given time frames for laparoscopic early cholecystectomy. These are the questions addressed in this thesis.

2 Literature review

2.1 Gallstone disease

Role of the gallbladder

The gallbladder is a storage unit for bile. Another important role is to concentrate the bile in order to optimize the physiologic properties of the bile in its digestion function. The gallbladder can absorb water and secrete lipids into the bile and in that way modify the contents of the bile. It has a motor function for releasing the bile into the bowel. The relaxation and contractions of the gallbladder leads to bile and bile salts release into the hepatic enteric circulation. This promotes the absorption of vitamins and fat-soluble lipids. During fasting approximately 20-30% of the content in the gallbladder is released in intervals between 1-2 hours and during a meal 70-80% of the content is released as a result of stimulus by cholecystokinin (8).

Formation of gallstones

Gallstones are divided into cholesterol stones and pigmented stones. There are two types of pigmented stones, black and brown. The prevalence of the two types of stones varies between populations. In western countries cholesterol stones are most common and account for approximately 80-90% of all stones. Cholesterol stones are formed from supersaturated bile in the gallbladder and consist mainly of cholesterol. They form due to a disturbed balance between the amount of biliary cholesterol and secretion of solubilizing bile salts or phospholipids which changes the bile's solubility (9). A mechanism associated with formation of cholesterol stones beside genetic factors is impaired motility of the gallbladder that may occur in patients who had extensive weight loss, gastric surgery, diabetes and pregnancy (10). Black stones account for approximately 10-20 % of gallbladder stones. They also form in the gallbladder due to excessive amount of bilirubin in the bile. The formation of black stones is associated with hemolytic anemias and disorders of the hematopoiesis which leads to excess of unconjugated bilirubin, Gilbert syndrome and increased recycling due to disease in the ileum in patient suffering from Chron´s disease or patient who had undergone resection of the small bowel. Brown stones are rare in western countries but common in Asia. Brown stones can form in the gallbladder or in the intra- or extrahepatic ducts as a complication to bacterial or parasite infection (11).

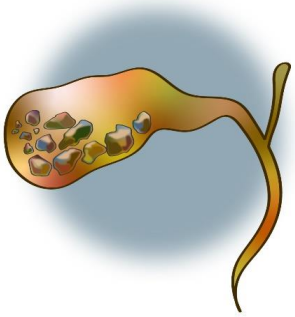

Figure 1: Gallbladder with stones. Illustration Mats Ceder, Koboltart.

Epidemiology of gallstones

The prevalence of gallstones differs between populations. In Europe and North America, the overall prevalence is estimated to be between 10-20% (12-14). In Sweden Muhrbeck et al showed that the prevalence of gallstone was 11% in women and 4% in men at the age of 40 and 25% in women and 15% in men at the age of 60 (15). The highest prevalence has been reported in North American natives were approximately 70% of women have gallstones and the lowest prevalence is reported in Asia and Africa where less than 5% of the population has gallstones (16).

Risk factors for development of gallstones

Pathogenesis of gallstones is multifactorial and polygenetic. Factors associated with development of gallstones are female gender, high age, multiple pregnancies, family history of gallstones, high BMI, rapid weight loss, high serum triglycerides, low levels of HDL, total parenteral nutrition and diets consisting of large amounts of cholesterol, fatty acids, carbohydrates and vegetables (17, 18). There are few reports on gallstones in children but after the age of 20 years the prevalence steadily increases with age (19).

Natural history of gallstone disease

The majority of people with gallstones, 70-80% are asymptomatic. Approximately 12% have mild symptoms and 8-15% severe symptoms (20, 21). Asymptomatic patients face an annual risk of 1-4% to develop symptoms or complications to the gallstones. Patients with mild symptoms have an annual risk 1-3% risk of developing complications and a 6-

8% chance of undergoing cholecystectomy due to symptom progress (22, 23). Halldestam et al described in a Swedish population a cumulative risk of 7.6% in previously asymptomatic patients of treatment due to symptoms or complications within 5 years (24).

Gallbladder sludge

Gallbladder or biliary sludge is a composition of particles that are bile deposits. Most common deposits in biliary sludge include calcium salts, calcium bilirubinate pigments and cholesterol crystals (25). Biliary sludge can present as any matter between aggregates of crystals to small stones and can be diagnosed by ultrasound where it is seen as a layer that gives a low echo signal without shadowing (26). Sludge and gallstones are often present together. The natural history of sludge varies, sometimes the sludge disappears other times it can give symptoms and complications in the same way as gallstones, or it can develop into stones. Main risk factors for sludge are pregnancy with a prevalence of 26%-31% of pregnant women, patients receiving total parental nutrition with a prevalence of approximately 50% and after 6 weeks in 100%, weight loss with a prevalence of approximately 25%. Some medical drugs are also known to cause sludge, e.g., ceftriaxone with a prevalence of approximately 25 - 40% of patients receiving this drug. In critically ill patients sludge can be seen after 5-10 days of fasting. If patients are asymptomatic no therapy for sludge is indicated but if they develop symptoms cholecystectomy is recommended (27).

2.2 Symptoms and complications of gallstone disease

Symptomatic gallstones

Symptoms attributed to gallstones are pain in the right upper quadrant or epigastrium, i.e., biliary colic. This symptom is more specific for gallstones if the patient does not experience heartburn, perceives pain radiating to the right shoulder, is unable to perform other tasks when the pain is present and the pain is not relieved by bowel movements. Biliary colic can be triggered by fatty food and often the pain presents short after meals although this is not a consistent symptom, sometimes the pain is not related to meals at all (28). The pain experienced is caused by a gallstone that obstructs the cystic duct or neck of the gallbladder and hinders the excretion of bile. This obstruction leads to a distention of the gallbladder. If the stone return back into the gallbladder or passes through to the common duct the patient experiences pain release (29).

Common bile duct stones

Gallstones can migrate from the gallbladder into the common bile duct. It is estimated that 10-18% of gallstone patients also have common bile duct (CBD) stones (30, 31). In a Swedish study 10.2 % of patients undergoing a cholecystectomy had CBD stones (32). Primary CBD stones that do not origin from the gallbladder are most often composed of bilirubin associated with stasis or result from infections. Most of the small CBD stones pass through the common bile duct into the duodenum without symptoms. CBS stones can cause complications such as obstructive jaundice, acute cholangitis, acute pancreatitis, and hepatic abscesses. It is estimated that 38% of all cases of acute pancreatitis are due to CBD stones (33). If the biliary obstruction due to stone obstruction is not relived it can cause biliary cirrhosis and portal hypertension. If CBD stones are found and are too large to be expected to pass spontaneously they should be removed (30).

Acute cholecystitis

Acute cholecystitis can be caused by an obstruction from a stone i.e., calculous cholecystitis, or develop as acalculous cholecystitis without obstruction. Acute calculous cholecystitis is caused by an obstruction by a gallstone or sludge of the cystic duct or the neck of the gallbladder, Hartmann´s pouch. This obstruction leads to an increased pressure in the gallbladder and triggers an inflammatory response. In approximately 20-78% of cases there is also a secondary bacterial colonization (34, 35). The Tokyo Guidelines for diagnostic criteria and severity of acute cholecystitis were published in 2007 (TG07) and updated in 2013 (TG13) and 2018 (TG18). They have been used worldwide to classify and standardize the severity of the inflammation as well as the diagnosis (36-38). In the 2018 update no change was made to the classification and therefore the Guidelines are now often written TG13/18.

Transabdominal ultrasound is currently the imaging modality of choice for diagnosis of acute cholecystitis. Transabdominal ultrasound is noninvasive, has a high availability, low cost, and high exactness for the diagnosis of stones (39). The sensitivity of ultrasound for diagnosing gallstones is 84% and specificity 99% (40). For diagnosis of cholecystitis the sensitivity and specificity are lower for ultrasound, in a meta-analysis the sensitivity was estimated to be 81% and specificity 83%. The sensitivity and specificity of CT for the diagnosis of cholecystitis was found to be 94% and specificity 56%. For MRI the sensitivity and specificity is 85% and 81% and for cholescintigraphy 96% and 90% (41).

The Tokyo Guidelines, TG13/18 diagnostic criteria for acute cholecystitis. (37, 38)

A: Local signs of inflammation

1: Murphy´s sign. 2: Right upper quadrant mass/pain/tenderness

B: Systemic signs of inflammation

1: Fever. 2: elevated CRP. 3: elevated WBC count

C: Imaging findings

Imaging findings characteristic of acute cholecystitis

- Suspected diagnosis: One item in A + one item in B
- Definitive diagnosis: One item in A + one item in B + C

The Tokyo Guidelines TG13/18 severity assessment criteria for acute cholecystitis. (37, 38)

Grade I: Acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder. Does not meet the criteria of grade II or III.

Grade II: Moderate acute cholecystitis associated with any one of the following conditions:

- Elevated WBC count (>18,000/mm^3)
- Palpable tender mass in the right upper abdominal quadrant
- Duration of complaints >72 h
- Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)

Grade III. Severe acute cholecystitis is associated with dysfunction of any one of the following organs/systems:

- Cardiovascular dysfunction: hypotension requiring treatment with dopamine> 5 µg/kg per min, or any dose of norepinephrine
- Neurological dysfunction: decreased level of consciousness
- Respiratory dysfunction: $PaO2/FiO_2$ ratio< 300
- Renal dysfunction: Oliguria, creatinine >2 mg/dl
- Hepatic dysfunction: PT-INR> 1.5
- Hematological dysfunction: platelet count< 100,000/mm^3

There are several potential complications to acute cholecystitis. Gangrenous cholecystitis is reported to develop in 2-30% of patients with acute cholecystitis. The most common location for gangrene is at the fundus where the vascular flow is most often compromised. In 10% of cases there is a gallbladder perforation. The most common location for perforations is at the fundus. Perforations may also predispose for development of fistulas between the gallbladder and the bowel. Most fistulas drain into duodenum or colon by the hepatic flexure. Gallstone ileus develops when a stone passes through a fistula into the bowel and obstructs the small bowel (34).

Mirizzi Syndrome

Mirrizi syndrome occurs when a gallstone that is impacted in the neck of the gallbladder or cystic duct provokes a local inflammation that obstructs the biliary tree and causes cholestasis. The impacted gallstone causes inflammation and adhesions and can with time fuse with the bile duct. This causes necrosis of the tissue, and the stone can erode into the common hepatic duct. This can cause a fistula between the gallbladder and the duct (42).

Acute acalculous cholecystitis

Acute acalculous cholecystitis (AAC) is sometimes seen in patients who are critically ill and suffer from multi organ failure, major trauma, or severe burns. In AAC there is an inflammation of the gallbladder without obstruction by a stone or sludge. It accounts for 2-15% of all cases of cholecystitis. Mortality rates have been reported as high as 50% (43). AAC is often due to ischemia of the gallbladder, sometimes in combination with stasis leading to hypoperfusion. In the critically ill patient hypoperfusion is aggravated by dehydration, hypotension and vasoactive drugs leading too decreased micro perfusion of the gallbladder. Arterial occlusion by micro thrombosis seen in critically ill patients is believed to contribute to AAC (44).

Chronic cholecystitis

If a patient has recurring episodes of cholecystitis it leads to scarring due to fibrosis in the subepthelial and subserosal layer of the gallbladder. This leads to a thickened dysfunctional gallbladder. The leading cause for chronic cholecystitis is an intermittent obstruction by a stone of the cystic duct. The clinical presentation is most commonly recurrent pain (19).

2.3 Management of gallstones and cholecystitis

Asymptomatic gallstones

The evidence on treatment of asymptomatic gallstones is limited. There are no randomized controlled trials and few observational trials with sufficient power. There are no evidence supporting routine cholecystectomy while also taking into consideration complications that can occur following surgery. Most authors recommend expectancy in patients with asymptomatic gallstones. Asymptomatic patients have a 1-4% annual risk of developing symptoms, the most common being pain attacks (21, 23, 45).

There is no evidence supporting treatment with extracorporeal shockwave lithotripsy (ESWL) or medical dissolution. ESWL has an acceptable stone clearance when solid single stones are presented but poor clearance in case of multiple stones. It has a five years recurrence rate of 43% (46). Medical dissolution of gallstones can be achieved with chenodeoxycholic acid (CDCA) or ursodeoxycholic acid (UDCA). Use of CDCA for more than six months dissolves 18.2% of stones if given in high dose. UDCA in high dose resolves 38% of stones. If UDCA and CDCA combined it can resolve up to 62% of stones (47). It is however shown that UDCA does not resolve symptoms in patients with recurrent gallstone colic (48).

Asymptomatic patients with porcelain gallbladder, i.e., calcifications of the gallbladder wall have an increased risk of developing gallbladder cancer and should therefore always be treated with cholecystectomy. The incidence of gallbladder cancer in a porcelain gallbladder is approximately 7% (49, 50).

Symptomatic gallstones

Evidence supports treatment of patients experiencing gallstone related pain (51). However in patients not fit for surgery a conservative strategy may be an option (52). Pain attacks can in up to 50% of patients subside with time (21, 22). Cholecystectomy is the only effective treatment of symptomatic gallstones. Medical dissolution and ESWL treatment are not effective in treatment of symptomatic gallstones (23).

Surgical technique of choice for cholecystectomy

The surgical options for cholecystectomy are open, laparoscopic, and small incision surgery. In a Cochrane systematic review of randomized trials, no significant differences in mortality or complications have been shown between these treatment modalities but

laparoscopic and small incision shows a faster recovery. Overall risk for complications for elective laparoscopic or small incision surgery was concluded to be approximately 17 %. For open surgery the overall complication rate was 10.1% vs laparoscopic 5.4%, however no significant difference could be found in low risk for bias trials. Because of the shorter convalescence time for laparoscopic surgery and with this its cost-effectiveness this is the technique of choice (53). Risk factors for intraoperative complication during laparoscopic surgery are male gender, ASA-score, and high bodyweight (4). Up to 40% of patients operated on due to gallstone pain report postoperative pain. This shows the importance of a proper preoperative evaluation as abdominal pain can often be misinterpreted as gallstone-related (54).

Figure 2: preparations for a laparoscopic cholecystectomy

Common bile duct stones

Natural history of CBS is not as well studied as for gallstones. There are several approaches to treat common bile duct stone. ERC with sphincterotomy is a widely spread technique which can be done with or without a cholecystectomy and with a high success rate. Complications associated with ERC are pancreatitis and perforations. Studies have shown that using the over the wire technique post ERCP pancreatitis rates are between 0 and 2.2% (32). If it is not possible to perform a sphincterotomy and endoscopic balloon dilatation of sphincter of Oddi of is an option. This technique has a higher risk for pancreatitis. To decompress the bile ducts an insertion of a biliary stent can be performed. CBS stones can also be removed during cholecystectomy with a trans cystic approach with comparable success and complication rates as endoscopic approach (23).

Acute cholecystitis

The only definitive treatment of acute cholecystitis is cholecystectomy. Early laparoscopic cholecystectomy is the gold standard. Many randomized controlled trials have shown that early cholecystectomy is a cost-effective safe treatment that leads to shorter hospital stay and lower or similar morbidity as delayed cholecystectomy. However, no significant differences are found in risk of conversion from laparoscopic to open, postoperative complications or the incidence of bile duct injuries between early and delayed surgery (55, 56). In one large randomized controlled trial, the ACDC study, the authors concluded that morbidity rates were lower in the early cholecystectomy group vs the delayed 11.8% vs 34.4%. in this trial the early group was within 24 hour and the late group was between 7-45 days (57). The most beneficial is to perform surgery within 72 hours of symptoms onset but patients operated on within 7 days still benefit from early cholecystectomy (58, 59). A recent study showed that the optimal timing for performing a cholecystectomy for acute cholecystitis seem to be within 2 days from admission (60). In the WESE guidelines it is stated that laparoscopic cholecystectomy should be performed within 10 days from symptom onset (39).

According to the Tokyo guidelines recommendations treatment of acute cholecystitis depends on the severity of the inflammation. In case of mild cholecystitis early laparoscopic surgery should be performed. If the disease is moderate a critical assessment of the patient's condition by an experienced surgeon should be undertaken and surgery performed when the patients general condition allows. If severe inflammation conservative treatment with tube placement is advised (61, 62). There are no randomized controlled trials comparing surgical treatment based on the severity of the inflammation. Törnqvist et al have showed a doubled risk for bile duct injuries if moderate inflammation and even higher risk if severe inflammation. No increased risk was seen for patients with mild disease (63). There is one randomized controlled trial comparing acute cholecystectomy with PC in patients with APACHE-score between 7 and 14, the CHOCOLOTE trial. This trial showed superiority for the acute surgery group (64).

In cases of severe inflammation or fibrosis where a safe dissection of Calot´s triangle is impossible, there is the option of subtotal cholecystectomy. Usually, the posterior wall or parts of the infundibulum are left in situ. A meta-analysis evaluating subtotal cholecystectomy finds it to be well tolerated and effective when a safe total cholecystectomy is not possible. Morbidity rates for subtotal cholecystectomy are low, postoperative hemorrhage occur in 0.3%, subhepatic collections in 2,9%, bile duct injury in 0.08%, retained stones in 3.1% but bile leakage occurs in 18% of patients. Mortality rate is 0.4% (65).

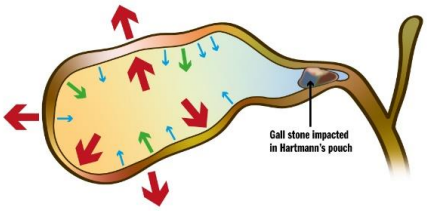

Figure 3: Development of choelecystits. ↑=Gallbladder distension ↑=Prostaglanding I_2 and E_2 secretion ↑=Fluid secretion. Illustration by Mats Ceder, Koboltart

Acute acalculous cholecystitis

Patients suffering from AAC are often critically ill and surgical management may not be an option. It is debated on if these patients should undergo surgery or conservative treatment. In a recent review it is proposed that if the patient is a candidate for surgery an early laparoscopic cholecystectomy should be performed. If the patient is not fit for surgery the AAC should be treated with percutaneous cholecystectomy (43).

Elderly and cholecystitis

The prevalence of gallstones increases with age leading to an enhanced risk of development of symptoms or complications caused by gallstones in the elderly population. With age comorbidity tends to increase as well as the risk for surgery and anesthesia (66). The safety to perform a cholecystectomy in the elderly population is a matter of debate. It is shown that laparoscopic cholecystectomy in the elderly is effective and feasible but compared to younger patients there is a higher rate of morbidity and mortality. Recommendations are to choose patients appropriately for surgery if the patient has a high age (67, 68). Studies on patients aged 80 and older have shown that if selected carefully a laparoscopic cholecystectomy can be performed safely (69, 70). Reports show that elderly and patients with significant comorbidity have an up to 41% morbidity and up to 18% perioperative mortality when cholecystectomy is performed in an acute setting (71, 72). Older patients tend mor often not to get emergency cholecystectomy in the acute setting (73). It has been suggested

in several studies that frail elderly patient who are not primarily selected for emergency surgery benefit from treatment with percutaneous cholecystostomy (74, 75).

Conservative treatment of cholecystitis

Despite several randomized controlled trials recommending early cholecystectomy for acute cholecystit many patients are still treated conservatively. Studies have shown that 45-67% of patients presenting with acute cholecystit are treated without an emergency cholecystectomy (76-78). The reason for this low numbers could be regional traditions, lack of operation room resources, the patient may be not a candidate for emergency surgery due to high co-morbidity, old age, or the severity of the disease. It has been shown that risk for bile duct injury rises with the severity of cholecystit, were moderate inflammation had doubled risk and the risk was even higher for severe cholecystitis (63). If a patient presents with a duration of symptoms of more than 10 days traditionally these patients are treated with a conservative approach (39). Long duration of inflammation may cause development of fibrosis in the triangle of Calot leading to difficult surgery with high risk for complications (60). Conservative management of acute cholecystitis has nevertheless the favors of early treatment proven safe, especially in case of mild disease. A consideration with a conservative approach is that approximately 20% of patients do get recurrent disease within one year (79). The general recommendations for patients not fit for surgery are initial treatment with antibiotics and, if the patient's health status doesn't improve, insertion of percutaneous cholecystostomy (71). Alternative treatments to percutaneous cholecystostomy are percutaneous gallbladder aspiration and endoscopic treatments.

Percutaneous Cholecystostomy

Percutaneous cholecystostomy (PC) was introduced in the 1980s as a minimally invasive technique for treatment of cholecystitis. It can be inserted transhepatically or transabdominally. The preferred route is the transhepatic due to lower risk for bile leakage. The drainage accomplishes a decompression of the gallbladder and provides continuous draining of the bile. When the gallbladder is decompressed the inflammatory process that causes the cholecystitis ceases. PC is often used in patients who need intervention due to deterioration of their clinical status but are not fit for emergency surgery (80, 81). Even though cholecystostomy is recommended in the Tokyo guidelines as a treatment strategy for patients unfit for surgery it is not fully evaluated. There is one randomized controlled trial, the CHOCOLATE trial where PC is compared to acute cholecystectomy. This trial was interrupted early after an interim analysis as major complication were seen in 65% of patients in the PC group vs 12% in the

cholecystectomy group. The timeline for major complications was 1 year and in the PC group major complications included patients needing reintervention due to recurrence of cholecystitis. However, 93% of patients in the PC group did improve clinically within 48 hours (64). Several retrospective studies have shown a good outcome of PC when used as a treatment of the critically ill patients or elderly (74, 75, 80-83). A retrospective study on 1725 extremely ill patients showed that PC had a superior outcome as treatment in this group of patients and especially compared to open cholecystectomy, were a high conversion rate from laparoscopic was seen (82). One randomized controlled trial has been performed on high-risk patients, APACHE score of 12 or more where they were randomized to conservative treatment with antibiotics or PC with antibiotics. In this trial PC was not shown to decrease mortality in this high-risk group but was suggested as a salvation treatment for patients not improving after 3 days (84).

PC has a success rate of 85.6 % and a procedure related mortality of 0.36% but 30 day mortality is reported to be 15.4% (83). PC-related complication rates are reported to range from 1.9% to 29%, catheter dislodgement in 4% to 12%, bile leaks in 0% to 3% and bleeding in 0% to 5% (85-88). Recurrence rates for a new cholecystitis within one year after a cholecystostomy are reported to range from 4 to 22%. (74, 89, 90) Complicated cholecystitis and WBC count > 18000 /µL are risk factors for recurrence (89).

The proposed time duration of the drainage differs between studies and range from three to six weeks. Optimal timing for drainage has not been fully studied (74, 89). It has been described that 2 weeks are sufficient for a tract to develop if the transhepatic route is used and 3 weeks for the transabdominal route (85, 91). D´Agostino found that for all cases a tract had matured after 20 days (92). Morbidity related to PC catheters has been described as high as 29% and to prevent this is suggested to remove the drain as soon as the inflammation subsides (93). Other has reported a higher recurrence rate of cholecystitis if the catheter is removed before 21 days (87) while some reported recurrence if the catheter is removed within 7 days (86). Keeping the drainage for a long drainage have been associated with increased recurrence of cholecystitis due to local irritation of the gallbladder mucosa (94). A Systematic review could not find any evidence that duration of the catheter has any impact on the outcome (95). It has been equally controversial whether a routine cholangiography should be performed before removal or not. Some state that a routine cholangiography in asymptomatic patients is not beneficial clinically and leads only to unnecessary testing and prolonged catheter duration (96). Others, however, state that routine cholangiography can change the management in approximately 30% of cases and should be always performed before removal (97).

PC is often thought of as a “bridge to surgery”, aiming at delayed elective cholecystectomy (98). However less than half of patients treated with PC undergo cholecystectomy. This proving that this treatment is used in a group not fit for surgery

and often serves as a definitive treatment (99, 100). For those patients who receive an interval laparoscopic surgery a recent systematic review and meta-analysis dividing the surgery into within 30 days and after 30 days showed no difference in outcome between these groups (101). However, studies have shown that when surgery is performed within 9 days after PC the surgery was technically more difficult, and complications occurred in 35.7% vs 7.6% when performed later (102). When comparing outcome for laparoscopic cholecystectomy after PC treatment a higher incidence of CBD injuries (1.6%) is seen compared to cholecystectomies carried out without previous PC (103).

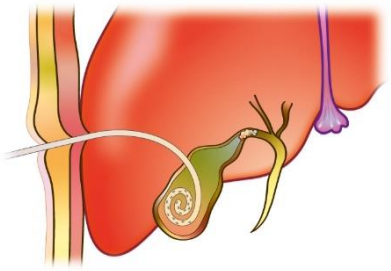

Figure 4: Percutaneous cholecystostomy. Illustration by Mats Ceder, Koboltart.

Gallbladder aspiration

Percutaneous gallbladder punction and aspiration (PGBA) is a technique used for similar purposes as percutaneous cholecystostomy, to establish a decompression of the gallbladder facilitating recovery. This technique is described in the Tokyo Guidelines as a simple alternative with fewer complications than PC. PGBA is performed under ultrasound guidance with a small gauge needle without leaving a drain. However, it needs more evaluation as it has only been described in a few small studies (104).

One aspiration is shown to be sufficient to relieve symptoms for 50- 93% of patients, but the success rate rises to 76-96% if two aspirations are performed (35, 105, 106). The reported complications rates are between 0% and 8% and unrelated to needle size used (35, 105-107). There is one randomized controlled trial where PGBA is compared to PC. In

this trial PC was superior to PGBA. PC proved to be more effective in this study, however only one aspiration was performed. In this trial there were no major complications in either group and minor complications were equal (108). PGBA have been described in other retrospective studies as safer than PC and with comparable clinical outcome (109).

Since decompression once performing PGBA occurs immediately it is believed that this is sufficient for reducing the intraluminal pressure in the gallbladder. In 30–78% of patients with acute cholecystitis positive bile cultures are found which indicated that infection is not a key mechanism in development of cholecystitis and therefore it may not be necessary to use a continuous drainage (35). However, there are two studies where antibiotic instillation was performed after aspiration and these studies showed a success rate of 95 and 96% (105, 106). It has been described that repetitive aspirations are not linked to higher complication rates and it seems that the amount of volume that is aspirated does not affect outcome (35). Due to the usage of smaller needle and no drain left in place that when dislocating can cause bile leakage lower rates of complications are reported for aspiration and it is suggested that PC can have a role as a salvage method when aspiration is not successful (109). An elective cholecystectomy can be safely performed after an PGBA regardless of timing of PGBA in the acute setting before or after 3 days of symptom presentation where no difference in complications and outcome after cholecystectomy can be seen (110, 111).

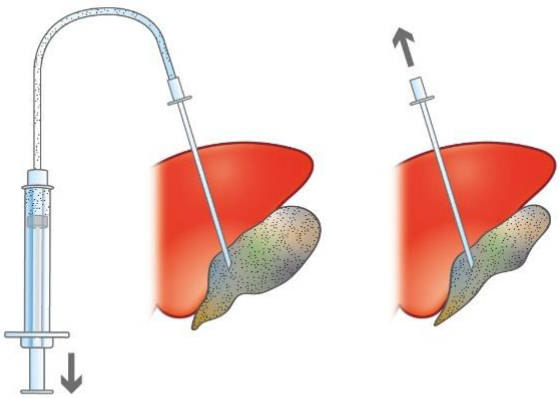

Figure 5: Percutaneous gallbladder aspiration. Illustration by Mats Ceder, Koboltart

Antibiotic treatment

The role of antibiotic treatment in acute cholecystitis is not fully determined. There is a lack of randomized controlled trials comparing antibiotics with other treatment strategies. There is one small study comparing conservative treatment with antibiotics with conservative treatment without and the conclusion from this small study was that no improvement of outcome was seen when intravenous antibiotics for acute cholecystitis are used (112). The same conclusion was drawn in a systematic review on antibiotic treatment where few studies could be included and in most of these studies the risk of bias was high. Antibiotic treatment had a described failure in approximately 20% of cases treated conservatively only with antibiotics (113). Many guidelines do recommend antibiotic treatment when acute cholecystectomy is not chosen, mainly due to described positive cultures in bile of patients with acute cholecystitis where bactibilia is found in 30-78% of bile aspirates in patients with acute cholecystitis (35, 114, 115).

Endoscopic treatment

New endoscopic drainage methods have been reported in the past few years and these have been added to the Tokyo Guidelines but with the reservation that these are new techniques that need further evaluation (116). Endoscopic naso-biliary gallbladder drainage (ENGBD) is a technique where a drainage tube is placed through the bile duct into cystic duct and to the gallbladder. This method can in most cases be used without a sphincterotomy but is a difficult technique and success rates are described to vary between 64 and 100%. Endoscopic transpapillary gallbladder stenting (EGBS) is a similar technique as ENGBD, but double pig-tail stent is placed through sphincter Oddi to the gallbladder. A third technique is endoscopic ultrasonography – guided gallbladder drainage (EUS – guided gallbladder drainage) where a stent is placed through the gastric antrum or duodenum to the gallbladder (116). EUS – guided gallbladder drainage has been described as comparable to PTGBD however with a slightly higher success rate but with fewer reinterventions and a lower risk for recurrence in cholecystitis (117, 118). However, EUS – guided gallbladder drainage has a known severe complication of bleeding in approximately 4.3% and perforation in 3.7% whereas ENGBD has a known risk of approximately 5,1% of pancreatitis. The technical success rate for EUS – guided gallbladder drainage is 95.3%, for EGBS 83% and for PTGBD 98.7% and the clinical success rate is 96.7%, 88.1% and 89.3% (118). In comparative study between PTGBD, PTGBA and EUS – guided gallbladder drainage the complication rate was 5.6%, 1.6% and 8.2% (119).

3 Research aims

The aims of the present thesis are as follows:

- What is the outcome after management of acute cholecystitis as practiced in Stockholm County?
- Have the routines regarding management of acute cholecystitis changed from 2003 to 2008?
- Is earl cholecystectomy as safe as delayed surgery for patients with cholecystitis?
- Is management with cholecystostomy a safe method as definitive treatment or "bridge to surgery" in acute cholecystitis in the elderly and those with high co morbidity?
- What is the recurrence rate of acute cholecystitis following initial treatment with cholecystostomy?
- Is gallbladder aspiration a safe alternative in the treatment of patients with acute cholecystitis deemed non-operable?
- When is the optimal timing of planned surgery following an episode of acute cholecystitis?
- For how long should a cholecystostomy drain be left in situ before removed in order to avoid bile leakage?
- Does an antegrade cholecystography reduce the risk of too early drain removal in patients treated with cholecystostomy?

4 Materials and methods

4.1 Data sources

GallRiks

The Swedish Registry for Gallstone surgery and Endoscopic Retrograde Cholangiopancreatography (ERCP) is a prospective nationwide register with the purpose to cover all gallstone-related interventions in Sweden. The aim is to follow and provide information on treatment methods, indication and complications to laparoscopic and open cholecystectomy and ERCP. The register is web-based and the surgeon or endoscopist enters data intra- or postoperatively. Data reported intra- or postoperatively include patient characteristics, surgical method, indication for surgery, intraoperative cholangiography and if immediate complications occurred. All units affiliated to GallRiks have a coordinator who after 30 days and 6 months after the procedure registers postoperative complications. Coordinators review medical records to find all complications and ensure that all performed cholecystectomies and ERCP are correctly registered. In case registrations or data are missing the coordinators reminds the surgeon or endoscopist to complete the form. New variables can be added to GallRiks if found required to meet the continuously development of medicine, making it a flexible register.

The registry was founded in 2005 and since 2011 is considered fully nationwide (2). Since 2011 the coverage is >80% of all cholecystectomies performed in the country. Match between data recorded in Gallriks and patient medical journal is as high as 98.2% (1). Today the national coverage is over 90% and the register is continuously validated by independent external reviewers (2).

National Patient Registry (NPR)

The Swedish hospital discharge registry, National Patient Registry (NPR) was started in 1964 and inpatient data is registered prospectively. Since 1987 it has complete national coverage including more than 99% of all hospitals both somatic and psychiatric in Sweden. This register includes the patients' medical and administrative data such as: gender, age, county, hospital, date of admission and discharge, diagnoses, medical interventions, and all surgical procedures. The NPR uses the diagnosis codes, International Classification of Diseases (ICD) according to WHO, World Health Organization. In Sweden every resident has a personal unique identification number that is a combination of birthday and a 4-digit additional number. The identification number for all patients is the same throughout life and is used I all registers in Sweden making it possible to cross-match data between registers (120).

4.2 Study design and data collection

Study I and II

Study I and II are based on the same study population. It is a retrospective review of all medical record of patients treated for acute cholecystectomy in Stockholm County in the years 2003 and 2008. Data was collected from seven hospitals. The patients were selected through the NPR using ICD codes for acute cholecystitis and patients' personal numbers.

Study I

Acute cholecystitis was diagnosed, and the severity score categorized according to the Tokyo guidelines (36). The Charlson co-morbidity index was used for categorization of co-morbidity (121). Definition of early cholecystectomy was cholecystectomy prior to discharge from hospital during the index admission for acute cholecystitis. Delayed cholecystectomy was defined as surgery performed after discharge. Patient records were reviewed and data on hospital stay, maximum white blood cell count (WBC) and CRP levels preoperatively or if conservative treatment maximum value prior to discharge, on surgical approach, conversion rate from laparoscopic to open, operation time, blood loss, peri and postoperative complication were noted. Complications were categorized according to the Clavien-Dindo classification (122). Data was cross-checked with GallRiks for validation.

Study II

This study was based on the same study population as study I and categorization on patient data is therefore the same as for study I. In study II focus was on patients treated with PC. Comorbidity for patients was categorized with Charlson comorbidity index (121) and complications after PC were categorized with Clavien-Dindo classification (122). Postoperative complications were defined as complications within 30 days of the procedure. No specific guidelines for the use of PC were available at these seven hospitals in Stockholm count during these years. The physician in charge was responsible for decisions regarding treatment choices for each patient. The PC tube was inserted using ultrasound by a radiologist. Patients received local anesthesia. Patients with cholangitis were excluded from this study. PC was defined as bridge to surgery if elective cholecystectomy was later performed. Definition of recurrence of

acute cholecystitis was if the patient had a new admission due to gallstone pain or acute cholecystitis. Hospital stay was accounted only for the index admission. Patients were followed to December 31, 2011.

Study III

Study 3 is based on the register GallRiks. All patients in Sweden during the years 2006-2013 registered in NPR where selected using the ICD-codes for acute cholecystitis and all gallstone-related inflammations of the gallbladder. Patients' personal registration numbers were used to cross-link this cohort with GallRiks. From NPR information on discharge was obtained and the outcome from the surgery and timing as well as technique for the surgery, intra- and postoperative complications, bile leakage and bile duct injuries were obtained from GallRiks. Definition of intraoperative complications were all the adverse events that happened during surgery and postoperative complications were those happening within 30 days of surgery. Infections, hemorrhage, bile leakage and bile duct injuries are the complications registered in GallRiks.

Data was divided into time intervals between primary admission for acute cholecystitis and the subsequent elective cholecystectomy. The six time intervals were: 0-10 days; 11-30 days; 31-90 days; 90-180 days; 181-364 days and > 365 days. Day 0 was the day of discharge. The cut-off points are round offs where the exponential intervals are equally distributed. The STROBE statement was used when reporting this study (123).

Study IV

Study IV is a prospective pilot study designed as a safety and feasibility study on percutaneous gallbladder aspiration. Initial inclusion was 30 patients, but 5 patients were later excluded, and the final study population consisted of 25 patients. Inclusion criteria was patients with acute cholecystitis not suitable for emergency surgery. This decision was made by the physician in charge. Written consent was obtained from all patients. Patients were then offered a PGBA. Exclusion criteria were gallbladder perforation, emphysematous cholecystitis, malignancy in liver or suspected malignancy, portal hypertension, cirrhosis, ascites, common bile duct stones and gallstone pancreatitis. Tokyo guidelines 2013 were used for diagnostic criteria of acute cholecystitis and severity assessment. On admission, blood samples were taken for CRP and WBC, duration of symptoms was noted and pain according to visual analogue score (VAS) as well as co-morbidity according to ASA classification was determined. Piperacillin/tazobactam 4 g was given to all patients prior to aspiration.

The PGBA was performed using the transhepatic route by an interventional radiologist with the guidance of ultrasound. Local anesthesia was given all patients and a fine needle, 0,9 mm was used for all punctions. If the bile could not be drained by this fine needle a thicker one could be used. During the ultrasound gallbladder size, thickness of the wall, the amount of aspirated bile and presence of stones was noted.

After the PGBA, CRP and WBC were taken daily as well as pain according to VAS twice a day. Total hospital stay and complications according to Clavien-Dindo classification within 30 days were noted. Treatment failure, bile leakage and need for surgery was noted. If there was no improvement in patient status the patient was offered a second aspiration.

All patients were followed for one year and after 2 months they were offered an appointment for checkup. If the patient did not show up, then a phone call was offered 3-6 months after the PGBA.

Study V

This was a retrospective study of medical records for all patients treated with PC at Stockholm South General Hospital between January 2016 and December 2021. All patients treated for acute cholecystitis during this period were identified through the hospital's medical record system using ICD codes for acute cholecystitis. These patients were then cross-linked using personal identification numbers with the hospital radiological image/medical record system (PACS) to find all patients receiving upper abdominal drainage. Record from these patients were reviewed and those receiving an PC were then included in the study.

From the medical records the comorbidity was quantified using Charlson co-morbidity index, days with cholecystit symptoms at admission were noted, indication for PC, complications to PC were classified by Clavien-Dindo classification of surgical complications, decision to perform a secondary cholangiography, decision for removal of PC and treatment plan after removal were noted. Mortality was registered as 30 and 90 days. Relapse of cholecystitis was noted, and definition of relapse was new episode of cholecystitis within 30 days to 2 years.

4.3 Statistical methods

Study I

ANOVA was used for testing difference in percentage for the years 2003 and 2008 for patients undergoing acute surgery with those undergoing surgery in the elective setting. Univariate and multivariate logistic regression analysis was used to adjust for gender, age, severity of the acute cholecystitis and co morbidity. Multivariate regression analysis was uses to test difference in blood loss and operating time between acute cholecystectomy and elective cholecystectomy and multivariate logistic analysis was used for testing difference in postoperative complications and proportion of laparoscopic surgery adjusting for gender, age maximal CRP and WBC cell counts and severity of cholecystitis. χ 2 test was used for p-values for baseline data, table 1. For the subgroup of patients undergoing acute cholecystitis before or after 5 days of symptom onset analyses were made adjusting for gender, age, maximal CRP and WBC and severity of the cholecystitis. For the patients undergoing elective surgery time periods were divided into 3- month intervals after the period of index admission to test the effect of time on the elective surgery. Kaplan Meier statistics were used for assessment of risk for re admission for new episode of acute cholecystitis in both groups receiving elective surgery and treated conservatively where readmission was the event and cholecystectomy the censored endpoint. For the conservatively treated group comparison was made for the years 2003 and 2008 with the groups treated with acute and elective cholecystectomy using the variables age, co morbidity, CRP and WBC count and degree of cholecystitis. P-value < 0.05 was considered statistically significant.

Study II

Multivariate regression analysis was used for testing difference in hospital stay and multivariate logistic analysis for risk for postoperative complications. Adjustment for both methods were made for gender, age where 70 years was a chosen as a cut off, degree och cholecystitis were Tokyo guidelines grade 1 was compared to grade 2 and 3, and for co morbidity were Charlson grade 1 was compered to grade 2 and higher. Complications were only included if Clavien-Dindo 2 or higher as data on Clavien-Dindo 1 was not reliable. Cox proportional hazard analysis was used to analyze time to readmission where elective surgery and death from other causes than related to cholecystitis were stated as censored events.

Study III

In study III univariate and multivariate logistic regression was used to analyze the impact of time interval between index hospital stay for acute cholecystitis and subsequent elective cholecystectomy on percentage of surgeries completed laparoscopically or with mini laparotomy, operation time, complications intra or postoperatively, bile leakage and bile duct injuries. Adjustments were made for age and gender. Reference category was the time interval 0–10 days, and each variable was tested in separate analyses for all the six time intervals. SPSS Statistics 24 was used for calculations.

Study IV

As study 4 is a prospective safety and feasibility study without a comparison group most of the statistic were observational values. Median values for CRP and WBC before and after puncture, amount of bile aspirated, and hospital stay were analyzed with interquartile range.

Study V

The Mann-Whitney U test for continuous variables was used for baseline data, management, complications, and removal of PC. Chi-two test was used for the categorical variables. Multivariate logistic regression was used for assessing the risk factors associated with removal of the PC adjusting for age, sex, comorbidity, days to removal, complications and performed secondary cholangiography. Kaplan Meier statics were used for analyzing recurrence of cholecystitis. SPSS statistics version 28.0.1 was used.

4.4 Ethical considerations

There are several ethical considerations that need to be addressed when performing studies where new treatments are tested or patient data used. One of the greatest ethical dilemmas we faced in this thesis was for the study IV. As this was a clinical trial, we discussed whether inclusion is defendable if patients are not able to completely understand the procedure and the implications of this method. The study group that is the focus of this clinical trial are older patients with high co-morbidity. When older patients get acute diseases there is a high risk for delirium. Dementias are also more

common in this group. If a patient was not able to give an informed consent to participate, consent was obtained from the relatives. If there was any doubt whether a patient should be included, we planned to get a second opinion from a resident surgeon who is not a member of the same research group. However, among the 30 patients included this turned out not to be a problem, all patients were capable to make an informed decision.

For study III data were collected from a register. Patients were identified based on their personal numbers and then cross-linked by these individual identification numbers with another register. However, no individual data was handled, data was analyzed only at group level and for analyses the identity numbers were coded. The coded data was kept on a server of Karolinska Institute. Patient registered in GallRiks should be informed about the inclusion in the register, although there is no routine to control that consent is provided. That could be questionable as their information is used for research purposes. However, another aspect that justifies this is that these studies are used to improve health care for patients suffering from the same condition. As data from all hospitals in Sweden is collected for GallRiks and all patients are included this provides the benefit of having accesses to large registers with high external validity for the data interpreted.

For studies I, II and V we used the medical records for retrospective reviews without the consent of these patients, albeit with permission from the ethical board. To ask that many patients for consent to perform these studies would have been very cumbersome. This can however be justified by the quality enhancement of the medical treatment for acute cholecystit that these studies provide.

5 Results

5.1 Paper I

Altogether 1632 patients were admitted for acute cholecystitis in Stockholm during the years 2003 and 2008. In the year 2003, 799 patients were admitted 850 times and in 2008, 833 patients were admitted 919 times. At first admission the mean age was 58 years, (SD 19 years). Patient characteristics are presented in table 1.

	2003	2008	Total	p
Gender				0.803
Male	340 (42.6%)	360 (43.2%)	700 (42.9%)	
Female	459 (57.4%)	473 (56.8%)	932 (57.1%)	
Number of admissions per patient				0.067
1	751 (94.0%)	760 (91.2%)	1,511 (92.6%)	
2	45 (5.6%)	64 (7.7%)	109 (6.7%)	
3	3 (0.4%)	5 (0.6%)	8 (0.5%)	
4	0 (0%)	4 (0.5%)	4 (0.2%)	
Charlson co-morbidity index				0.426
0	417 (52.2%)	457 (54.9%)	874 (53.6%)	
1	123 (15.4%)	158 (19.0%)	281 (17.2%)	
>1	127 (15.9%)	157 (18.8%)	284 (17.4%)	
Data missing	132 (16.5%)	61 (7.3%)	193 (11.9%)	
Degree of severity (Tokyo classification)				0.405
1	354 (44.3%)	388 (46.6%)	742 (45.5%)	
2	291 (36.4%)	320 (38.4%)	611 (37.4%)	
3	11 (13.8%)	20 (2.4%)	31 (1.9%)	
Data missing	143 (17.9%)	105 (12.6%)	248 (15.2%)	
Management				0.053
Conservative	169 (21.2%)	124 (14.9%)	293 (18.0%)	
Cholecystostomy (sole treatment)	13 (1.6%)	31 (3.7%)	44 (2.7%)	
EC/ELC	343 (42.9%)	395 (47.4%)	738 (45.2%)	
DC/DLC	132 (16.5%)	124 (14.9%)	256 (15.7%)	
Data missing/undefined	142 (17.7%)	159 (19.1%)	301 (18.4%)	
Complications related to surgery or cholecystostomy				0.232
Clavien 2	37 (4.6%)	27 (3.2%)	64 (3.9%)	
Clavien 3	43 (5.4%)	53 (6.4%)	96 (5.9%)	
Clavien 4	4 (0.5%)	1 (0.1%)	5 (0.3%)	
Clavien 5	2 (0.2%)	1 (0.1%)	3 (0.2%)	

p values represent differences between the 2 years.

Table 1. Baseline data

Early laparoscopic surgery increased from 42.9% to 47.5% from 2003 to 2008, an increase found to be significant (p= 0.019) in the univariate logistic analysis but not significant when adjusted for gender, age, co-morbidity, and severity of cholecystitis. No other changes were seen between the groups undergoing early cholecystectomy and delayed cholecystectomy between these two years (tables 2 and 3).

	2003	2008	Total
Laparoscopic	260 (75.8%)	266 (67.3%)	526 (71.3%)
Laparoscopic, conversion to open	45 (13.1%)	50 (12.7%)	95 (12.9%)
Open	38 (11.1%)	21 (5.3%)	59 (8.0%)
Data missing	0 (0%)	58 (14.7%)	58 (7.9%)
Total	343	395	738

No significant difference was seen between the 2 years (p = 0.075).

Table 2. Patients undergoing EC/ELC

	2003	2008	Total
Laparoscopic	107 (81.1%)	82 (66.1%)	189 (73.8%)
Laparoscopic, conversion to open	12 (9.1%)	11 (8.9%)	23 (9.0%)
Open	7 (5.3%)	2 (1.6%)	9 (3.5%)
Data missing	6 (4.5%)	29 (23.4%)	35 (13.7%)
Total	132	124	256

No significant difference was seen between the 2 years (p = 0.403).

Table 3. Patients undergoing DC/DLC

Patients undergoing early cholecystectomy were younger, had lower grade of cholecystitis and less co-morbidity than those who underwent conservative treatment and delayed surgery (table 4). A positive statistically significant correlation ($p < 0.001$) was seen between time to surgery in the early cholecystectomy group and low Charlson co-morbidity index. However, no significant association was found between time to surgery and severity of cholecystitis. In multivariate logistic analysis adjusting for gender, age, maximal CRP, and WBC counts and severity of inflammation, early cholecystectomy had a significantly shorter operating time then delayed cholecystectomy, but more procedures were completed laparoscopically and with less bleeding in the delayed group. No significant difference was seen between these groups for intra- or postoperative complications, where Clavien-Dindo 2 or higher was analyzed, table 5. There were 337 patients in the conservative treatment group. This group had a higher mean age of 73.5 years (SD 14.8 years) and higher co-morbidity than the groups treated with early and delayed surgery, both $p < 0.001$. No difference was seen between the years 2003 and 2008 in this group.

	EC/ELC	DC/DLC	Conservative	p
Mean age, years (SD)	51.9 (17.0)	55.9 (15.0)	73.5 (14.8)	<0.001
Charlson co-morbidity index[1]				<0.001
0	563/874 (64%)	158/874 (18%)	103/874 (12%)	
1	122/281 (43%)	48/281 (17%)	91/281 (32%)	
>1	48/284 (17%)	48/284 (17%)	142/284 (50%)	
Degree of severity (Tokyo classification)[1]				0.082
1	400/742 (54%)	136/742 (18%)	161/742 (22%)	
2	316/611 (52%)	114/611 (19%)	154/611 (25%)	
3	7/31 (23%)	4/31 (13%)	10/31 (32%)	
Mean peak CRP, mg/l (SD)	114 (107)	129 (106)	165 (107)	<0.001
Mean peak WBC, $10^3/mm^3$ (SD)	12.7 (8.8)	12.5 (10.9)	13.9 (14.4)	0.193

The numbers in the denominators for CCI and Tokyo classification represent the number of patients in each respective subgroup. Percentages are based on all patients, including those for which data are missing. [1] Numbers in the denominator represent the total number in each subgroup.

Table 4. Patients undergoing EC/ELC, DC/DLC and conservative treatment without surgery

	EC/ELC	DC/DLC	Total	p[1]
Procedures completed laparoscopically	526/680 (77.4%)	189/221 (85.5%)	715/901 (79.4%)	0.001
Mean blood loss, ml (95% CI)	97 (80–114)	70 (50–89)	89 (75–102)	0.007
Mean operative time, min (95% CI)	93 (89–97)	106 (98–114)	96 (92–100)	0.023
Peri- or postoperative complication, Clavien 2 or higher	127/738 (17%)	37/256 (14%)	164/994 (16%)	0.159

[1] Significance tested with adjustment for age, gender, degree of cholecystitis, maximal CRP and maximal LPK.

Table 5. Outcome after early (n=738) and delayed surgery (n=256)

In the early cholecystectomy group the operation time was found to be shorter (p=0.010) if surgery was performed within 5 days of onset of symptoms, however no other significant impact of timing was found on the amount of bleeding, procedures completed laparoscopically and risk for postoperative complications, table 6. The majority (71%) of patients in the early cholecystectomy group were operated within 5 days from symptom onset. For patients treated with early laparoscopic cholecystectomy mean hospital stay was found to be 4.2 days (SD 2.6 days), if open cholecystectomy was performed mean hospital stay was 9.2 days (SD 9.5 days) and for those that had a conversion from laparoscopic to open 7.1 days (SD 4.9 days, p< 0.001). Timing from onset of symptoms of acute cholecystitis till surgery did not have any impact on operation time, bleeding, procedures completed laparoscopically or postoperative complication, table 7.

	Symptoms ≤5 days	Symptoms >5 days	Total	p[1]
Procedures completed laparoscopically[2]	378/488 (78%)	140/180 (78%)	518/668 (78%)	0.171
Mean blood loss, ml (95% CI)	103 (82–124)	89 (59–119)	98 (81–116)	0.368
Mean operation time, min (95% CI)	90 (85–95)	102 (92–111)	93 (89–98)	0.010
Peri- or postoperative complication, Clavien 2 or higher	77/518 (15%)	50/207 (24%)	127/725 (18%)	0.110

[1] Significance tested with adjustment for age, gender, degree of cholecystitis, maximal CRP and maximal WBC.
[2] Data missing on 57 procedures.

Table 6. Outcome after acute surgery by length of AC history, ≤ 5 days (n=518) or ≥ 5 days (n=207)

	0–3 months	3–6 months	>6 months	p
Procedures completed laparoscopically	51/60 (85.0%)	68/75 (90.7%)	68/84 (81.0%)	0.297
Mean blood loss, ml (95% CI)	61 (42–81)	75 (59–92)	70 (56–97)	0.852
Mean operative time, min (95% CI)	104 (96–112)	113 (106–120)	99 (92–116)	0.342
Peri- or postoperative complication, Clavien 2 or higher	10/68 (14.7%)	10/81 (12.3%)	17/95 (17.9%)	0.588

Table 7. Outcome in the delayed surgery group (n=256) in relation to time for admittance and surgery

In patients who did not undergo surgery (including the conservatively treated group) the cumulative readmission rate after the index admission for 1 year was 17.8%, n = 593 (95% CI 14,1-21,5). No difference was seen between the two years cohorts, figure 6.

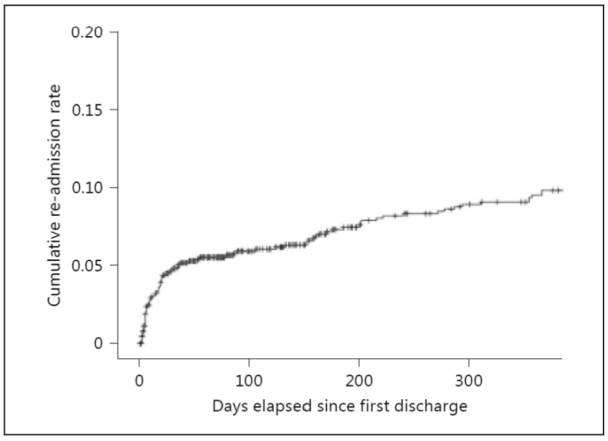

Figure 6. Cumulative readmission rate 1 year after the index

Data Validation

Data from record reviews was cross-checked with GallRiks to test inter-observer reliability. For the patients treated with acute cholecystectomy in the year 2008, 339 patients were identified in both the study and GallRiks with a intra-class correlation for date of surgery of 0.996 ($p<0.001$), for operating time 0.902 ($p<0.001$), for hospital stay 0.719 ($p< 0.001$) for those patients operated on during index admission and for postoperative complications the κ value was 0.59, (Clavien-Dindo >1).

5.2 Paper II

Patient characteristics are presented in table 8. No great differences were found in number of patients, incidence of readmissions or mean age at first admission between the years of 2003 and 2008. There were slightly more females admitted for acute cholecystitis for both years. We saw an increasing number of patients treated with PC between these two years, 2,6% (21/799) in 2003 and 6% (50/833) in 2008. Patients treated with PC had a mean hospital stay of 11.4 days. Patients treated with PC had a higher degree of inflammation and higher co-morbidity. A similar grade of inflammation was seen in patients treated with early cholecystectomy, conservatively and those with elective cholecystectomy. Patients treated with PC had a lower complication rate (2.8%) than those treated with early cholecystectomy (17.1%). In the "bridge to surgery" group all complications were related to the elective cholecystectomy. Clavien-Dindo 2 complications in the PC group included one urinary retention and one local infection around the draining tube, Clavien-Dindo 3: one patient with abscess intraabdominally and one patient with Clavien-Dindo 5 had myocardial infarction and septicemia. The hospital stay was found to be significantly longer for patients treated with PC compared to early cholecystectomy ($p<0.001$) but the risk for complications related to intervention significantly lower ($p<0.001$) when adjusting for gender, age, degree of inflammation and comorbidity.

	Conservative management, no intervention (N = 293)	Early surgery (N = 736)	Cholecystostomy as sole treatment (N = 61)	Cholecystostomy as bridge to surgery (N = 10)	Delayed surgery (N = 248)
Women	157 (53.6%)	403 (54.8%)	35 (57.4%)	8 (80.0%)	146 (58.9%)
Men	136 (46.4%)	333 (45.2%)	26 (42.6%)	2 (20.0%)	102 (41.1%)
Mean age, years (standard deviation)	72 (15)	52 (17)	79 (13)	64 (15)	56 (15)
Charlson comorbidity index					
0	99 (33.8%)	562 (76.4%)	8 (13.1%)	4 (40.0%)	155 (62.5%)
1	80 (27.3%)	121 (16.4%)	14 (23.0%)	3 (30.0%)	46 (18.5%)
≥2	113 (38.6%)	48 (6.5%)	39 (63.9%)	3 (30.0%)	45 (18.1%)
Data missing	1 (0.3%)	5 (0.7%)	0 (0%)	0 (0%)	2 (0.8%)
Cholecystitis severity					
Grade 1	152 (51.9%)	399 (54.2%)	12 (19.7%)	3 (30.0%)	134 (54.0%)
Grade 2	126 (43.0%)	316 (42.9%)	35 (42.9%)	5 (50.0%)	109 (44.0%)
Grade 3	4 (1.4%)	6 (0.8%)	11 (18.0%)	2 (20.0%)	3 (1.2%)
Data missing	11 (3.8%)	15 (2.0%)	3 (4.9%)	0 (0%)	2 (0.8%)
Median hospital stay	4	4	9	8.5	3
Complications related to cholecystostomy and/or cholecystectomy (Clavien-Dindo)					
2		51 (6.9%)	2 (3.3%)	0 (0%)	10 (4.0%)
3		70 (9.5%)	1 (1.6%)	2 (20.0%)*	24 (9.7%)
4		3 (0.4%)	0 (0%)	0 (0%)	2 (0.8%)
5		2 (0.3%)	1 (1.6%)	0 (0%)	0 (0%)

*Both registered complications related to the cholecystectomy.

Table 8. Patient characteristics. Information missing about management or inconsistent for 284 patients.

Univariable and multivariable regression analysis was used to test hospital stay and for the complication rate a univariate and multivariate logistic regression analysis was used to test the difference between PC group and acute cholecystectomy adjusting for gender, age, degree of inflammation and co-morbidity, table 9 a and b.

(a)

	Cholecystostomy group (N = 71)	Acute cholecystectomy group (N = 736)	Difference	P (univariate analysis)	P (multivariate analysis)
Mean hospital stay, days (95% confidence interval)	11.4 (8.9–13.8)	5.1 (4.8–5.4)	6.3 (3.6–9.0)	<0.001	<0.001

(b)

	Cholecystostomy group (N = 71)	Acute cholecystectomy group (N = 736)	Odds ratio (univariate analysis)	Odds ratio (multivariate analysis)
Complication rate (Clavien-Dindo ≥2)	2 (2.8%)	126 (17.1%)	7.1 (1.7–29.4)	15.1 (3.4–66.8)

Table 9. (a) hospital stay, (b) complication rate

The risk for recurrence of acute cholecystitis was found to be 19% for those treated conservatively and 28% for the PC group. When adjusting for gender, age, degree of inflammation and co-morbidity the risk for readmission for new acute cholecystitis did not differ significantly between patients treated with PC with other groups. Figure 7 shows the Kaplan-Meier plot of cumulative recurrence rate of acute cholecystitis after the index admission for patients treated conservatively and with PC for a three-year follow-up. Readmission for new episode of cholecystitis was defined as a terminal event whereas death, scheduled surgery or reaching end of follow up, (dec 31, 2011) was considered censored events. No statistically significant difference was found in univariate or multivariate analysis, (p=0.056 and p=0.051). Adjustments for gender, age, degree of inflammation and co-morbidity were used in Cox proportional hazard analysis.

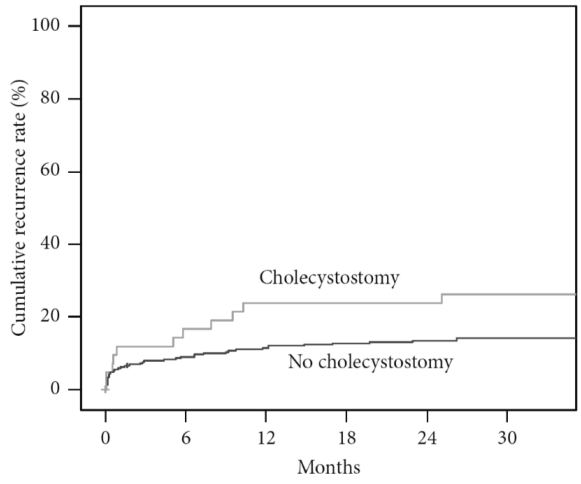

Figure 7: cumulative recurrence rate for new episode of cholecystitis

5.3 Paper III

Altogether 31 091 patients were admitted to hospitals for acute cholecystitis in Sweden during the years 2006 and 2013. A total of 7232 were treated conservatively, 12 207 with acute cholecystectomy and 8532 patients with elective cholecystectomy after discharge. There were 3120 patients not registered and GallRiks. Fig 8 shows the flowchart of the assembly of the cohort. For the 8532 patients treated with elective surgery after discharge and included in this study the characteristics are presented in table 10. In this group 57.2 % were female, 14.9% had an intra or postoperative complication, 2.3% a bile leakage, or bile duct injury.

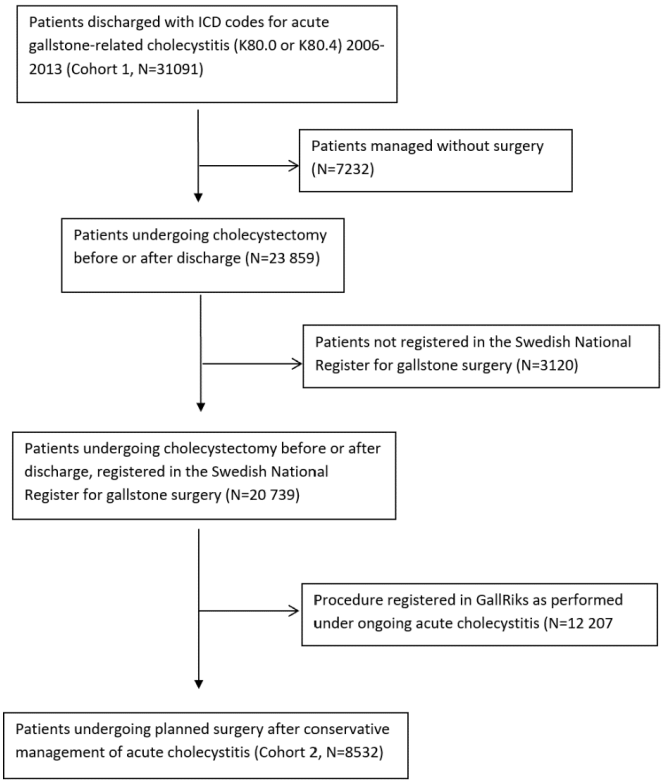

Figure 8. Flow chart of cohort assembly

Mean age, years (standard deviation)	54.1 (16.3)
Gender	
Men	3652 (42.8%)
Women	4880 (57.2%)
Management	
Laparoscopic	6564 (76.9%)
Laparoscopic, conversion to open	1120 (13.1%)
Minilaparotomy	102 (1.2%)
Open	716 (8.4%)
Other/information missing	20 (0.2%)
Mean operating time,	
Minutes (standard deviation)	113 (55)
Intra-/postoperative complication	1271 (14.9%)
Bile duct injury/bile leakage	196 (2.3%)

Table 10. Patient characteristics (N=8532)

Patient distribution is presented for each time interval in table 11 and 47.8 % of patients were treated with surgery within 10 days after discharge from hospital.

Days	Frequency	Per cent	Cumulative per cent
0–10	4078	47.8	47.8
11–30	306	3.6	51.4
31–90	1693	19.8	71.2
91–180	1485	17.4	88.6
181–365	671	7.9	96.5
> 365	299	3.5	100
total	8532	100	

Table 11. Patient distribution over time

Univariable and multivariable logistic regression analyses with adjustments for gender and age and the outcome after surgery in relation to the time intervals after discharge are presented in tables 12-16. Mortality within 30 days after surgery was low, 17 patients in the cohort. No statistically significant impact of time from primary admittance to elective cholecystectomy was found on postoperative mortality in univariate or multivariate logistic regression analysis.

If the elective cholecystectomy was performed after 30 days a 50% reduction was found in procedures completed with a minimally invasive technique, table 12, fig 9.

	Incidence	Univariate analysis		Multivariate analysis	
		Odds ratio (95% confidence interval)	*p*	Odds ratio (95% confidence interval)	*p*
Time elapsed from discharge to surgery (days)					
0–10 (Reference)	2964/4069 (72.8%)				
11–30	247/305 (81.0%)	1.588 (1.183–2.131)	0.002	1.637 (1.210–2.2124)	0.001
31–90	1416/1684 (84.1%)	1.970 (1.699–2.283)	< 0.001	2.277 (1.956–2.651)	< 0.001
91–180	1242/1478 (84.0%)	1.962 (1.680–2.292)	< 0.001	2.467 (2.102–2.897)	< 0.001
181–365	559/669 (83.6%)	1.895 (1.527–2.351)	< 0.001	2.363 (1.894–2.948)	< 0.001
> 365	238/297 (83.6%)	1.504 (1.122–2.016)	0.006	1.816 (1.344–2.454)	< 0.001
Sex					
Women (reference)	3967/4869 (81.5%)				
Men	2699/3633 (74.3%)	0.657 (0.592–0.729)	< 0.001	0.690 (0.619–0.768)	< 0.001
Age					
< Median (reference)	3661/4246 (86.2%)				
≥ Median	3005/4256 (70.6%)	0.384 (0.344–0.428)	< 0.001	0.350 (0.313–0.392)	< 0.001

Table 12. Procedures completed as minimally invasive technique

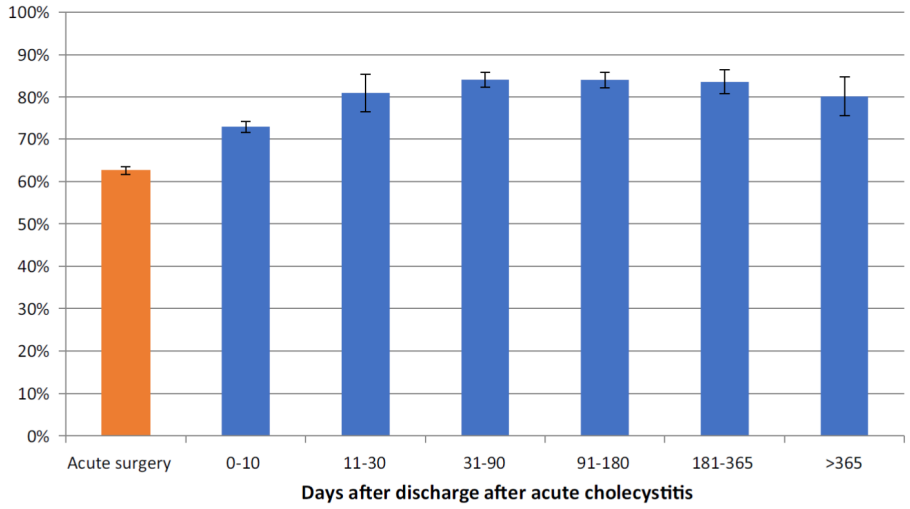

Figure 9. Procedures completed as minimally invasive technique (error bars 95% CI)

No significant differences were found in operating time, table 13 and fig 10.

	Incidence	Univariate analysis		Multivariate analysis	
		Odds ratio (95% confidence interval)	*p*	Odds ratio (95% confidence interval)	*p*
Time elapsed from discharge to surgery (days)					
0–10 (Reference)	2004/4078 (49.1%)				
11–30	148/306 (48.4%)	0.969 (0.768–1.223)	0.793	0.959 (0.759–1.211)	0.723
31–90	870/1693 (51.4%)	1.094 (0.977–1.225)	0.120	1.059 (0.945–1.187)	0.325
91–180	752/1485 (50.6%)	1.062 (0.943–1.196)	0.323	1.000 (0.887–1.128)	0.997
181–365	356/671 (53.1%)	1.170 (0.993–1.377)	0.060	1.108 (0.940–1.306)	0.223
> 365	151/298 (50.7%)	1.063 (0.840–1.345)	0.610	1.013 (0.800–1.283)	0.914
Sex					
Women (reference)	2313/4879 (47.4%)				
Men	1968/3652 (53.9%)	1.296 (1.190–1.413)	< 0.001	1.261 (1.157–1.376)	< 0.001
Age					
< median (reference)	1990/4255 (46.8%)				
≥ median	2291/4276 (53.6%)	1.314 (1.207–1.430)	< 0.001	1.275 (1.170–1.390)	< 0.001

Table 13. Procedures exceeding 100 min

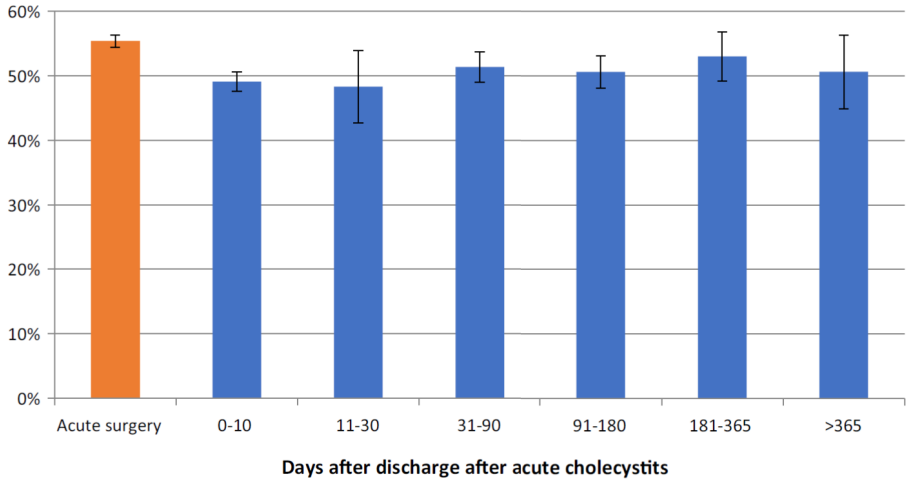

Figure 10. Procedures exceeding 100 min (error bars 95% CI)

Regarding time there was a tendency to decrease in perioperative complications and after 30 days this tendency became statistically significant in multivariate analysis, table 14 and fig 11.

	Incidence	Univariate analysis		Multivariate analysis	
		Odds ratio (95% confidence interval)	*p*	Odds ratio (95% confidence interval)	*p*
Time elapsed from discharge to surgery (days)					
0–10 (Reference)	651/4078 (16%)				
11–30	41/306 (13.4%)	0.814 (0.580–1.144)	0.236	0.811 (0.576–1.141)	0.229
31–90	232/1693 (13.7%)	0.836 (0.711–0.983)	0.030	0.788 (0.670–0.928)	0.004
91–180	214/1485 (14.4%)	0.886 (0.750–1.048)	0.158	0.801 (0.676–0.949)	0.010
181–365	96/671 (14.3%)	0.879 (0.697–1.108)	0.275	0.797 (0.631–1.007)	0.057
> 365	37/299 (14.9%)	0.743 (0.522–1.059)	0.101	0.682 (0.478–0.974)	0.035
Sex					
Women (reference)	665/4880 (13.6%)				
Men	606/3652 (16.6%)	1.261 (1.119–1.421)	< 0.001	1.208 (1.071–1.364)	0.002
Age					
< median (reference)	495/4255 (11.6%)				
≥ median	776/4277 (18.1%)	1.684 (1.491–1.902)	< 0.001	1.699 (1.502–1.923)	< 0.001

Table 14. Perioperative complications

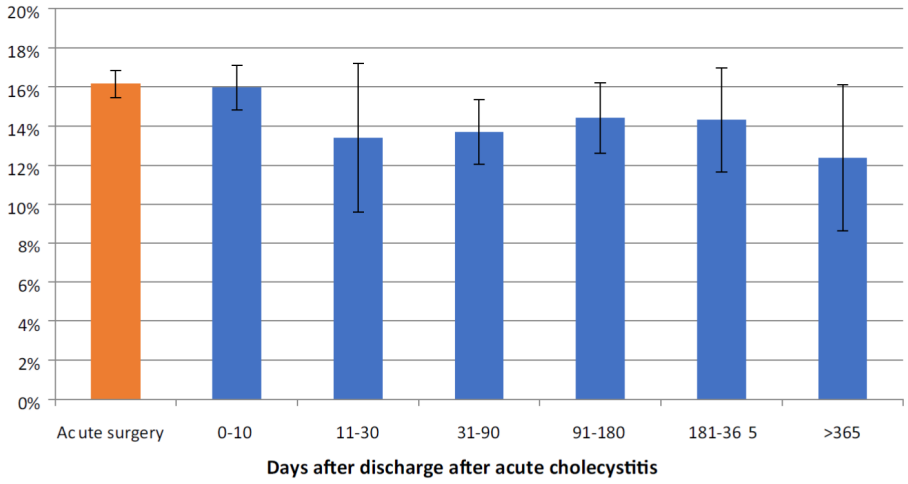

Figure 11. Perioperative complications

There was steady decrease in bile duct injuries up to one year albeit not statistically significant, but a significant increase was seen in the category operated on after one year. Variability, however, was great in this group, table 15 and fig 12.

	Incidence	Univariate analysis		Multivariate analysis	
		Odds ratio (95% confidence interval)	*p*	Odds ratio (95% confidence interval)	*p*
Time elapsed from discharge to surgery (days)					
0–10 (Reference)	21/4078 (0.5%)				
11–30	2/306 (0.7%)	1.271 (0.297–5.446)	0.747	1.240 (0.289–5.316)	0.772
31–90	9/1693 (0.5%)	1.032 (0.472–2.259)	0.936	0.979 (0.452–2.169)	0.990
91–180	13/1485 (0.9%)	1.706 (0.852–3.416)	0.131	1.572 (0.781–3.166)	0.205
181–365	4/671 (0.6%)	1.159 (0.396–3.386)	0.788	1.079 (0.368–3.165)	0.889
> 365	5/299 (1.7%)	3.286 (1.230–8.776)	0.018	3.075 (1.147–8.241)	0.026
Sex					
Women (reference)	24/4880 (0.5%)				
Men	30/3652 (0.8%)	1.676 (0.978–2.871)	0.060	1.582 (0.919–2.721)	0.098
Age					
< median (reference)	22/4255 (0.5%)				
≥ median	32/4277 (0.7%)	1.450 (0.841–2.500)	0.181	1.314 (0.756–2.283)	0.333

Table 15. Bile duct injuries

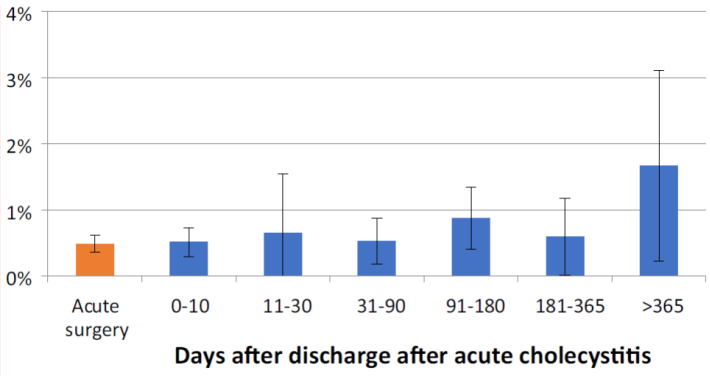

Figure 12. Bile duct injuries

A decrease in bile leakage was seen after 30 days, table 16, fig 13.

	Incidence	Univariate analysis			
		Odds ratio (95% confidence interval)	*p*		
Time elapsed from discharge to surgery (days)					
0–10 (Reference)	40/4078 (1.0%)				
11–30	4/306 (1.3%)	1.337 (0.475–3.762)	0.582	1.302 (0.462–3.667)	0.617
31–90	5/1693 (0.3%)	0.299 (0.118–0.759)	0.011	0.295 (0.116–0.750)	0.010
91–180	7/1485 (0.5%)	0.478 (0.214–1.070)	0.072	0.465 (0.207–1.045)	0.064
181–365	3/671 (0.4%)	0.453 (0.140–1.470)	0.187	0.445 (0.137–1.448)	0.179
> 365	2/299 (0.7%)	0.680 (0.163–2.827)	0.596	0.668 (0.160–2.776)	0.577
Sex					
Women (reference)	30/4880 (0.6%)				
Men	31/3652 (0.8%)	1.384 (0.836–0.291)	0.206	1.457 (0.875–2.426)	0.148
Age					
< median (reference)	32/4255 (0.8%)				
≥ median	29/4277 (0.7%)	0.901 (0.544–1.492)	0.685	0.955 (0.572–1.595)	0.955

Table 16. Cystic duct leakage

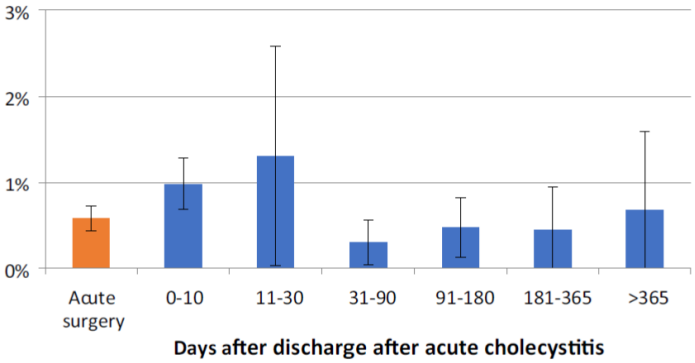

Figure 13. Cystic leakage

The number of surgeries that were completed laparoscopically increased during the study period, fig 14.

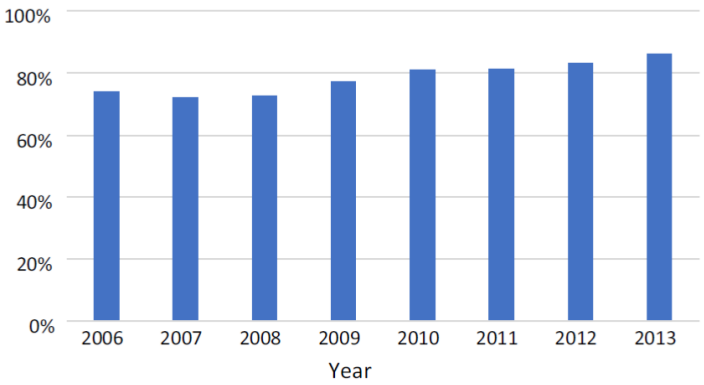

Figure 14. Surgeries completed laparoscopically

5.4 Paper IV

In study IV 30 patients were included but only 25 did underwent gallbladder aspiration, PGBA. Inclusion time was between the years 2014 and 2017. Reason for exclusion of the five patients were deterioration in clinical status before PGBA, necessitating emergency surgery, common bile duct stones, coagulation disorder, lack of resources at the radiology department and treatment with PC due to misunderstanding of the radiologist. In table 17 patient characteristics are described. Aspiration was technically successful in all patients. According to Tokyo classification TG13, 24patients (96%) had a grade 2 cholecystitis and 12 patients (48%) were ASA classification grade 3. In 96% av aspirations bile was sent for culture and was found positive for bacteria in 50%. A fine needle, 0,9 mm was used for all aspirations and 65 ml was the median bile volume aspirated. One complication was found after aspiration, this patient had pain, but no other serious complication was found during investigation and no other intervention was performed. One patient did not improve after one aspiration and needed a second aspiration. Elective cholecystectomy was planned for seven patients (28%) but in two cases could not be completed as one patient was found to have severe adhesions due to chronic cholecystitis and in one patient surgery was interrupted due to malignancy suspicion. No malignancy was later found in this case. These patients had a median hospital stay after aspiration of 3 days with an interquartile range of 2-4 days. Recurrence within one year was found in 28% of patients. No patients needed reintervention of any kind within 30 days except for that one patient that underwent two aspirations. After inclusion one patient died 6 months after aspiration not related to the intervention or gallstone related complication/cholecystitis.

Mean age, years (standard deviation)	75.0 (13.8)
Gender	
Men	13 (52%)
Women	12 (48%)
Median CRP before puncture, mg/L (Interquartile range)	138 (109–257)
Median white blood cell count before puncture, 10^9/L (Interquartile range)	15.7 (10.3–17.5)
Median CRP one day after puncture, mg/L (Interquartile range)	129 (96.5–217.5)
Median CRP two days after puncture, mg/L (Interquartile range)	75 (58.25–150.25)
Classification according to Tokyo	
2	24 (96%)
3	1 (4%)
ASA classification	
1	3 (12%)
2	7 (28%)
3	12 (48%)
4	3 (12%)
Positive cultures	12 (50%)
Median bile volume aspirated, ml (Interquartile range)	65 (50–102.5)
Complications	1 (4 %)
Patient needed reintervention	1 (4%)
Median hospital stay after punction, days (Interquartile range)	3 (2–4)
Early recurrence of cholecystitis < 3 months	6 (24 %)
Late recurrence of cholecystitis > 3 months	1 (4 %)
Planned cholecystectomy	7 (28%)

Table 17. patient characteristics.

5.5 Paper V

Between January 2016 and December 2021 241 patients were treated with PC for acute cholecystitis. Flow chart of selection is presented in fig 15. There was a slight preponderance of males, 51% and median age was 77 years (IQR 67.0 – 84.0 years). Inflammation grade according to the Tokyo Classification, TG13/18 was grade 2 in 82.6% and grade 3 in 14.1% of patients, median WBC was 13.8 10^9/l (IQR 10.8 10^9/l -17.8 10^9/l) and median CRP 266,5 mg/L (IQR 188 mg/L -326 mg/L). The assessment that a patient was not fit for surgery was the most common indication for management with PC, 37.3% and symptoms for too many days was the second most common reason, 24.1%, table 18. A 30-day mortality of 9.1% was seen and the 90-day mortality was 14.1 %. Patient characteristics are presented in table 18.

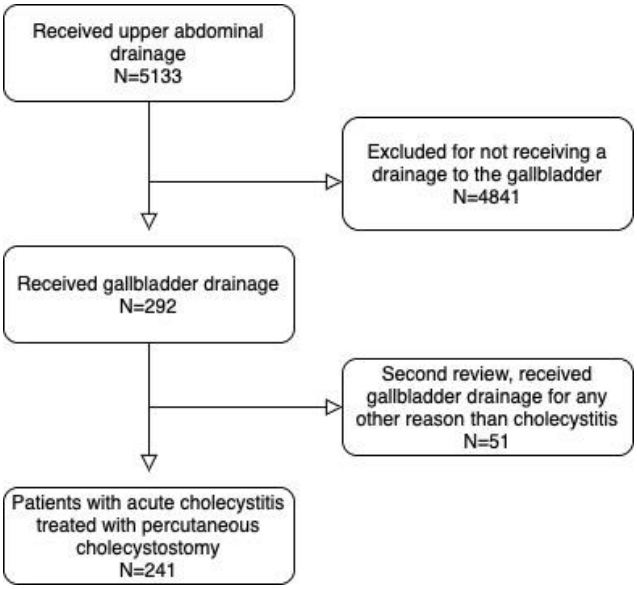

Figure 15. Flow chart of study population.

Characteristics	Total
Number of patients	N=241
Demography:	
Male, n (%)	123 (51.0)
Female, n (%)	118 (49)
Age, years, median (IQR)	77.0 (67.0-84.0)
BMI, median (IQR)	26.9 (23.9-30.2)
Charlson comorbidity index:	
0, n (%)	49 (20.3)
1, n (%)	70 (29.0)
2, n (%)	52 (21.6)
≥3, n (%)	70 (29.0)
Tokyo guidelines score:	
1, n (%)	8 (3.3)
2, n (%)	199 (82.6)
3, n (%)	34 (14.1)
Laboratory results:	
CRP, mg/L, median (IQR)	266.5 (188.0-326.0)
WBC, 10^9/L, median (IQR)	13.8 (10.8-17.8)
Indication for cholecystostomy:	
Too high comorbidity for acute surgery, n (%)	90 (37.3)
Local abscess/perforation, n (%)	43 (17.8)
Too long history for acute surgery, n (%)	58 (24.1)
Organ failure, n (%)	19 (7.9)
Other, n (%)	31 (12.9)
Outcomes:	
30-day mortality, n (%)	22 (9.1)
90-day mortality, n (%)	34 (14.1)
Elective cholecystectomy, n (%)	71 (29.5)
Relapse of cholecystitis	29 (12.0)

Data are presented as median (IQR) for continuous variables and as n (%) for categorical variables.

BMI = body mass index, CRP = C-reactive protein, WBC = white blood cells, IQR = interquartile range, SD = standard deviation

Table 18. Patient characteristics and outcomes. Baseline data comprising of patient characteristics and outcomes.

The transhepatic route was the preferred method and used in 95.9% of cases. In 78.8% of cases a cholangiography was performed but the decision to remove a PC was only based on cholangiography findings in 40.7%. The PC was removed based on clinical judgement in 32.8% of cases and an accidental dislodgment occurred in 14.9% of cases. PC was removed in median after 5 days (IQR 3.1-8.0) and within 7 days 71.8% of drains were removed, table 19.

Characteristics	Total
Number of patients	N=241
Insertion method:	
Transhepatic, n (%)	231 (95.9)
Transperitoneal, n (%)	10 (4.1)
Cholangiography, n (%)	190 (78.8)
within 2 days, n (%)	63 (26.1)
within 3-4 days, n (%)	90 (37.3)
>4 days, n (%)	88 (36.5)
Days to removal, median (IQR)	5.0 (3.0-8.0)
≤7 days, n (%)	173 (71.8)
>7 days, n (%)	68 (28.2)
Reason for removal:	
Cholangiography results, n (%)	98 (40.7)
Clinical judgement, n (%)	79 (32.8)
Accidental dislodgement, n (%)	36 (14.9)
Death	14 (5.8)
Other	14 (5.8)

Data are presented as median (IQR) for continuous variables and as n (%) for categorical variables.

Table 19. Cholecystostomy management**.** Data comprising of variables reflecting management of cholecystostomy

Complications related to PC, Clavien-Dindo gr 1-5 were found in 28.6% of patients, of these Clavien-Dindo grade 1 accounted for 31.9%. Complications grade 2-5 were seen in 19.5% of cases, table 20.

Degree of complication	Total
Clavien-Dindo 1-5, n (%)	69 (28.6)
Clavien-Dindo 1	
Increased pain, n (%)	22 (31.9)
Clavien-Dindo 2	
Bile leakage, n (%)	11 (15,9)
Clavien-Dindo 3	11 (15,9)
Septicemia, n (%)	7 (10.1)
Leaking requiring repeated interventions, n (%)	4 (5.8)
Clavien-Dindo 4	
Septicemia requiring ICU care, n (%)	3 (4.3)
Clavien-Dindo 5	
Death within 30-days, n (%)	22 (31.9)

Data are presented as n (%) for categorical variables.

ICU = intensive care unit

Table 20. Intervention-related complications.

Risk factor for complications with drain removal was female sex, however not statistically significant. Performing a cholangiography had a lower odds ratio for complication but not statistically significant, table 21.

Variables	aOR	95% CI	p-value
Demography:			
Sex (female)	1.19	0.68-2.09	0.550
Age > 77 years	1.00	0.57-1.77	0.989
CCI ≥3	1.027	0.56-1.90	0.933
Cholecystostomy management:			
Cholangiography performed before removal	0.78	0.39-1.54	0.473
Removal ≤ 7 days	0.78	0.42-1.46	0.444

Data is presented as aOR with 95% CI.

Abbreviations: aOR = adjusted odds ratio, CI=confidence interval, CCI = Charlson comorbidity index.

Table 21. Risk factors for any complication following cholecystostomy. Results from a multivariate logistic regression analysis.

Risk factors for abscess or bile leakage were female sex and cholangiography performed before removal, but these were not statistically significant, table 22.

Variables	aOR	95% CI	p-value
Demography:			
Sex (female)	1.16	0.52-2.63	0.717
Age > 77 years	1.08	0.48-2.44	0.854
CCI ≥3	0.87	0 .35-2.17	0.757
Cholecystostomy management:			
Cholangiography performed before removal	1.73	0 .56-5.39	0.344
Removal ≤ 7 days	1.20	0.47-3.05	0.700

Data is presented as aOR with 95% CI.
Abbreviations: aOR = adjusted odds ratio, CI=confidence interval, CCI = Charlson comorbidity index.

Table 22. Risk factors for bile leakage and/or abscess formation following cholecystostomy. Results from a multivariate logistic regression analysis.

In this study cohort a relapse of cholecystitis was seen in 12% of patients, figure 16. No statistically significant risk for relapse was seen if the decision to remove the PC was based on clinical judgment, a cholangiography or dislocation as well if the drain was removed within seven days or after, table 23.

	Total	No relapse	Relapse 30 days – 2 years	p-value
	N=241	N=212	N=29	
Reason for removal:				
Clinical judgment, n (%)	79 (32.8)	69 (32.5)	10 (34.5)	0.84
Accidental dislodgement, n (%)	36 (14.9)	32 (15.1)	4 (13.8)	0.85
No blockage on cholangiography, n (%)	98 (40.7)	83 (39.2)	15 (51.7)	0.20
Days with drainage:				
7 days or less, n (%)	173 (71.8)	151 (71.2)	22 (75.9)	0.60
8 days or more, n (%)	68 (28.2)	61 (28.8)	7 (24.1)	0.60
Cholangiography:				
Performed before removal, n (%)	190 (78.8)	167 (78.8)	23 (79.3)	0.95

Table 23. Relapse of cholecystitis and management of cholecystostomy. Management of cholecystostomy in patients with relapse of cholecystitis within 30 day- 2 years following cholecystostomy treatment vs. patients with no relapse of cholecystitis.

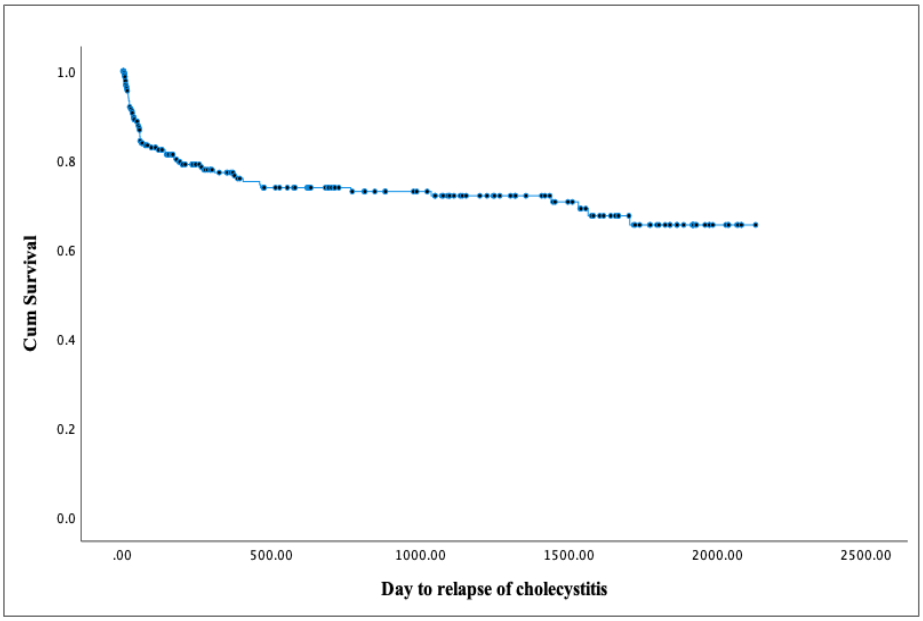

Figure 16. Relapse of cholecystitis. Kaplan-Meier statistics displaying incidence of relapse of cholecystitis following cholecystostomy treatment.

6 Discussion

6.1 General discussion

Gallbladder removal, drainage of the enclosed bile and microbial control are the targets of treatment for acute cholecystitis. This can be achieved with different approaches, but the general condition of the patient and the risks of the treatments must be taken into consideration when deciding on strategy. At the age when the incidence of acute cholecystitis peaks, the physiological function of the gallbladder has, in most patients a limited role for digestion and gastrointestinal symptoms. Hence, there is no need for concern about the absence of the gallbladder following a cholecystectomy, the challenges are to remove or resect the gallbladder safely, without causing more harm than necessary (124). In the acute phase, damage control is usually sufficient. Draining the gallbladder may have an instant effect, but in contrast to most other situations where percutaneous drainage is attempted, the primary goal is to reduce the pressure of the hollow viscus organ and not evacuating infected contents. An acute cholecystitis is caused by obstruction of the gallbladder outflow, increased pressure due to osmosis and ischemic changes in the gallbladder wall due to the increased pressure. This may be instantly relieved by reducing the pressure with a cholecystostomy or percutaneous aspiration. Antibiotics have a limited role in the treatment of acute cholecystitis since the bacterial contamination has a secondary role in the pathogenesis of acute cholecystitis (113). The crucial issue is therefor to find ways that effectively and safely drain the contained bile, without risk of bile leakage or hemorrhage and without imposing the discomfort and need of repeated maintenance in case a drain is left in situ.

Early or delayed cholecystectomy for high-risk patients

The pathogenesis of calculous acute cholecystitis is primarily related to the presence of gallbladder stones and secondarily by the inflammation provoked by the presence of such stones. Ideally the stones and inflammation should be addressed at an early stage. The only way to achieve this is by early cholecystectomy during the index admission of acute cholecystitis. In case this is not possible, the management is usually focused on the acute inflammation. The presence of gallbladder stones, despite being the primary underlying cause of the inflammation, may be left for later intervention. The optimal approach to reducing the local and systemic inflammation is, however, still a matter of debate.

There are numerous studies showing that early laparoscopic cholecystectomy is the strategy of choice for this patient group (64, 125-127). However, most studies have been conducted on homogenous populations of patients without severe comorbidity and without other factors rendering emergency surgery an inappropriate alternative. A very large proportion of patients admitted for acute cholecystitis has at least one factor of relative contraindication for emergency surgery, including protracted history of acute cholecystitis, previous upper abdominal surgery, treatment with anticoagulants, advanced age, or severe comorbidity.

Ideally, resources and experienced staff should be available at all units managing patients with acute cholecystitis. Nevertheless, all too often this is not case. Many patients admitted with acute cholecystitis out of office hours are given low priority in relation to other patients with conditions requiring more urgent management. This can lead to the decision to offer these patients the second-best alternative, i.e., conservative management and delayed surgery. Although this may be considered a safe choice, it leads to protracted hospital stay, risk of repeated attacks of pain and higher health care costs (128). In most cases, the decision between emergency surgery and conservative management is taken based on individual patient-related factors and resources available at the moment of patient hospital admission.

Patients that are found unfit for emergency surgery constitute a very heterogenous group, which makes it difficult to conduct well-designed prospective studies with uniform outcome measures. There are often factors that complicate shared decision-making, including impaired mental function, dementia and lack of optimal resources and competence when the patient is admitted. Despite the difficulties in performing well-designed studies on this group, these patients can face greater risk of lethal outcome or serious complications from acute cholecystitis than younger and healthier patients (67). However, studies have also suggested that refraining from acute cholecystectomy based on advanced age may be unfavorable for the patient as well. There are several studies showing that early cholecystectomy in elderly can be just as safe as for younger patients and that abstaining from surgery in this group is also associated with higher mortality. More and more studies favors early cholecystectomy (129). Despite the obstacles in designing appropriate studies for this group, there is a great need to improve the management for these often elderly and frail patients.

In the one randomized controlled trial comparing PC to surgery, the CHOCOLATE study, all complications within one year were registered showing a significantly higher complication rate in the PC group. However, the study includes reintervention rate within one year as a major complication. The conclusion in this trial was that patients with APACHE scores of 7-15 should be treated with emergency surgery. In the CHOCOLATE study the sickest patients, i.e., those with APACHE scores > 15, patients in need of ICU care at admission and those with symptoms for more than 7 days were

excluded. In this trial there was an incidence rate of 12% for major complications in the acute group. For the patients treated with PC, 93% were reported to improve quickly after PC (64). This proves that PC remains an effective treatment strategy, even though consideration must be taken to the recurrence rate. This trial proves that more patients with increased risk should be treated with emergency surgery although conservative strategies are still important as, inevitably some patients will still not undergo emergency surgery. Most of the randomized controlled trials have not shown a risk reduction in complication rate, but instead shown early cholecystectomy to be safe and cost-effective as patients only require one hospital admission instead of two as in the case of delayed surgery. This must be kept in mind when choosing the perfect treatment option for each individual patient.

In study I we saw that less than 50% of patients were treated with emergency surgery. This result is surprising since guidelines at the time of the study favored early surgery as the primary choice of treatment. We did not see any large increases in the proportion of patients that underwent treatment with early surgery during these five years. This shows that making changes in clinical treatment can be a long and slow process and that there is a need for great dedication from clinicians for changes to be achieved. We concluded that early surgery is a safe management option of acute cholecystitis. However, one must keep in mind that patients receiving this treatment were younger and healthier than the conservative group in this study.

In study III we concluded that if conservative treatment is chosen when patients are admitted for acute cholecystitis and an elective surgery is planned at a second stage, this surgery should be performed more than 30 days after discharge but preferably within 3 months. Recurrence rate of cholecystitis must be considered when planning elective surgery. In study I, we saw a recurrence of cholecystitis in 17.8% of patients and for those treated with PC the recurrence rate was 28% in study II. We could also see in study II that few patients from the PC group did go on to elective surgery showing that PC is often a sole treatment and not "bridge to surgery". Reports show that approximately 40% of patients treated with PC do get an elective cholecystectomy (83). We saw in both studies that the recurrence rate is higher in the first months after cholecystitis. There are few studies on the optimum timing of elective cholecystectomy. Most studies where elective surgery is performed there is a stated timepoint for the elective surgery. In one large multicenter randomized trial, the ACDC study where optimal timing for cholecystectomy was studied by comparing early vs delayed surgery, the delayed surgery was planned between 7-45 days after hospital admission (57). This timeframe is proven by the results of study III not to be good timing for surgery.

Percutaneous cholecystostomy or gallbladder aspiration as treatment in high-risk groups

PGBA as a treatment option needs further evaluation but if proven safe it could be a safe first step in the management of acute cholecystitis in high-risk patients and PC a salvation treatment. The appealing feature of PGBA is its simplicity, this treatment option is far simpler than PC or any endoscopic treatments. It may be an easily accessible treatment with few complications if proven safe. Handling of a drainage as well as tolerating an endoscopic procedure can be difficult for the elderly patients with impaired cognitive function or physical disability. In study IV we could see that PGBA seems to be a safe choice for the high-risk group. Our study demonstrates good outcomes with only one minor complication and short hospital stays however, this is a very small study group. Hospital stay was medium 3 days (IQR 2-4 days) for patients receiving gallbladder aspiration in study IV whereas we found a mean hospital stay of 11.4 days for patients treated with PC in study II. The hospital stay for gallbladder aspiration is similar to that reported from other studies (11).

In study II we saw that treatment with PC increased during the 5-year study period. It was proven a safe option for the high-risk group. We saw low complication rates, keeping in mind that this was a small study group. In study V we found a 19.5 % complication rate for the group treated with PC. The complication rate in our studies is lower than that of the CHOCOLATE trial, where a 65% complication rate was demonstrated (64). In our study we considered intervention-related complications only, whereas the CHOCOLATE trial also included reinterventions as a complication. In study II we found a 28% recurrence rate for cholecystitis following PC and in study V the recurrence rate was 12%. Consequently, the CHOCOLATE trial can show us a bigger picture of the disease and what to expect for our patients when conservative treatment is chosen. However, despite the high complication rate 93% of patients in the PC group did improve promptly. In a systematic review of retrospective studies PC showed a complication rate of 6% only (83). With a reported overall success rate of 85.6% for PC and 76%- 96% for PGBA these methods are good treatment choices for a patient with acute cholecystitis that deteriorate in clinical status and are unfit for emergency surgery (83, 105, 106)

There have been contradictive reports on how long a PC should be in place and the importance of an antegrade cholangiography. We could in study V conclude that an early removal of the drain based on clinical judgment is a safe approach and timing of drainage does not seem to impact on recurrence rate. A cholangiography may be used only for selected cases and not routinely for everyone.

6.2 Methodological considerations

Selection bias

The studies included in this thesis are all observational. This makes selection bias unavoidable. In studies I and II we adjusted for Charlson co-morbidity index. To some extent, this reduces the bias related to co-morbidity. Nevertheless, there is still a great risk of residual confounding. The CCI estimations were based on retrospective reviews of the patients records, which has limitations.

The cohorts of study I and II were identified through the National Patient Register. Ideally, this would imply that all patients with acute cholecystitis in the Stockholm catchment area were included. There are, however, several sources of selection bias. Patients could have sought acute health care outside the Stockholm catchment area and, on the other hand, patients from other regions could have been admitted at emergency units within Stockholm. The routines for recording the ICD codes for acute cholecystitis may also have varied between the units as the diagnostic criteria for acute cholecystitis are relatively vague (37).

Inclusion criteria of study III was a primary decision to refrain from emergency surgery and instead offer a delayed procedure, i.e., contrary to present recommendations. In other words, all analyses were based on outcomes following a deviation from the standard of care. Even if this is relatively common in routine health care this patient group constitute of a heterogenous group that does not fit in to the patterns of care defined by most guidelines. The reasons for refraining from emergency surgery, *e.g.*, lack of compliance to guidelines or presence of relative contraindications to surgery is not possible to identify in GallRiks or the National Patient Register. The same factors could also be present when the delayed cholecystectomy was carried out.

The management of cholecystostomy drain once it has achieved the primary aim of draining the gallbladder is to a great extent dependent on local routines. Study V was conducted at Södersjukhuset, which is a unit where cholecystostomy is not considered a favorable conservative alternative unless a clear deterioration of patients treated only with antibiotics is seen. Cholecystostomy as bridge to surgery is rarely practiced at Södersjukhuset, it is in most cases practiced as a final treatment option for patients in poor conditions who are not found fit either for acute or planned surgery (130). This may have been a source of selection bias and a limitation of the external validity. At units where cholecystostomy is considered a first-hand alternative, there is probably a more active dialogue between the radiology and surgery departments and the routines to evaluate the status of the cholecystostomy more defined (131). One of the most common complications from cholecystostomy drainage is drain dislocation and bile

leakage. With radiologists and surgeons being aware of this, appropriate efforts to ensure adequate insertion of the cholecystostomy and careful catheter maintenance may reduce this risk (132).

Confounding

The data on management of acute cholecystitis in the first two studies was based on retrospective reviews of patient records. This could also have caused a bias since all data were interpreted the way they were primarily recorded. In real life, treatment decisions are often based on circumstances that are not described in detail in the patient records. Whether a patient is found fit for surgery or a conservative approach is in most cases decided on a trade-off between the will expressed by the patient and relatives, access to resources when the patient is admitted, previous history and comorbidities and an overall assessment of the general condition of the patient. It is impossible to obtain all these aspects in a retrospective patient record review.

Despite the fact that acute cholecystitis primarily is a sterile condition, and that bacterial contamination may be present as secondary manifestation of the disease, antibiotic treatment is often considered a cornerstone in the management of acute cholecystitis. In the present study, we chose to focus on other aspects of the management than antimicrobial treatment. Nevertheless, antibiotics may play a crucial role in managing the systemic complications of acute cholecystitis. This is especially the case in patients with Tokyo grade 3. Antibiotics have little effect on bacterial contamination of the bile in the gallbladder as it only slowly diffuses into the hypertonic bile, but it may reduce the risk of systemic inflammatory response syndrome and local abscess in case acute surgery is attempted (133).

External validity

Several well-designed randomized controlled trials have shown favorable and cost-effective outcomes from early laparoscopic cholecystectomy for acute cholecystitis. These studies have formed the base for guidelines on acute cholecystitis, including the Tokyo guidelines. These studies, should, however, be interpreted with some caution. Most of them have been carried out at tertiary referral centers, with devoted surgeons that give high priority to surgery for acute cholecystitis. This limits the external validity of these studies since the outcome from conservative management and delayed surgery differs little between centers of excellence and units where acute cholecystitis is given low priority, whereas emergency surgery is safe only if conducted by experienced surgeons. Accordingly, the outcome presented study I of this thesis did not

show as favorable outcome after early laparoscopic surgery as that seen in the previous randomized controlled trials. This may reflect that the present study relied on population-based data and not only the outcome from centers of excellence.

In all studies of the present thesis, elderly and frail patients predominated. This may affect the external validity as the readiness to suggest surgery to frail patients varies from time to time as well as between different healthcare systems. Surgery was rarely offered to octogenarians in Sweden until the 1990's. During the last decades, the threshold for surgery for benign as well as malignant conditions has been lowered. The same tendency has been seen in other parts of the Western world as well, but it is often a matter of the preparedness of the healthcare system to allocate resources to the aging population. Managing an elderly patient with acute cholecystitis or any other gallstone condition requires more resources, more active monitoring and longer hospital stay than for a younger patient, regardless of which treatment is chosen. Hence, the management of elderly patients is a matter of health insurance, access to resources and priorities between different patient groups in need of surgery.

The study sample of study IV was relatively small, which limits the validity of the study. Rare but serious complications from bile aspiration may not have been observed in the sample of 25 patients. Complications such as bile leakage or bleeding from the liver parenchyma in a small minority of the groups undergoing bile aspiration may have devastating consequences and could not be justified by a favorable outcome for the majority of patient (134). To adequately evaluate the safety of bile aspiration as an alternative for managing acute cholecystitis, samples large enough to quantify risks with incidences of a few percent are needed.

Percutaneous cholecystostomy as well as percutaneous gallbladder aspiration rely on the access to skilled radiologists. Furthermore, the radiologists at each unit will acquire the experience in ultrasound-guided drainage unless the responsible clinicians consider percutaneous cholecystostomy or gallbladder aspiration a preferable option. The outcome is thus to a great extent depending on local routines that cannot easily be extrapolated to units where percutaneous drainage is done scarcely.

Strengths

Studies I-III in the present thesis are based on unselected Stockholm populations. This strengthens the external validity as it included patient groups that are rarely studied in prospective studies from tertiary referral centers. Hence, they reflect the effectiveness of the different approaches as they are practiced in the community at large. Most randomized controlled trials, on the other hand, reflect the efficacy of treatments as they are practiced under ideal circumstances.

The outcomes from studies IV and V are limited to a single surgical unit and reflect the management from units with high turnover of acute cholecystitis and staffs that are familiar with the routines regarding gallstone conditions. Patients included in study IV were monitored by the research nurses at the department of acute care surgery, Huddinge. They were followed according to a standardized protocol to register any potential adverse events following the first admission. In case no other intervention than the aspiration was needed, the treatment was considered successful. Strict criteria for monitoring the patients were defined, the risk of neglecting treatment failure was thus minimized.

Patients in study V were all managed at Södersjukhuset. It is thus a single-center study, i.e., based on a well-defined sample from a unit with uniform and standardized routines, albeit with an external validity that is limited to other units with similar resources and routines. The long follow-up also minimizes the risk of neglecting late occurring adverse events from the management.

Implications

The present studies show that careful considerations must be taken for patients with acute cholecystitis, especially if the first-hand surgical alternative is not an option. Early laparoscopic cholecystectomy may be the ideal treatment for patients without contraindications for surgery. However, the same factors that limit the possibility for emergency surgery, e.g., frailty, prolonged history of acute cholecystitis and advanced age, tend to be factors that increase the risk in case of conservative management. Even in cases where emergency surgery is not considered, effective control of the acute inflammation is required.

The findings of these studies should be confirmed in studies with larger patient groups and, ideally, in randomized controlled trials. Although it is difficult to carry out a randomized controlled trial on elderly and frail patients such as those found unfit for acute cholecystectomy, there is room for great improvement in their quality of care. They constitute an often-neglected population with poor ability to express their specific needs. Bile aspiration could be an alternative as a bridge to surgery as well as final treatment as it is relatively atraumatic and associated with little risk of bile leakage and local fibrosis. Before bile aspiration is introduced as a standard, more studies are needed to show that it provides results equal to other techniques.

In case delayed surgery after an initial episode of acute cholecystitis is planned, the timing of the procedure should be carefully considered. In many cases, a patient treated for acute cholecystitis is eager to get a final treatment as soon as possible. As shown in study III, carrying out the delayed procedure at a too early stage may increase the hazards as the local inflammation and tissue regeneration is still ongoing. On the other hand, postponing the procedure too much may result in the risk of readmission for

relapsing acute cholecystitis. Watchful waiting may be an option in case early cholecystectomy has not been carried out on patients without severe comorbidity, but this requires preparedness to reconsider the conservative management and opting for surgery in case new gallstone symptoms develop.

An alternative to surgical treatment for acute cholecystitis that is rapidly gaining recognition is endoscopic ultrasound-guided transmural gallbladder drainage (135). When studies I and II of the present thesis were carried out, this had not yet been established as an alternative. Transmural gallbladder drainage has the advantage of not requiring general anesthesia and thus being a safe alternative also for patients who are not candidate for acute surgery. Furthermore, the stent in the gallbladder provides a permanent drainage to duodenum or the stomach, which prevents new episodes of acute cholecystitis. Although ultrasound-guided transmural gallbladder drainage is still considered an experimental therapy, the rapid development of endoscopic techniques will probably promote the introduction of this as well as other techniques for conservative management of inflammatory intraabdominal conditions.

7 Conclusions

- Less than 50% of patients in Stockholm County are treated with early cholecystectomy

- Early cholecystectomy as a treatment option increased slightly from 2003 to 2008.

- There are no differences between early and elective cholecystectomy in patients with acute cholecystitis regarding peri and postoperative complications however early cholecystectomy seems to be associated with higher blood loss and higher risk for conversion to open surgery.

- Management with cholecystostomy is a safe option both as a definitive treatment and as "bridge to surgery" in high-risk patients.

- Recurrence rate of acute cholecystitis following treatment with cholecystostomy is between 12-28%.

- Gallbladder aspiration seems to be a safe option for high-risk patients with acute cholecystitis.

- Optimal timing to perform an elective cholecystectomy after a conservatively managed cholecystitis is after 30 days after discharge from hospital but not later than 90 days.

- A cholecystostomy can safely be removed within one week if patient have improved clinically and the drain is inserted through the transhepatic route.

- Performing an antegrade cholecystography routinely does not seem to reduce the risk in patients treated with cholecystostomy.

8 Points of perspective

Since the start of this thesis more and more studies have been published proving the advantages of early laparoscopic cholecystectomy, however only a hand full of these include patients from the high-risk group. Many patients are despite this still treated conservatively. There has been a development of new techniques for conservative treatment with new endoscopic approaches during the last couple of years, but these techniques are still only used in specialize centers. This proves that a need to develop and study conservative strategies is still high as this is the treatment most often given patients with high risk for surgery.

It is clear that there is a need for good randomized controlled studies where comparison is made between PC and surgery, between PC and aspiration as well studies on the endoscopic approaches. Many RCTs are made on early vs delayed surgery but this high-risk group is often excluded from those.

The future goal after this thesis is to make a randomized controlled trial comparing PC with PGBA in patients not suitable for emergency surgery. Study four is constructed as pilot study for this RCT. We are planning on a randomized controlled trial to assess the safety and effectiveness of bile aspiration as a method for conservative management of acute cholecystitis. The study is registered in clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT03012243). This study will hopefully shed more light on percutaneous bile aspiration as we as cholecystostomy for treatment of acute cholecystitis.

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