Complicated gallstone disease in Sweden 1988-2006

A register study

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Science is one of the very few human activities - perhaps the only one – in which errors are systematically criticized and fairly often, in time, corrected.

Karl Popper (in Conjectures and Refutations)

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Abstract

Background The gallstone prevalence in the western world is 10-20%. Most gallstones are silent, but symptoms and complications appear in 20-40%. The incidence of symptom development in patients with silent gallstones is 2-4% per year. The indication for surgical (including endoscopic) treatment of gallstones is symptoms of certain magnitude, and no contraindications.

During the past three decades an intense technical development in imaging (ultrasound, computerised tomography and magnetic resonance imaging), endoscopic therapy, and surgery has taken place.

The aim of this thesis is to scrutinize changes in management of complicated gallstone disease on a population-based level, using national register data. Have the new methods improved the treatment of acute pancreatitis, common bile duct stones and acute gallbladder disease?

Methods Data is collected from National Patient Register (NPR) run by The Swedish National Board of Health and Welfare. NPR collects discharge data from every admission from every Swedish hospital. Mortality is calculated as standardised mortality ratio (SMR) using age-, gender-, and calendar year specific survival estimates.

We have studied both general trends in admissions and treatment alternatives and outcomes in defined patient cohorts. Length of hospital stay, readmission, and mortality has been used as proxy indicators of the effectiveness of treatment strategies used.

Results During the study period mortality in acute pancreatitis (SMR within 90 days of admission) improved and hospital stay for all patients with acute pancreatitis decreased.

Cholecystectomy rate at or shortly after index stay for mild acute biliary pancreatitis increased from 14.5 % to 22.7 %. Of all patients with acute pancreatitis 68.4 % of the patients had no aetiological diagnosis in the register.

The incidence of bile duct interventions increased 27.8% from 1988 through 2006. The favoured treatment of bile duct stones changed from open choledocholithectomy to endoscopic sphincterotomy with stone extraction during the same period. However, in 2006, still 19.6% of bile duct interventions for stones were performed as choledochotomy and in the great majority of these cases as open surgery. This indicates a continuing need of education in open bile duct surgery. Mean hospital stay for treatment of common bile duct stones decreased significantly (4.5 days) during the period studied. The mortality (SMR) diminished although without statistical

significance during the time period, and there was no significant difference in SMR between choledochotomy and endoscopic sphincterotomy.

For acute gallbladder disease a moderate increase of admissions occurred from 1988 through 2006. The relation between acute cholecystectomies versus all cholecystectomies did not change during this period. Of all patients admitted with acute gallbladder disease 32.3 % were cholecystectomised during their first hospital stay, whereas 20.3 % underwent elective cholecystectomy and 6.1 % emergency cholecystectomy within two years of first admission. 41.4 % of patients were not operated on for gallbladder disease within two years of first admission with this diagnosis. Mortality from first admission and 90 days onwards was elevated three-fold during the entire period without time trend, without statistical difference between age groups, and between patients who had cholecystectomy at first admission or later.

Conclusion During the audit period treatment of acute pancreatitis improved. However, etiological classification and timing of cholecystectomy in mild acute biliary pancreatitis fell below accepted guidelines. Interventions on the common bile duct for gallstone disease increased significantly. Common bile duct clearance has been separated from cholecystectomy, and cholecystectomy often not done. Only one third of all patients with acute gallbladder disease underwent cholecystectomy at first admission. There is room for improvement in treatment of complicated gallstone disease, and, gallstone surgeons still need good knowledge in open biliary surgery.

List of original papers

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I. Sandzén B, Haapamäki M, Nilsson E, Stenlund HC, Öman M. First attack of acute pancreatitis in Sweden 1988-2003: incidence, aetiological classification, procedures and mortality – a register study.
BMC Gastroenterology 2009;9:18

II. Sandzén B, Haapamäki M, Nilsson E, Stenlund HC, Öman M Cholecystectomy and sphincterotomy in patients with mild acute biliary pancreatitis in Sweden 1988 – 2003: a nationwide register study.
BMC Gastroenterology 2009;9:80

III. Sandzén B, Haapamäki M, Nilsson E, Stenlund HC, Öman M Treatment of common bile duct stones in Sweden 1989–2006 An observational nationwide study of a paradigm shift.
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IV Sandzén B, Haapamäki M, Nilsson E, Stenlund HC, Öman M Surgery for acute gallbladder disease in Sweden 1990-2004- a register audit.
In manuscript

Abbreviations

BMI	Body mass index
CBD	Common bile duct
CBDE	Common bile duct exploration
CBDS	Common bile duct stones
CFR	Case fatality ratio
CI	Confidence interval
ERCP	Endoscopic retrograde choledocho-pancreaticography
ES	Endoscopic sphincterotomy
FAAP	First attack of acute pancreatitis
ICD	International classification of diseases and related health problems
LCBDE	Laparoscopic common bile duct exploration
LOS	Length of stay
MABP	Mild acute biliary pancreatitis
NPR	Swedish national patient register
RCT	Randomised controlled trial
SIC	Small incision cholecystectomy
SMR	Standardised mortality ratio
UDCA	Ursodeoxycholic acid

Sammanfattning på svenska

Om gallstenssjukdomen

Gallsten är vanligt, från undersökningar av ett statistiskt urval av svenskar i alla åldrar, antas 10-20% av befolkningen bära på gallsten. Samma är förhållandet i västvärlden i övrigt. Gallsten blir vanligare med stigande ålder och är vanligare hos kvinnor än män, särskilt i yngre åldrar. Av de som har gallsten, beräknas 20-40 % förr eller senare få besvär relaterade till sina gallstenar. Det finns anledning till behandling av gallsten med uttalade symptom, men det kan vara svårt att skilja besvär från gallsten från andra vanliga besvär från mag-tarm kanalen. Det som betraktas som det typiska gallstenssymtomet, är attacker av kraftig smärta i bukens övre högra och övre mellersta del. Smärtan varar från en halv till upp till 5-6 timmar, ibland längre. Den kommer ofta kvällstid och under förnatten, ofta med smärtutstrålning mot ryggen och kombinerade med allmänna symptom som sura uppstötningar, illamående, kräkningar och uppkördhet. Den behandling som blir aktuell är kirurgiskt avlägsnande av gallbllåsan.

Komplicerad gallstenssjukdom uppstår när gallstenarna får andra konsekvenser än gallstensanfall som beskrivits ovan. Den vanligaste komplikationen till gallsten är akut inflammation i gallblåsan. Den uppstår vanligen när en gallsten täpper till gallblåsans förbindelse med djupa gallgången och fastnar där. Då ökar trycket i gallblåsan och om denna tryckökning kvarstår kan en från början kemisk inflammation i gallblåseväggen uppstå, som leder till ömhet över gallblåsan, allmänsymtom och feber. Detta brukar leda till inläggning på sjukhus. Detta anses vara en klar anledning att kirurgiskt avlägsna gallblåsan, och det är en fördel om detta görs under det första vårdtilllfälle.

En annan komplikation uppstår då gallstenar som bildas i gallblåsan kommit ned i den djupa gallgången. Här kan gallstenarna förutom att ge upphov till smärtor också orsaka ett hinder för gallans flöde från levern till tarmen, vilket ger upphov till gulsot av varierande grad. Om bakterieväxt uppstår p.g.a. hindret kan akut gallgångsinflammation tillstöta, vilket är ett allvarligt tillstånd. Gallgångsstenar hos patienter med symptom skall avlägsnas. Det kan göras antingen genom att skära upp den djupa gallgångens öppning till tarmen med hjälp av ett s k endoskop, och den vägen ta ut gallstenarna, eller genom ett kirurgisikt ingrepp genom bukväggen, varvid man öppnar gallgången och tar bort stenarna. Det har visats fördelaktigt att avlägsna gallblåsan, där ju stenarna bildats, i anslutning till att man tar bort stenarna från den djupa gallgången Det förstnämnda alternativet är numera det vanligaste, men det pågår en

diskussion om det lämpligaste sättet att avlägsna gallgångsstenar och varianterna på dessa båda alternativ är flera.

Den djupa gallgången har en gemensam öppning i tarmen med bukspottkörteln och ibland täpper gallstenar till bukspottkörtelns utförsgång. Detta kan öka trycket i denna så att inflammation uppstår i bukspottkörteln, en akut gallstenspankreatit. Denna kan utvecklas till ett livshotande tillstånd, som kräver intensiv stödjande behandling på olika sätt. För att förhindra återfall i denna sjukdom bör eventuella kvarvarande gallstenar i den djupa gallgången avlägsnas, samtidigt som gallblåsan tas bort.

Syftet med avhandlingen

Under de senaste 30 åren har en omfattande teknisk utveckling ägt rum beträffande utredning och behandling av gallstenssjukdom. Ultraljud, datortomografi och magnetkameraundersökning har introducerats.. Undersökning och behandling med böjliga och styrbara instrument i magtarmkanalen har introducerats och blivit alltmer avancerade. Laparoskopisk kirurgi (“titthålskirurgi”) hade ett snabbt genombrott i början av 1990-talet, och har kommit att bli den vanligaste operationstekniken vid avlägsnande av gallblåsan.

Syftet med denna avhandling är att utgående från socialstyrelsens register se vilka förändringar i vården av komplicerad gallstenssjukdom som skett under denna brytningstid. Frågan är i vilken utsträckning vården förbättrats beträffande säkerhet och effektivitet.

Metoder

Uppgifter har hämtats från socialstyrelsens patientregister. Patientregistret får enligt lag utskrivningsuppgifter från alla vårdtillfällen från samtliga svenska sjukhus. Sedan 1987 omfattar registret alla svenska sjukhus. Dessa uppgifter har samkörts med data från dödsorsaksregistret för att beräkna dödlighetsrisk vid olika tillstånd och med olika behandlingar. Denna uttrycks i ett jämförelsetal (SMR), där den påvisade dödligheten jämförs med förväntad dödlighet. Den förväntade dödligheten för ålder, kön och tidsperiod har hämtas från statistiska centralbyrån.

Vi har undersökt både allmänna tendenser avseende vårdtillfällen och behandlingsmetoder, men också följt vissa definierade patientgrupper. Dessa har undersökts med olika indikatorer på vårdens effektivitet och säkerhet

som vårdtider, återinläggningar, dödlighet, samt följsamhet gentemot accepterade riktlinjer.

Resultat

Under den studerade tidsperioden sjönk dödligheten i akut bukspottkörtelinflammation och medelvårdtiden för sjukdomen minskade.

Det är önskvärt att gallblåsan med sina stenar avlägsnas samtidigt med eventuella stenar i den djupa gallgången i anslutning till en attack av gallstensutlöst inflammation i bukspottkörteln. Frekvensen av denna operation ökade från 14.5 till 22.5% under den studerade perioden. Det är värdefullt om orsaken till den akuta bukspottkörtelinflammationen fastställs, men i registret fattades information om detta hos 68.4% av patienter med förstagångsinsjuknande. Ett önskvärt mål är att mindre än 20% av vårdtillfällen för akut bukspottkörtelinflammation skall vara utan orsaksdiagnos, då tidig diagnos förbättrar handläggningen.

Behandlingen av gallstenar i djupa gallgången ändrades från öppen kirurgi via hudsnitt till endoskopiskt stenavlägsnande med klyvning av gallgångsslutmuskeln under perioden 1988 till 2006. Totalantalet ingrepp på den djupa gallgången ökade under denna tid med 28%. År 2006 gjordes 20% av ingreppen för gallgånsstenar kirurgiskt, och det stora flertalet av dessa genom öppen kirurgi. Andelen patienter som fick gallblåsan borttagen i samband med att stenar i den djupa gallgången avlägsnades, minskade från 60% 1989-1994 till 30% 2001-2006. Medelvårdtiden för behandling av sten i den djupa gallgången minskade med 4 ½ dag under den studerade tidsperioden. Den relativa dödligheten (SMR) minskade något men inte statistiskt säkerställt. Det var ingen säkerställd skillnad beträffande SMR mellan borttagning av sten i djupa gallgången via kirurgiskt insnitt i gallgången eller endoskopisk klyvning av gallgångsmuskeln.

Vid akut gallblåsesjukdom ökade inläggningarna måttligt från 1988 till 2006. Förhållandet mellan akuta och alla cholecystectomier var väsentligen oförändrat under perioden. 32.2% av alla patienter som lades in akut med gallblåsesjukdom fick gallblåsan bortopererad vid det första vårdtillfället, ytterligare 20.3 % återkom planerat inom två år för gallblåseoperation och 6.1% återkom akut och blev opererade vid detta tilllfälle. 41.4% blev ej gallblåseopererade inom två år efter det första akuta vårdtillfället. Dödligheten inom 90 dagar efter första vårdvistelse för akut gallblåsesjukdom var drygt 3 gånger högre än för normalbefolkningen(SMR) och ändrades inte under den studerade tiden. Beträffande SMR förelåg heller ingen skillnad mellan olika åldergrupper.

Sammanfattning

Under den studerade perioden förbättrades behandlingen av akut inflammation i bukspottkörteln. Då det gäller orsaksklassifikation av bukspottkörtelinflammation, och då det gäller operation med tidigt avlägsnande av gallblåsan vid mild gallstensutlöst bukspottkörtel inflammation, nåddes inte de mål som anges i accepterade riktlinjer. Antalet ingrepp på djupa gallgången ökade klart under den studerade tidsperioden. Avlägsnande av stenar i djupa gallgången görs nu stor utsträckning vid ett annat tillfälle än vid bortagandet av gallblåsan. En tredjedel av alla patienter med akut gallblåsesjukdom fick gallblåsan bortopererad vid första vårdtillfället.

Det finns utrymme för förbättringar i handläggningen av akut gallblåsesjukdom, och kirurger behöver fortfarande goda kunskaper i öppen gallstenskirurgi.

Introduction

Since 1970s important changes have taken place in the management of gallstone disease. With the introduction of endoscopy, initially by means of fiberoptics and later with the computer-chip video technique(1), new possibilities for therapeutic measures were realised. Among these were sphincterotomy of the papilla of Vater and gallstone extraction from the biliary tract(2, 3). The computer-chip camera technique was also crucial for the success of laparoscopic surgery(4), where cholecystectomy became a model operation with a very fast implementation from its introduction at the end of the 1980s(5). A third important factor in the treatment of gallstone disease is the development of new diagnostic tools such as ultrasound investigation, computerised tomography, and later magnetic resonance imaging(6). These technical advantages all have to be scrutinised through evidence based medicine (EBM)(7), in which evidence, applicable to your own setting, is searched for and evaluated. The next step in EBM is the assessment of the outcome of different treatment methods. The modern computer technology is important in seeking and evaluating evidence, and it is also an invaluable tool in building registers and data for analyses. Register data cannot produce cause and effect results like prospective randomised controlled trials, but they may tell us about the overall results of our efforts.

Background

Historical notes

The disease

The oldest gallstone known was found in a 4000 thousand year old tomb on Gotland in Sweden(8). The most famous gallstone so far was from one thousand years later and found in an Egyptian mummy, a priestess from the 21st Dynasty(9). It was destroyed in a bombing raid over London during the Second World War.

The knowledge of gallstones and their connection to different disease manifestations evolved slowly. One important occurrence was the first autopsy in Bologna in 1281(10), performed in the beginning of an era lasting for several centuries, during which new knowledge of human anatomy and pathology evolved in northern Italy with Padua as a centre. In the 16th century, still in northern Italy the connection between gallstones and possible diseases was described in works by Andreas Vesalius, Gabriele Fallopio, and Jean Fernelius, among others(9).

By the 18th century physicians knew that gallstones caused abdominal pain and jaundice(10). An efficient treatment was still missing though, and this state of affairs continued until the end of the 19th century.

The diagnosis

The diagnosis of the gallstone disease was essentially a clinical evaluation of suspected symptoms or complications, until the peroral cholecystography was invented by Graham and Cole in 1924(11). Peroral cholecystography became available in Sweden during the 1930s, but was used in greater scale at the end of the 1940s(12). It remained the main diagnostic tool for gallstone disease until the introduction of transabdominal ultrasonography, which evolved during the 1970s, as an efficient method for the diagnosis of gallstones and acute cholecystitis(13).

Many methods for the diagnosis of gallstones and the diseases of the biliary tract were introduced. Mirizzi initiated peroperative cholangiography in 1931(14). A new contrast agent for intravenous investigation with few side effects of bile ducts and gallbladder, in combination with tomography, was introduced in 1953. Percutaneous transhepatic cholangiography (PTC) was developed with giving many therapeutic possibilities(10). Scintigraphic methods introduced in 1952, are still used as an alternative investigation in acute cholecystitis, and for examination of gallbladder motility(15, 16). MR

(magnetic resonance tomography) and endoscopic ultrasound have added new possibilities in diagnosing biliary diseases, and have substantially improved visualisation of disease processes in the biliary ducts(6). Endoscopic retrograde choledocho-pancreaticography (ERCP) will be discussed later.

The treatment

The first cholecystectomy by Carl Langenbuch in 1882 was not the first operation on the gallbladder. It was preceded by a few cholecystotomies, the first of which being credited to John S. Bobbs of Indianapolis, Indiana in 1867. The next published cholecystostomy by J Marion Sims took place 1878 and in one account Langenbuchs cholecystectomy is said to be the 6th gallbladder operation after Bobbs´s(17). The first cholecystectomy was received with hesitation and its victory was by no means immediate. The famous British surgeon Lawson Tait, himself a proponent of cholecystostomy, labelled Langenbuchs operation ”absurd” in commenting it in the British Medical Journal(18). By 1890 close to fifty cholecystectomies had been done, half of them by Langenbuch himself(19). In 1886 in Sweden according to ”the humble report of the royal medical board”, 16 gallbladder operations were performed, 14 cholecystostomies and 4 cholecystectomies, with two deaths among the former(20). There was a vivid discussion among surgeons of the relative merits of cholecystectomy and cholecystostomy(21). After 1915 cholecystectomy was considered the best operation in the US(17). During the 1920s case series with biliary surgery were presented with mortality rates of 6-10%, and the on-going debate between internists and surgeons when to operate patients with gallstone disease was understandable(8).

Cholecystectomy incidence in Sweden was low until 1930. It started to increase during the 1930s, to reach an incidence of 100/100 000 inhabitants/year in Stockholm and Jönköping counties. A sharp rise is observed in the end of the 1940s to well over 300/100 000/year for men and over 600/100 000/year for women between 1964 and 1970. After this the incidence declined to around 100/100 000/year 1990(22, 23). The variation was also wide between different Swedish counties(22). These variations in cholecystectomy incidence cannot be explained by variations in gallstone prevalence, but rather to variations in surgical resources and indications. A Scandinavian study showed a median cholecystectomy rate for 1989 to 1995 of 62.3 per 100 000 inhabitants in Norway, 68.2 in Denmark, 121.7 in Sweden, and 142.0 in Finland. Differences in patient selection is the most obvious explanation for this variation(24)

Epidemiology of gallstone disease

Prevalence

Ultrasound screening for gallstones in the gallbladder is an excellent tool to study the prevalence of gallstone disease. It is fast, painless, non-invasive, reliable and thus suitable for population investigations, and can be repeated to study incidence. Many of these investigations have been made in western Europe with prevalence findings of 10-20%(25). There are marked gender and age differences. Prevalence in the Stockholm area for gallstone disease were 11% for 40 year old women, 4% for 40 year old men, 24% for 60 year old women and 15% for 60 year old men in 1992(26). In Gothenburg during the same period the prevalence for gallstone disease was 51% for 77-78 year old women(27). Ultrasound surveys disclosed gallstone disease prevalence in middle aged women in Malmö to 22%(28), 30% in middle aged men and women in Linköping(29), and to 22% in all ages in Norway(30). This age and gender difference prevails around the world, but the total prevalence is below 5% in China, Japan and Thailand and parts of Africa(25). The other extreme of prevalences are the North American Indians where the Pima Indians in Arizona had a prevalence of 73% in females over the age of 30(31)

Prevalence data over longer time periods have to rely on necropsy studies, and there are inherent weaknesses in these, as selection bias and lack of standardisation with reference to then contemporary population. In a Danish study the prevalence of gallstone disease increased from 1914 till 1960 after which there was a moderate decrease. Comparing five necropsy studies, Persson(22) identified a rise between 1929 and 1969, and a possible turning point among women younger than 50 years between 1943 and 1961. But data from later years concerning possible prevalence changes in the western world are sparse, but a Scottish necropsy study found an increased prevalence in Dundee 1974-1998, compared to 1953-1973(32).

Incidence

Incidence data are scarce, but a few ultrasound surveys in Europe (Italy and Scandinavia) demonstrate an overall gallstone incidence of 0.34-0.97% per year, with a markedly higher incidence in older age groups(33) One of these studies also showed that gallstones may disappear (4.5% in 5 years between two surveys), by dissolution or/and spontaneous passage(34). Recent surveys from Italy and Sweden have observed incidence rates of 0.67% and 1.37%, respectively(35, 36)

Pathogenesis

Over 70% of gallstone carriers in the western world have stones of the cholesterol variety, whereas 2-30% carries black pigment stones(37, 38). Both gallstone varieties are formed in the gallbladder. Cholesterol is kept in a soluble state by forming micelles with bile salts and phosphatidylcholine. Cholesterol stones form when the cholesterol concentration is too high or to low with respect to bile salts and phosphatidylcholine. Decreased gallbladder motility has a role in gallstone formation(39). The main component of black pigment stones is calcium bilirubinate, and their formation is depending upon the biliary excretion of bilirubin. Bilirubin excretion is much increased in haemolytic diseases like hereditary spherocytosis and sickle cell anaemia but it also depends on the entero-hepatic cycling of bilirubin, which can be disturbed in other ways. Brown pigment stones consist of calcium salts of unconjugated bilirubin and varying amounts of cholesterol and protein. They are formed primarily in the bile ducts and are related to bacterial infection or parasite infestation in the biliary tract(39).

Risk factors

Age**:** Gallstones are rare in young children, but when present are associated with black pigment stones and haemolytic diseases. All prevalence studies demonstrate a steady increase in the ultrasonic presence of gallstones (or previous cholecystectomy) with age; well over 50% in women older than 80 years(25, 33, 40).

Gender: The gallstone prevalence in women is almost double the prevalence in men. The difference is more pronounced in younger ages and diminishes after 50 years of age (after menopause). This gender difference is commonly explained as mediated by female sex hormones. Child birth, oral contraceptives and oestrogen therapy increase the risk for gallstone disease according so some authors(41, 42), but this has been questioned by others(36)

Obesity**:** Several studies identify an increased risk for gallstone disease with high BMI, and the risk is enhanced for women(26, 43-47). One study found increased prevalence in obese children(48). In some ultrasound surveys no connection between BMI and gallstone prevalence was found(26, 29). Rapid weight loss, caused by dietary means or by surgery is associated with the development of gallstones(26, 47, 49)

Genetics**:** Familial and epidemiological studies indicate a genetic susceptibility in the formation of gallstones(38). The high prevalence of gallstones in native Indians in America might relate to genetic traits(25).

According to one model using the Swedish twin-register, genetic effects accounted for 25%, shared environmental effects for 13% and unique environmental effects for 62% of the phenotypic variance among twins(50).

Other**:** Physical activity may help prevent cholecystolithiasis; reduced activity increases the risk(51). The risk connected to diet, metabolic syndrome, smoking, and socio-economic status is unclear(52)

Medical treatment and extracorporeal shockwave lithotripsy as alternatives to surgery

The so far most promising alternatives to cholecystectomy as treatment for gallstone disease have been oral dissolution therapy with bile salts and extracorporeal shockwave lithotripsy (ESWL).

Perorally given bile salt therapy was introduced during the 1970s. Ursodeoxycholic acid (UDCA), with fewer side effects than earlier alternatives, is suitable for only a minority of patients with non-calcified gallstones of the cholesterol variety. The cystic duct must be open and a typical success rate with treatment is 30%. Gallstones frequently recur after oral bile salts are stopped and the medication is expensive(53).

ESWL was tried during the 1980s, and like dissolution therapy, ESWL has important limitations. It can only be performed in patients with functioning gallbladders and with small numbers of stones(53) Less than 30% of referred patients have been found suitable for lithotripsy(54, 55). Two RCTs comparing ESWL and cholecystectomy concluded that the latter is preferable for symptom relief(56, 57)

Endoscopic sphincterotomy

Introduced in the 1960s and widely dispersed during the 1970s gastrointestinal, fiberendoscopy was found a tangible diagnostic improvement(1). First as gastroscopy, then as colonoscopy and endoscopic retrograde cholangio-pancreaticography (ERCP). ERCP was initially a diagnostic tool, but already 1974 endoscopic sphincterotomy and extraction of stones from the common bile duct was described(2, 3). This invention also met a need of handling retained stones after open choledochotomy as an alternative to stone retrieval from T-drain fistula or laparotomy for re-exploration of the common bile duct. Endoscopic sphincterotomy (ES) was used for primary treatment of common bile duct stones (CBDS) initially in

old and fragile patients(58). ERCP with sphincterotomy using fiberoptic instrument is a demanding procedure, and was introduced at clinics with a special interest. In 1980 there were 293 and in 1981 406 ES performed in Sweden(59). The invention of the computer chip camera and other instrument improvements contributed to the increasing use of ERCP and ES. When laparoscopic cholecystectomy entered the scene in the 1990s, ERCP/ES became a convenient tool in handling CBDS in connection with laparoscopic gallbladder surgery.

The initial hopes of ERCP and ES, as a complication free investigation and treatment for common bile duct disease have not been fulfilled. ERCP as a primary investigation method is not recommended. Not only is it resource demanding, but also connected with serious complications(6, 60). As an alternative balloon dilatation of the sphincter of Oddi before stone extraction has been tried. In a meta-analysis of 8 RCTs endoscopic balloon dilatation has a similar rate of complication compared to ES(61), but an increased risk of postprodecure pancreatitis, and inferior stone clearance with balloon dilatation was found in a later trial(62). Endoscopic lithotripsy by laser and electro hydraulic methods are advanced techniques that can be used with difficult stones(63). ESWL is also used in problematic bile duct stones(64). Endoprosthesis as a permanent treatment should be reserved for patients with severe co-morbidity as the complication rate is high, including biliary related mortality(65).

Complications in connection with ERCP and ES are mainly post-ERCP pancreatitis, gastrointestinal haemorrhage, cholangitis, duodenal perforation and cardio-pulmonary complications. The risk for complication after ERCP varies widely with indications for the procedure, and is raised after concomitant ES(66, 67). However, the effect of ES on mortality has been questioned in a recent study by Strömberg(68). In a compilation of observational studies and RCTs Tranter found ES to be associated with a morbidity of 2-24% and mortality of 0-6%(69).

The introduction of small incision cholecystectomy

Traditional open cholecystectomy techniques were refined during 1970s to diminish postoperative pain, shorten convalescence, and improve cosmetic results(70, 71). The initial rationale of small incision cholecystectomy (SIC) was to use a small muscle sparing incision located over the junction of the cystic duct and common bile duct. With the help of headlights, magnification loops and suitable retractors the operator has complete visual control of the dissection. If not, an extension of the incision is made(72). During the 1980s several series with small incision cholecystectomies were reported(73-78),

and the following years, a number of RCTs compared SIC with both regular open and laparoscopic cholecystectomy. In 2010 a summary of earlier Cochrane reviews comparing SIC and standard cholecystectomy concluded that there were shorter hospital stays for SIC, no other differences. This was based on 7 trials and 571 patients. In 13 RCTs comprising 2 337 patients comparing SIC with laparoscopic cholecystectomy no differences were found other than shorter operation time for SIC, which also seemed as a less costly alternative(79). The quick recovery and short convalescence associated with SIC made it appropriate for day surgery(76, 80).

The introduction of laparoscopic cholecystectomy

The history of laparoscopy traces back to the beginning of the 20th century(81). Not until laparoscopy and laparoscopic surgery were pioneered by gynaecologists during 1960s and 1970s with automatic insufflation devices and glass-rod optics, and with development of a variety of surgical instruments, there were significant steps taken forward(82). The introduction of video-laparoscopy in the end of the 1980s was instrumental for the development of laparoscopic surgery. Cholecystectomy has many benefits as a model operation for laparoscopy; it is common, standardised, dissection takes place in a limited space, with no suturing and fairly easy to convert to an open operation(83).

Laparoscopic cholecystectomy was introduced very rapidly. In the US there was a 20% increase in total cholecystectomy incidence from 1991 to 1992(5), and a corresponding increase appeared from 1992 to 1993 in Denmark and Sweden(5, 84). Of all cholecystectomies performed, the percentage done laparoscopically changed from 0% to 80% from 1989 to 1992 in the US and from 0% to 80% from 1991 to 1993 in Stockholm. A NIH consensus meeting concluded that laparoscopic cholecystectomy was the preferred method in symptomatic gallbladder disease(85); the advantages compared to standard open cholecystectomy seemed obvious. Some small randomised controlled studies were done initially(86) Later RCTs has confirmed the merits of laparoscopic over conventional open cholecystectomy(79). Like SIC, laparoscopic cholecystectomy is suited for day surgery(87, 88).

Surgical complications

Compilations of observational studies show a wide variation in morbidity and mortality after cholecystectomy. In conventional open cholecystectomy complications vary from 4.1-14.7%, bile duct injury 0.06-0.45% and

mortality 0-1.9%. For laparoscopic cholecystectomy corresponding values are complications 2-10.4%, bile duct injury 0.14-1.09% and mortality 0-0.9%. For small incision cholecystectomy the data for complications are 0-10.5%, bile duct injury 0-0.3% and mortality 0-0.12%. Data are obtained from a review by Keus et al(89), and should be considered as low level evidence.

In a overview of earlier Cochrane reviews, a relatively high level of complications were found for both small-incision and laparoscopic cholecystectomy, up to 17% excluding intraoperative gallbladder perforations(79), but the mortality was low (0-0.2%).

The rate of bile duct injury appeared to increase during the introduction of laparoscopic cholecystectomy (90). The incidence of these lesions have remained at an increased level(91). A register study in Sweden found a small to moderate long-term in risk of reconstructed bile duct injury after the introduction of the laparoscopic cholecystectomy compared to the pre laparoscopic era.(92). The true occurrence of bile duct lesions are higher than observed (0.47% in 2001-06) as the majority of bile duct lesions can be treated with endoscopic methods(93). Bile duct injuries are associated with increased perioperative morbidity and mortality, reduced long-term survival and quality of life(91).

Comparison between endoscopic sphincterotomy and surgical common duct exploration

In a Cochrane report comprising 13 trials and 1351 patients, endoscopic treatment was compared with surgical treatment for CBDS(94). Open surgery produced better initial bile duct clearance (93.3%) compared to ES (80.4%). Open surgery also had fewer additional procedures and required less average number of procedures than ES. There was no difference in morbidity but a tendency for surgery to be associated with less mortality. The comparison of open surgery and ES was commented on as a little out-dated, as most studies were performed around 1990.

Laparoscopic common bile duct exploration (LCBDE) was compared with both pre- and post-operative ES. There was no difference in stone clearance, morbidity, mortality, and duration of procedure. In three studies hospital stay was assessed, and in two of these studies hospital stay was significantly shorter by 3 and 2 ½ days for LCBDE.

There are no RCTs comparing long-term results of surgery and ES for CBDS. There is, however, a concern regarding cholangitis and stone recurrence after ES. Stone recurrence rates range between 6-24% in observational follow-up studies, and this risk is valid even after

cholecystectomy(95). On the other hand, long-term follow-up after LCBDE show few recurrent CBDS or other bile duct related problems(96, 97).

A risk for cancer following ERCP and ES has been discussed(98, 99). A recent Swedish register study showed a three-fold increased risk for cancer in the liver, bile ducts and pancreas after ERCP, which was not further increased after ES(100).

The enigma of symptomatic gallstones

Gallstones without symptoms are with rare exceptions no indication for cholecystectomy, as the incidence of symptom development and gallstone complication is too low to warrant prophylactic cholecystectomy considering the cost and risk for complications by cholecystectomy(89, 101). However, there are still proponents for cholecystectomy of all diagnosed gallstones(102). An exception to the rule of non-intervention for silent gallstones is cholecystectomy in conjunction with other major surgery. No incremental risk was noted in such circumstances(103, 104).

Patients with symptomatic gallstone disease without complications are generally offered cholecystectomy. The main indication is bouts of biliary pain. These are characterised by an intense, persistent pain localised in right hypochondria and epigastrium referred to the back in 60% of the patients and retrosternal in a few percent. The duration is more than half an hour, and lasts up to six hours, seldom longer. The pain attacks are mostly occurring during late evening and early night, and in 70% combined with an urge to walk around(105, 106). The attack of bile pain is accompanied by symptoms of dyspepsia, gastroesophageal reflux and irritable bowel syndrome(106). There is some connection with food intake(105). Biliary colic is a misnomer as the pain is intense but even.

However, the presence of gallstone symptoms is not clear-cut and the prevalence of abdominal symptoms in a western world population is high. In a Danish randomised population sample in the ages 30-60 years the prevalence of various abdominal symptoms during one year was 30-50%(107). The predictive power of no abdominal pain or discomfort was 93.2-94.2% for absence of gallstones, but it was concluded that in a random population, it is difficult to define the symptoms specific for gallstones(108). Some Scandinavian studies found no correlation between symptoms and presence of gallstones(29, 109). In a meta-analysis by Berger(110) of 24 studies of abdominal symptoms, ”steady right upper quadrant abdominal pain lasting for more than one hour”, ”radiating pain”, and ”analgesic used” were the only symptoms consistently related to gallstones, but with a low

diagnostic accuracy. However, in this analysis biliary pain occurred in 20% of the patients with gallstones and in 6% of those without gallstones.

If strict criteria for cholecystectomy, i. e. typical symptoms of biliary pain, is applied, after 12 months 91.3% had total remission or reduction of preoperative pain compared to 77% reduction or disappearance of preoperative pain for patients with atypical symptoms (111). But in another study on patients in the care of general practitioners the correlation between preoperative symptoms, cholecystectomy and post-operative results were more complex. Patients with biliary pain, gallstones and cholecystectomy, patients with biliary pain and gallstones and no cholecystectomy, and patients with biliary pain and no gallstones were compared. The improvement of biliary pain was similar in the three groups(112).

Complicated gallstone disease

Acute pancreatitis is not per se a complicated gallstone disease, but gallstone disease is the most common form of the disease. Our interest was wider than just biliary pancreatitis as we had the possibility throw light on some questions connected with acute pancreatitis.

Acute pancreatitis

Population based studies indicate a rising incidence of acute pancreatitis(113). There is a marked difference between different European countries, with a low incidence in UK and Holland, around 10/100 000 inhabitants, compared to the rest of Europe and the US (113, 114), where it is around 30/100 000. In Japan a hospital survey arrived at an incidence of 12.1 to 14.4/100 000 inhabitants/year from 1987 to 1998(115)

The mechanism behind acute pancreatitis is not fully known, but premature activation of trypsin within the pancreatic acinar cells is a key event(116). Transient blockage of the pancreatic duct by passing gallstones from common bile duct increases the pressure in pancreatic ducts and activates pancreatic enzymes within acinar cells. This leads to autodigestion of pancreatic tissue and ensuing inflammation(117). Present theories of alcohol pancreatitis emphasise direct toxic effects of ethanol and its metabolites on the pancreatic acinar cells leading to autodigestive injury and ensuing inflammation(117). Drugs, viruses, hypercalcemia, hyperlipidemia, ERCP and surgery are more uncommon causes of acute pancreatitis. There is a remaining group of pancreatitis patients without known aetiology, some of which may have the above mentioned but undiscovered aetiology, whereas others may have a genetic background.

In 10-20% of the patients the pancreatic inflammation evolves to a more serious condition, termed systemic inflammatory response syndrome (SIRS), predisposing to multi-organ dysfunction and pancreatic necrosis. It is important to predict the degree of severity early in the course of the disease in order to give early and intense resuscitation of severe cases(118)

The mortality as case fatality rate in acute pancreatitis (without differentiation between the first or recurrent attacks) varied from 2.1 – 9.2% in 12 studies, the highest rate in the oldest studies. There was a tendency towards decreasing mortality over time(115). In severe pancreatitis the case fatality rate is considerably higher, 22-38%, according to one review(115)

Initially the treatment of acute pancreatitis is supportive, correcting fluid-electrolyte imbalances, and relieving pain. An aetiologic diagnosis should be made, risk factors should be evaluated, and a severity stratification should be made within 48 hours from diagnosis(119).

All patients with biliary pancreatitis should undergo definitive treatment of gallstones during the same hospital admission if possible, otherwise a planned definitive treatment within two weeks. Definitive treatment is cholecystectomy if there is no serious contraindication(116, 119-121).

Common bile duct stones

The prevalence of CBDS is not possible to define in any population-based investigation, but it is estimated to 10-15% of gallstone patients scheduled for surgery(122, 123). In patients with lower age, no history of jaundice and no dilatation of the biliary tree the risk for CBDS is lower, close to 5%(124).

The two common varieties of CBDS, cholesterol and black pigment stones, are formed in the gallbladder before they enter the common bile duct through the cystic duct. Brown pigment stones, uncommon in the western world, are formed in the biliary ducts. They are related to infection and biliary stasis, and can be a problem as recurrent biliary duct stones(95, 98).

In the common bile duct gallstones can be silent or cause symptoms in different ways. Bile duct stones considered asymptomatic are discovered in connection with cholecystectomy(125).

Biliary pain can be induced by intermittent CBD obstruction. The character of the pain is very similar to the pain described as caused by gallbladder stones.

Varying degrees of obstructive jaundice ensues after impaction of CBDS in the bile duct, the degree depending on the completeness of obstruction. Lasting cholestasis must be treated without undue delay, as the risk for complication is high.

Cholestasis in combination with bacteria causes cholangitis, which quickly can develop into a life threatening septic state. The mortality is still high with a case fatality rate of 10-30%(126).

Acute biliary pancreatitis is caused by gallstone migration to and through the papilla of Vater. Smaller CBDS and gallbladder stones have been associated with an enhanced risk for acute pancreatitis(127).

The diagnosis of CBDS

Transabdominal ultrasound is valuable as a first investigation for suspected CBDS. It has a high sensitivity for gallbladder stones and likewise for detecting intrahepatic and extrahepatic dilatation of bile ducts. The sensitivity of transabdominal ultrasound to detect CBDS is 10-63% compared to endoscopic ultrasound and ERCP(128, 129). But looking for CBDS with transabdominal ultrasound is useful as the specificity is high(128).

Computerised tomography (CT) is a readily available radiological investigation, which can diagnose other reasons for cholestasis than CBDS. Infusion helical CT can have a sensitivity and specificity similar to magnetic resonance imaging (MR)(130, 131).

Considering MR recent UK guidelines for CBDS concluded that MR is likely almost as good as ERCP in diagnosing CBDS, although its ability to consistently detect stones of a few millimetre in diameter has yet to be demonstrated(6)

Endoscopic ultrasound (EUS) , a duodenoscope with a built-in ultrasound probe, has a limited use in Sweden although the technique has been available for two decades. EUS has sensitivity and specificity comparable to ERCP of detecting CBDS (132, 133).

Surgical treatment open surgery

Before the days of endoscopic sphincterotomy and laparoscopy there was only one way to initially treat CBDS. It was through open choledocholithectomy in combination with cholecystectomy. CBDS were often detected by intraoperative cholangiography, and the patient had a one stage complete treatment of the gallstone disease. The common bile duct explorations were mostly done blindly with the help of malleable instruments. This involved a risk of injury to the sphincter Oddi with ensuing bleeding or oedema, and sometimes penetration of the bile duct and making of a fistula to the duodenum. But many surgeons of that time were skilful in extricating gallstones of varying sizes. Sometimes a rigid right angle choledochoscope was used. A cholangiogram through a T-drain was repeated until no stones could be seen, and the operation was ended. Now and then an open papillotomy was necessary to deal with a stone jammed in the papilla of Vater. In the 1990s with decreasing experience with open choledochotomy complications increased markedly(134). The development

of open surgical choledochotomy halted in front of endoscopic sphincterotomy and laparoscopic bile duct exploration, but it has been shown that SIC with primary suture of the common bile duct and accompanying short hospital stay is possible and a cost-effective alternative(135)

Surgical treatment, laparoscopic surgery

When an intraoperative cholangiography finds contrast lacunae the laparoscopic surgeon has to decide first whether they are caused by CBDS, and secondly if the proposed stones are likely to pass spontaneously to the duodenum. An interesting study was made by Collins et al(136), who placed a remaining thin catheter in the cystic duct if CBDS were suspected or found during laparoscopic cholecystectomy. New cholangiographies were made two days and six weeks after operation. After 6 weeks 22 of initial 46 suspected CBDS were left and treated by ES. Size or number did not predict stone passage. If there are narrow bile ducts, no earlier obvious symptom, and small stones some surgeons leave them for spontaneous passage, but evidence for this policy is scanty. If LCBDE is decided upon, there are two alternatives, a transcystic exploration or a choledochotomy(137, 138). There is a greater risk for complications after choledochotomy, some of them T-tube related (139, 140). Primary closure of CBD seems to have fewer complications than closure over T-tube(139-141), but in a Cochrane review on only one RCT Gurusamy(142) found that no conclusion can be made.

Endoscopic treatment

ES is today the preferred treatment for CBDS(6). ES is an attractive method as it involves no abdominal wall incisions.

ERCP/ES is widely available in Sweden. As in many invasive interventions the success and quality of the procedure is operator dependent. An endoscopist is proposed to do 40-50 ERCP a year to maintain good ability(6). In some circumstances it is not technically possible to do ES, as after certain bariatric surgery procedures, some gastric operations or when anatomy otherwise precludes cannulation of the papilla.

Acute cholecystitis

Acute cholecystitis is the most common gallstone complication, and the risk for mildly symptomatic gallstone patients is estimated to 10 % in long-term follow up studies(143), with a yearly incidence of 1-3% being highest the first years after diagnosis(126, 143, 144).

The main event in acute cholecystitis is the impaction of a gallbladder stone in the cystic duct. In the beginning as an attack of biliary pain, but after continuous impaction and increased intraluminal pressure, together with cholesterol supersaturated bile an initially sterile inflammation occurs(145). The inflammatory response is mediated by prostaglandins I_2 and E_2. Later on secondary bacterial infection in the gallbladder may supervene in 20-60% of patients(146, 147). In around 5% there is an acalculous cholecystitis, and the pathogenic mechanism is supposedly related to an impaired emptying of the gallbladder. This is the case in intensive care patients and in-patients on total parenteral nutrition.

The inflammatory process in acute cholecystitis may progress to gangrene in the wall of the gallbladder and perforation. The perforation may be walled off by adjacent organs like the colon and omentum majus or became a more generalised peritonitis.

The acutely inflamed gallbladder with localised gangrene may adhere to and perforate to the gastrointestinal tract, most commonly to the duodenum and the hepatic flexure of the colon. A fistula to duodenum and a large enough gallstone is the prerequisite of gallstone small bowel obstruction(148).

Clinically there is pain in the right upper quadrant with local tenderness, often fever, leucocytosis and increased CRP from the inflamed gallbladder. The pain continues for a longer time than an attack of biliary pain, and the patients' general condition may deteriorate to a varying degree.

The diagnosis of acute cholecystitis is based on the clinical picture, and elevated inflammatory laboratory tests. In some patients an elevation of liver enzymes and bilirubin takes place. A marked obstructive jaundice can be seen if there is a Mirizzi syndrome, which consists of a stone impacted in the gallbladder neck compressing the common bile duct. The inflammation around the impacted stone may cause destruction of the common bile duct to a varying degree(149).

Acute cholecystitis is recognised as an indication for cholecystectomy, if the patient has an acceptable general health(150, 151). Cholecystectomy will relieve the patient from symptoms, prevent progression with complications and prevent recurrence. Initially conservative supportive therapy can be an alternative therapy. In patients judged to be at high surgical risk and or critically ill, percutaneous drainage of the gallbladder can improve their condition. In a review successful gallbladder drainage was seen in 85% of patients with acute cholecystitis(152). However, no RCTs comparing cholecystectomy and percutaneous gallbladder drainage have yet been performed(153).

The timing of the cholecystectomy in acute cholecystitis has been a controversy, as it was noted that emergency cholecystectomy is a more technically demanding operation. With elapsing time, the acute

inflammatory reaction will subside, although cholecystectomy still at this point is more difficult than elective cholecystectomy for biliary pain. This principle was questioned, and beginning in Scandinavia, the need for RCTs was realised; the first RCT was performed already in 1970(154-156). In the beginning of the laparoscopic era acute cholecystitis was considered a contraindication for laparoscopic cholecystectomy(157, 158), but with increasing experience new RCT showed the efficacy of early laparoscopic cholecystectomy for acute cholecystitis. A recent meta-analysis of early vs. delayed cholecystectomy for acute cholecystitis included five trials and 451 patients and concluded there was no difference in complication and conversion rates, but four days less total hospital stay and 17.5% acute re-admissions before planned cholecystectomy in the delayed group(159). One trial showed a benefit for early cholecystectomy within 48 hours(160).

Today´s treatment vs. guidelines. Need for epidemiological data

Best medical evidence as presented in systematic reviews, guidelines and reviews has to be seen both in a cost-utility context and in the context of everyday clinical reality. Resources are limited. The introduction of new treatment options requires not only committed doctors, but also monetary investments in equipment, training programs and organisational changes.

Epidemiological studies may be used to evaluate suggested improvements by comparing outcomes of these new options with other outcomes reached by previous treatment strategies. In this process unexpected findings in the short and in the long-term effects can be noticed.

Present surgical guidelines

The following examples are given in an attempt to illustrate the type of knowledge that is readily available to the busy clinician.

Asymptomatic gallstones: No explicit guidelines, no meta-analyses(161), but frequent statements in reviews, that cholecystolithiasis with vague symptoms and absence of biliary pain attacks is not an indication for cholecystectomy(5, 101, 102)

Symptomatic gallstones: No guidelines, but cholecystectomy is recommended. Some authors advocate no unnecessary delay if symptomatic gallstone disease is present to prevent complications(127, 162). Others think that watchful waiting in patients with mild symptoms can be appropriate, especially if no history of complicated gallstone disease is presented, and no

information regarding specificity, frequency, and intensity of symptoms is available(144, 163, 164).

Acute cholecystitis: Meta-analyses(159, 165), Japan- Tokyo guidelines for the management of acute cholangitis and cholecystitis(166). It is concluded Cholecystectomy at first admission is safe and cost-effective.

Common bile duct stones: Meta-analyses(94, 167). UK guidelines. ES is the usual treatment, and LCBDE is fully comparable. Cholecystectomy is recommended in connection with bile duct clearance.

Acute pancreatitis: Sweden-Läkartidningen 2000(120), Europe-IAP Guidelines for the Surgical Management of Acute Pancreatitis 2002(168), UK-British Society of Gastroenterology: UK guidelines for the management of acute pancreatitis 2005(119), USA- American College of Gastroenterology: Practice guidelines in Acute Pancreatitis 2006(116), Japan JPN guidelines for the management of acute pancreatitis 2010(169).

Early diagnosis of severity and aetiology, conservative attitude to surgical revision and early treatment of gallstone disease are recurrent recommendations.

Aims

General aims

To analyse outcomes of gallstone treatment in Sweden during a period when open surgery was replaced by endoscopic and laparoscopic procedures to a great extent.

Specific aims

The hypothesis is that new innovative technology has improved the possibilities to adhere to existent guidelines, made it possible to shorten hospital stay, decreased the need for re-admittance for additional procedures, and reduced mortality in complicated gallstone disease. Four areas have been investigated:

1. First attack of acute pancreatitis (FAAP)
2. Mild acute biliary pancreatitis (MABP)
3. Common bile duct stones (CBDS)
4. Acute gallbladder disease including acute cholecystitis

Materials and methods

In Sweden patients can be identified through a personal registration number unique for each resident. The Swedish National Board of Health and Welfare's Epidemiology Centre compiles data on individual hospital discharges in the National Patient Register (NPR)(20). Since 1987 NPR includes all in-patient care in Sweden.

The NPR data consist of:

1. Patient data: personal registration number, sex age, and place of residence
2. Geographical data: county council, hospital/clinic and department
3. Administrative data: date of admission, date of discharge, length of stay, acute/planned admission, admitted from and discharged to
4. Medical data: main diagnosis, secondary diagnosis, external cause of injury and poisoning, procedures

The diagnoses at discharge are coded according to the Swedish version of the International Classification of Diseases (ICD), from 1987 through 1996 the 9th revision and from 1997 the 10th revision. Surgical procedures are classified according to the Swedish version of Classification of Operations 1985 (revised 1988) and Classification of Surgical procedures 1997.

Dates of death and underlying causes of death were obtained for all patients from Death Certificates, which have to be written for each patient after death in Sweden, and are also coded by the ICD-9 and ICD-10 classifications.

To strengthen patient anonymity during analysis the personal registration numbers were replaced by serial numbers.

First attack of acute pancreatitis

Patients

Data from NPR were retrieved for all patients with an in-hospital admission from January 1st 1987 through December 31st 2003 for acute pancreatitis (577A in ICD-9 or K85 in ICD-10) called the AP base material. Information on hospital admissions and procedures one year prior to and one year after first admission were collected for all patients. As in all studies in this thesis, patients with a concurrent diagnosis of malignancy in the stomach, liver, biliary ducts, and pancreas were excluded.

Definitions and study design

First attack acute pancreatitis (FAAP) is defined as acute pancreatitis, without hospital stay with this diagnosis during a minimum of one-year preceding index admission. The aetiological diagnosis of FAAP refers to primary or secondary diagnoses during index admission classified as biliary disease, alcohol-related disease or other diagnoses. Relevant ICD codes in addition to K85 and 577A used for aetiological classification of causes of death are given below.

Biliary disease:
ICD-10: K80, K81, K82, K83, ICD-9: 574, 575, 576
Gallstone disease:
ICD-10: K80, ICD-9: 574
Alcohol-related disease:
ICD-10: K70.0, K70.2-4, K70.9, F9.0-9, F10.0-9, G31.2, T54.0, and Z72.1
ICD-9: 571A-D, 571F, 572W, 291a-F, 291W, 291X, 304H, 305N, 305X, 303, 980O.

Procedures were classified as biliary procedures or operations on pancreas (codes introduced 1997 with capital letters)

Biliary procedures:
Open cholecystectomy JKA20, 5350, -51, -52, -56, -57, -59
Laparoscopic cholecystectomy JKA21, 5353
Common bile duct exploration JKB00, JKB01, 5300, -02, -04, -06, -09, 5351, -52, -56, -57
Operations on pancreas:
Exploration, biopsy of pancreas JLA, 5580, -81
Incision, drainage of pancreas JLB, 5500, -02, 0061, -66
Resection of pancreas JLC, 5510, -11, -12, -14, -15, -16
Other operations on pancreas, open or laparoscopic JLW, 5520, -21, -5590, -91, -92,-93, 5599

Mortality was calculated both as case fatality rate (CFR), i.e. deaths per 1000 patients, and as standardised mortality ratio (SMR). Mortality was determined for 0-90 days and 91-365 days after the 1st day of index admission. The time of the audit was divided into three time periods to study time trends.

Mild acute biliary pancreatitis

Patients

Data were retrieved from NPR concerning all patients with hospital admission for acute pancreatitis (ICD-9: 577A, ICD-10: K85) and biliary disease (ICD-9: 574, 575, 576; ICD-10: K80-83) from January 1st 1987 through December 31st 2004, called the AP base material. Patients from 2004 were included in the analysis as a one-year follow up was intended.

Data from death certificates were also retrieved for patients included in the study.

Definitions and study design

First attack of acute biliary pancreatitis was defined such as in study 1, as acute pancreatitis with a synchronous diagnosis of biliary disease.

Study cohort extracted from the AP base material: For this study, mild acute biliary pancreatitis (MABP) was defined as an attack of acute biliary pancreatitis without mortality during an index stay of ten days or shorter.

Our cohort of patients with MABP was subdivided into 4 groups corresponding to different ways of treating the underlying gallstone disease. This was to mirror different degrees of adherence to current guidelines for acute pancreatitis(116, 119, 120, 168). Group 1 had cholecystectomy during index stay. Group 2 had no cholecystectomy during index stay, but within 30 days of index admission (scheduled or unscheduled readmission). Group 3 had endoscopic sphincterotomy (ES) but no cholecystectomy within 30 days of index admission (at index admission or at an early readmission). Patients in group 4 had either cholecystectomy or ES within 30 days of index admission.

Procedure codes used:
Open cholecystectomy: 5350, 5351, 5352, 5356, 5357, 5359, JKA20
Laparoscopic cholecystectomy: 5353, JKA21
Endoscopic sphincterotomy: 5388, 5394, JKE02

The different subgroups in the study cohort were analysed up to one year after index stay concerning initial length of stay, age, re-admissions, rate and time of cholecystectomy. The distribution between groups 1-4 during three time periods was also examined. Mortality was calculated both as CFR and SMR for each group.

Common bile duct stones

Patients

NPR data were retrieved from the 1st January 1988 through the 31st of December 2006 concerning all patients with biliary diagnoses including acute pancreatitis, the CBDS base material. Patients with diagnoses of malignant tumours of the stomach, liver, gallbladder, bile duct or pancreas were excluded from analyses.

Biliary diagnoses:
ICD-9:574, 575, 576. ICD-10: K80, K81, K82, K83 (including all sub-diagnoses specified with third code number)
Acute pancreatitis diagnoses:
ICD-9: 577A, ICD-10: K85
CBDS diagnoses:
ICD-9:574D-E-F, ICD-10: K80.3-4-5

The Following codes were used for identifying different interventions:
Cholecystectomy: 5350-51-52-53-56-57-59. JKA20, JKA21
Endoscopic sphincterotomy: 5388, 539. JKE02
Choledochotomy: 5300-02-04-06-09, 5351-52-56-57. JKB00, JKB01
Transcystic laparoscopic CBD exploration: JKB11

Definitions and study design

The yearly incidence of different biliary interventions in the base material is calculated.
Study cohort extracted from the CBDS base material: Index admission for intervention on the common bile duct is defined as the first hospital stay both with a CBD intervention (choledochotomy, ES or both) and a diagnosis of CBDS. Patients in the cohort had no admissions with these diagnoses during at least one preceding year. Thus, patients with index admissions from the 1st of January 1989 to the 31st of December 2006 and hospital discharge before 31st December 2006 were included in the study cohort and followed with respect to subsequent hospital admissions, and when relevant, date and cause of death. To study time trends within the study cohort we divided the time of audit into three six-year periods.

A comparison between choledochotomy (open or laparoscopic) and endoscopic sphincterotomy in the study cohort was our main interest. The small group of index admissions with both choledochotomy and ES was analysed separately. Transcystic stone extractions, was not included in the study cohort. Patients with choledochotomy or/and ES at index stay were compared regarding age and gender, frequency of cholecystectomy at index

stay, length of index stay, readmission with any biliary diagnosis (including acute pancreatitis), readmission with acute pancreatitis, and readmission with intervention on the CBD.

Mortality within 90 days of index admission was expressed as SMR and CFR. As mortality for patients with gallstone surgery exceeds that of the background population up to 90 days after operation(170), 0-90 days after index admission was considered appropriate for calculating mortality.

Acute gallbladder disease

Patients

For study 4, data from NPR and from death certificates were retrieved for all patients with hospital admission for the main diagnosis cholecystitis or gallbladder stones between January 1st 1990 and December 31st 2004 in Sweden (Primary diagnosis 574 A-E 575 A in ICD-9 and K80.0-80.2, K80.4. and K 81.0 in ICD-10), called the gallbladder disease base material. Patients with a concurrent diagnosis of malignancy in the stomach, liver, gallbladder, biliary ducts and pancreas were omitted.

Definitions and study design

Acute gallbladder disease is defined as acute hospital admission with a primary diagnosis of gallstones in the gallbladder with varying degrees of inflammation. A diagnose of acute acalculous cholecystitis is also included in the definition. We have chosen this definition as the delineation between acute cholecystitis, a prolonged attack of biliary pain, or an on-going subacute cholecystitis not is clear. Preoperative imaging, operative findings and postoperative microscopy can give a picture of a mixture of acute and chronic inflammatory changes(171).

For each year the incidences of hospital admissions for gallbladder disease, as defined above, acute or elective, are calculated. The incidences of cholecystectomy, acute/elective, open/laparoscopic are also calculated, and all incidences are given for 100 000/inhabitants per year, as crude figures. To study changes over time the incidence data are separated into three 5-year time periods: 1990-94, 1995-99, and 2000-04.

Study cohort extracted from the gallbladder disease base material: From the base material we excluded all patients with hospital admission for biliary disease within at least two years before index admission. The study cohort had an emergency admission with the main diagnosis cholecystitis or gallbladder stones between January 1st 1990 and December 31st 2004 in Sweden. Each patient was followed for two years after index admission. The

study cohort was subdivided in 4 groups, A: cholecystectomy at index admission, B: elective re-admission with cholecystectomy, C: acute re-admission with cholecystectomy, D: no cholecystectomy.

These four groups were compared regarding mortality and accumulated hospital stay for biliary diagnoses.

Statistics

Data are presented as means and standard deviations, median values with 25% and 75% percentiles, or proportions. Proportions have been compared using the chi-square test, Poisson-regression test and Fischer exact test when appropriate. Location of two or more groups of ratio scale variables was compared using independent samples t-test or Mann-Whitney U-test. Post hoc tests are done using Bonferroni adjustment of p-values. In study 3 and 4 Cox-regression survival curves are used to illustrate time to recurrent event. Differences between curves were tested using the log-rank test. In study 4 Kaplan-Meier curves were used to show time to cholecystectomy. Mortality within a defined timed period (within 90 days of admission) was calculated as standardised mortality ratio (SMR), using age-, gender-, and calendar year- specific death rates from statistics Sweden(172). Case fatality rate (CFR), i.e. deaths per 100 (or 1000) patients treated is given as comparison.

Calculations were performed with SPSS 15.0 (SPSS Inc. Chicago, IL, USA). A p-value less than 0.05 was considered significant.

Results

A summary of the results for each of the four investigations is presented.

Acute pancreatitis

Incidence

From January 1st 1988 through December 31st 2003, there were 43 415 patients (23 801 men and 19 614 women) admitted for first attack of acute pancreatitis (FAAP) in Sweden. During the studied period the incidence (age and gender adjusted to the Swedish population at 1988-2003) rose modestly but significantly from 27.0/100 000/year for 1988-1992 to 32.0 for 1998-2003. This increase was entirely caused by a rise in incidence for women from 21.1 to 31.0/100 000/year, and most pronounced between the first and second time period (Figure 1).

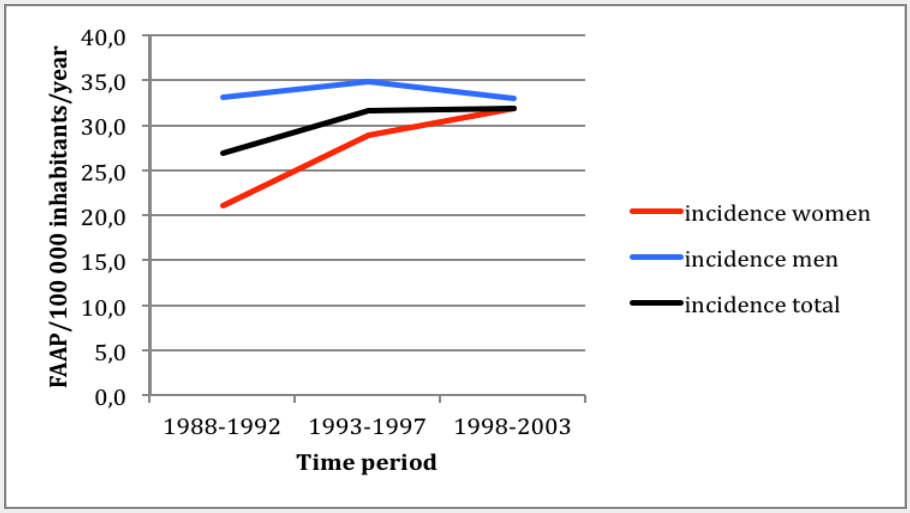


Figure 1. *The incidence of first attack of acute pancreatitis in Sweden in three time periods. The incidence increased significantly (p<0.001) in women and totally.*

The incidence of first attack of acute pancreatitis increases with age, and the age specific incidence also increased from the first time period to the next two periods. This increase was significant for both men and women over the age of 69 years (p<0.001) (Figure 2).

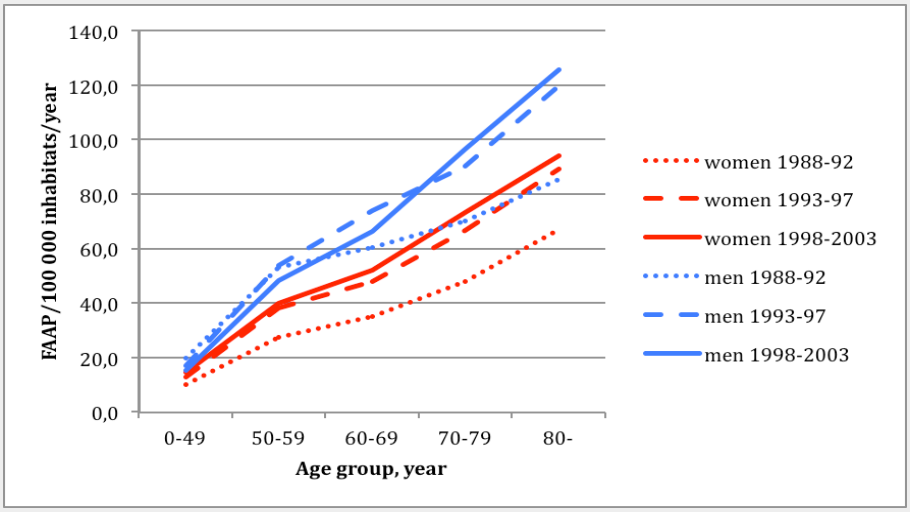


***Figure 2**. Incidence of first attack of acute pancreatitis in age groups in men and women in three time periods.*

Aetiological diagnoses

The etiology of FAAP is based on concurrent diagnosis of biliary or alcohol-related disease. Patients with both alcohol-related and biliary diagnoses (N=51) were included as alcohol-related pancreatitis. Biliary and alcohol-related diagnoses were identified in 26.8% and 4.8%, with a considerable gender difference (Table 1). Aetiological diagnosis was missing in 68.4%.

***Table 1.** Aetiological diagnosis at first attack of acute pancreatitis for men and women from 1988 through 2003.*

Diagnosis	Women	Men	Total
Biliary	35.4 (6943)	19.7 (4693)	26.8 (11636)
Alcohol related	2.1 (410)	7.1 (1691)	4.8 (2101)
Other	62.5 (12261)	73.2 (17417)	68.4 (29678)
Total	100 (19614)	100 (23801)	100 (43415)

Percent at index. Number at index within brackets

Patients with alcohol-related acute pancreatitis were significantly younger than patients with biliary pancreatitis (49 (42-58) years compared to 65 (50-77) years (median, 25-75 percentiles).

Recurrent attacks of acute pancreatitis after FAAP

Out of 43 415 patients, 7 329 (16.9%) had at least one recurrent attack of acute pancreatitis during the first year following index admission, and of these, 1 246 (2.9%) had at least two attacks with the same diagnosis. Recurrent attacks were more common after alcohol-related cause, than biliary FAAP.

Length of hospital stay

During the last time period the length of hospital stay was one day shorter ($p<0.001$), with no difference in gender or time. (Table 2).

Table 2. *Length of index stay for patients with first attack of acute pancreatitis 1988-2003 in different time periods*

Time period	Women, LOS	Men, LOS
1988-1992	7 (4-11)	6 (3-10)
1993-1997	6 (4-10)	6 (3-10)
1998-2003	5 (3-9)	5 (3-9)

LOS = Length of hospital stay in days, median (p25-p75). P<0.001 between time periods.

Interventions

Interventions on patients during and one year after index admission for FAAP are presented in Table 3.

Table 3*. Proportion of interventions in all patients (N= 43415) in time periods during and within one year after index admission for first attack of acute pancreatitis.*

	C		ES		CBDE		P		
Time period	**I**	**A**	**I**	**A**	**I**	**A**	**I**	**A**	**N**
1988-1992	3.6	14.1	1.2	1.5	1.6	3.0	1.2	1.1	11590
1993-1997	4.2	16.4	4.0	2.8	1.1	1.7	1.3	1.1	14126
1998-2003	5.2	20.2	7.7	3.8	1.0	1.6	1.1	2.0	17699
Total									43415

Proportions given as percent. C = cholecystectomy, ES = endoscopic sphincterotomy, CBDE = choledochotomy, P = operation on the pancreas, I = at index admission, A = after index admission.

Of 11 363 patients with biliary diagnoses 6 386 (55.7%) had a cholecystectomy during the first year, which for 1 648 (14.2%) patients was performed during index stay. Cholecystectomy rate increased slightly during and after index admission, throughout the audit period. ES increased

slightly, both during and after the index admission. There was no time trend in pancreatic surgery (drainage, exploration or resection), and it was done on 1 346 of 43 415 patients.

Mortality

The overall mortality expressed as case fatality rate within 90 days from index admission was 7. 1 per cent during the period studied. Compared to background mortality, the 90 days mortality was almost 11.8 (11.34-12.17) times the expected (SMR with 95% CI).

The mortality deceased significantly during the total period, being more pronounced for SMR data, as patients were older during the later time periods. (Table 4).

***Table 4**. Mortality within 90 days for all patients in 3 time periods*

Time period	Patients	Deaths	CFR	SMR
1988-1992	11590	757	8.2	16.82(15.65-18.06)
1993-1997	14126	1252	7.6	12.52(11.84-13.23)
1998-2003	17699	1092	6.2	9.25(87.1-9.82)

CFR = case fatality rate as percent, SMR = standardised mortality ratio with 95 % confidence interval within brackets.

The mortality was correlated to the age of the patient. The risk for dying following an admission for a first attack of acute pancreatitis (FAAP) increased with age. This is illustrated by case fatality figures (CFR). However, compared to the mortality of the background population the mortality risk following an admission for FAAP decreased with age. This is shown in Figure 3 and Table 5.

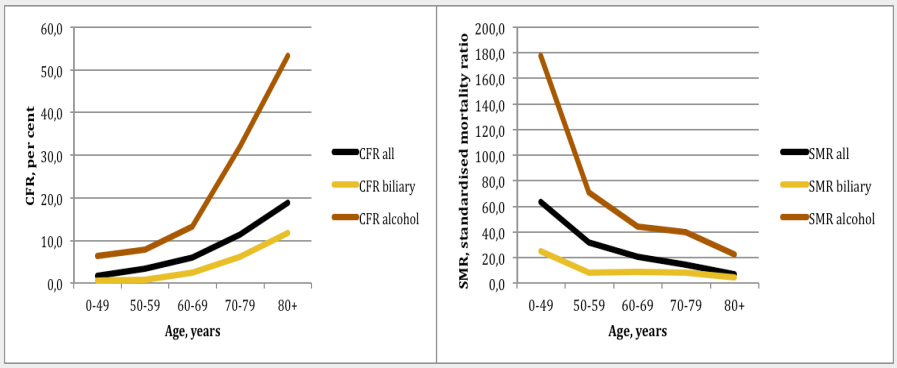


***Figure 3**. Mortality as case fatality rate (CFR) and Standardised Mortality Ratio (SMR) in different age groups and different aetiology in FAAP*

***Table 5**. Mortality 0-90 and 91-365 days at first attack of acute pancreatitis*

Age years	Patients	Deaths	CFR	SMR 0-90 days
0-49	13822	243	1.8	63.51(55.77-72.01)
50-59	7499	257	3.4	31.67(27.91-35.79)
60-69	7449	448	6.0	20.92(19.02-22.95)
70-79	8339	959	11.5	14.60(13.69-15.55)
80-	6306	1194	18.9	7.24(6.84-7.66)
Total	**43415**	**3101**	**7.1**	**11.75(11.34-12.17)**
Age years	**Patients**	**Deaths**	**CFR**	**SMR 91-365 days**
0-49	13579	178	1.3	15.51(13.31-17.96)
50-59	7242	182	2.5	7.48(6.43-8.64)
60-69	7001	276	3,9	4.30(3.80-4.83)
70-79	7380	441	6.0	2.24(2.03-2.46)
80-	5112	527	10.3	1.07(0.98-1.16)
Total	**40314**	**1604**	**4.0**	**2.03(1.93-2.13)**

CFR = case fatality rate in per cent, SMR = standardised mortality ratio, 95% confidence intervals within brackets.

Mild acute biliary pancreatitis

According to our definition 74% of patients with diagnoses concurrent with acute biliary pancreatitis had a mild acute biliary pancreatitis (MABP). Of all MABP patients 61% were women.

The allocation to the different initial treatment groups during the three time periods is presented in Figure 5. All procedures increased over time, especially ES.

Within one year after index admission, 31% of patients with only initial endoscopic sphincterotomy had undergone cholecystectomy, whereas 48% of patients with no initial intervention at index admission were cholecystectomised. All together 56% of the 8 419 in the cohort of MABP, had a definitive treatment for their biliary pancreatitis at one year. The readmission rate for biliary diagnoses (including acute pancreatitis) during the first year for patients with no initial cholecystectomy was high (62.5-76.3%) compared to 5% re-admissions for those with cholecystectomy at index admission.

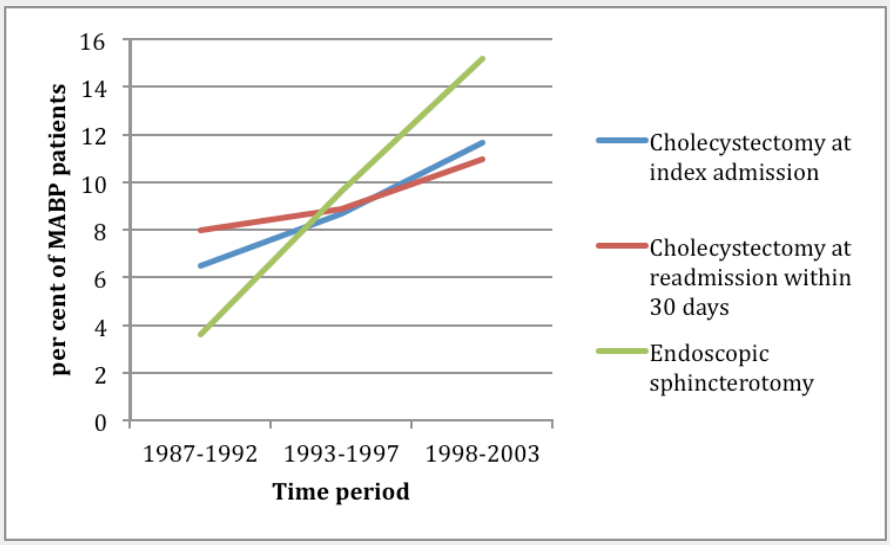


***Figure 5**. Change of procedures within 30 days of index admission over time, in patients with MABP.*

There was no difference in SMR between the treatment groups, and for all patients with MABP the SMR was 1.6 (CI:1.42-1.75). The median age for patients with index stay cholecystectomy was 47 years, compared to 70 years for patients with initial ES.

Common bile duct stones

Interventions during hospital admission for benign biliary disease

Cholecystectomy incidence increased 21% from 1991 to 1993, and it stayed at the same level until 2005. The cholecystectomy technique changed from open to laparoscopic surgery from 1991 to 1993. Laparoscopic cholecystectomy varied between 93.9–85.7/100 000/inhabitants/year in 2000-2006, whereas open cholecystectomy declined to 25.3/100000/inhabitants/year in 2006.

Interventions on the bile ducts increased from 24.5 to 31.3/100 000 inhabitants/year from 1989 to 2006. During the same time period a change from open choledochotomy to endoscopic sphincterotomy took place. In 2006, 26.1 ES, 4.6 open choledochotomies, 1.8 transcystic common bile duct explorations, and 0.6 laparoscopic choledochotomies per 100 000 were registered. This is illustrated in Figure 6.

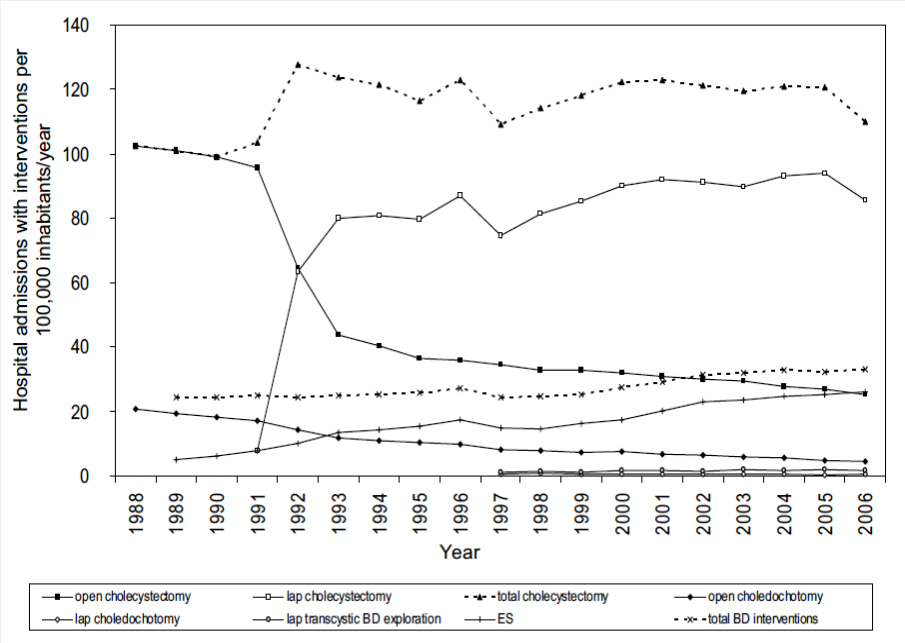


Figure 6. *Hospital admission /100 000 inhabitants /year with cholecystectomy, choledochotomy, and endoscopic sphincterotomy. CBD = common bile duct. Lap = laparoscopic. ES = endoscopic sphincterotomy. Total CBD interventions = choledochotomy + transcystic exploration + endoscopic sphincterotomy*

Endoscopic sphincterotomy & choledochotomy for common bile duct stones

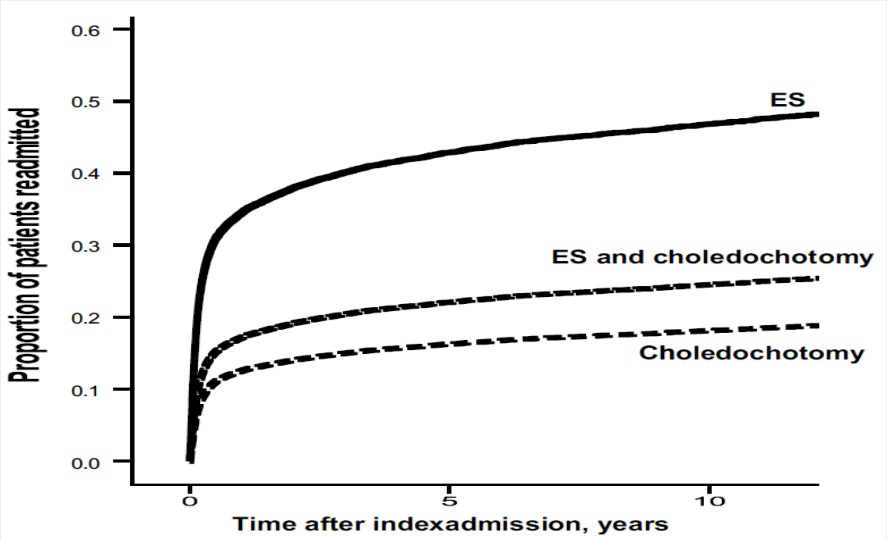
The proportion of CBDS treated by choledochotomy during the three time periods decreased from 61.1% to 19.6%. The choledochotomy was performed as open surgery in most cases. Laparoscopic choledochotomy was performed in 8.5% during the last period. ES rate increased from 36.4% to 78.2% during the audit.

Cholecystectomy at first admission decreased from 60.1% to 30.1% from first to last time period. Total cholecystectomy rate decreased from 66.1% to 51.2% between the two first time periods. Choledochotomy patients were cholecystectomised in 90.9% compared to 10.1% in patients with ES at first admission.

Re-admissions

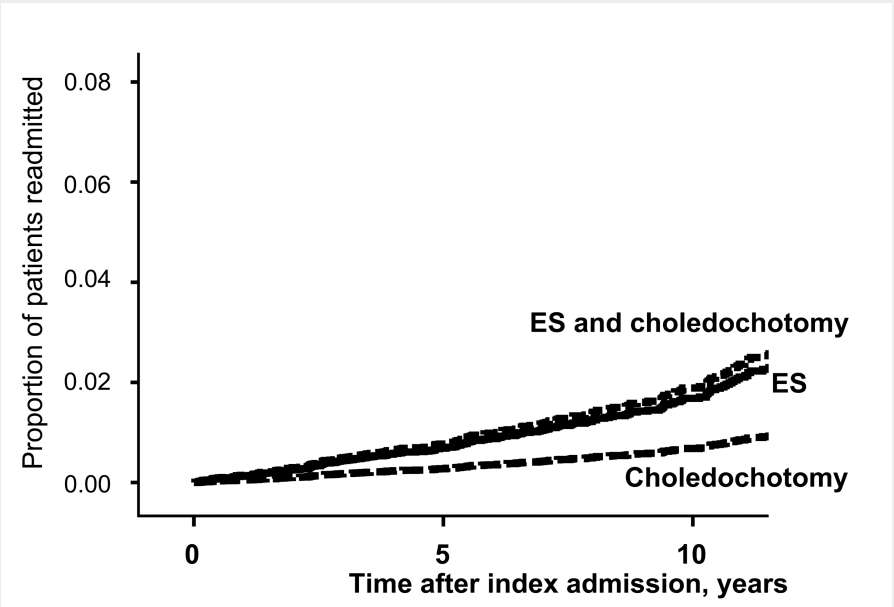
Figure 7 illustrates the cumulative proportion of patients readmitted at least once with a biliary diagnosis in relation to time after index admission.

Patients having had ES were significantly more likely to require re-admission with biliary diagnosis than patients who had undergone choledochotomy. Ten years after an index admission with ES, 46% of patients had been readmitted at least once with a biliary diagnosis, compared to 18% of patients with choledochotomy at index admission, and 24% of patients with both interventions during index admission. Figures 8 and 9 illustrate the cumulative proportion of patients re-admitted with acute pancreatitis specifically, and with re-intervention, in relation to time following an index admission. ES increased the risk for subsequent re-admission with acute pancreatitis (Figure 8), and requiring re-intervention on the CBD (Figure 9).



Patients at risk	0 years	5 years	10 years
ES	16286	3756	1159
Choledochotomy	9892	5977	3478
ES and choledochotomy	637	272	118

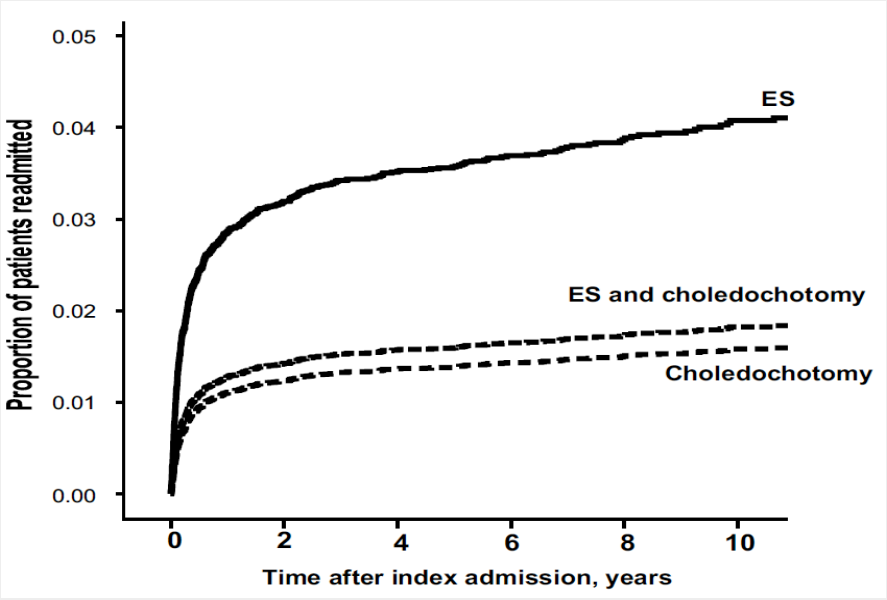
Figure 7*. Time to first re-admission with a biliary diagnosis, including acute pancreatitis after index admission (N=26815). ES = endoscopic sphincterotomy. Patients at risk = number of patients entering the time interval. The differences between choledochotomy and ES, and between choledochotomy versus ES and choledochotomy are highly significant (p<0.001 for both comparisons)*



Patients at risk	0 years	5 years	10 years
ES	16286	6793	2366
Choledochotomy	9892	6989	4099
ES and choledochotomy	637	343	150

Figure 8. *Time to first readmission with acute pancreatitis after index admission of study group (N = 26815). Legends: ES = endoscopic sphincterotomy. Patients at risk = number of patients entering the time interval. The differences between choledochotomy and, ES and between choledochotomy versus ES and choledochotomy are highly significant (p<0.001) for both comparisons.*

The cumulative risk of re-admission at least once with acute pancreatitis 10 years after index admission was 0.6% with choledochotomy, 1.7% with ES at index stay, and 1.9 with both choledochotomy and EX at index stay (p<0.001 for both comparisons). Ten year after index admission, the cumulative risk of re-admission with re-intervention was 1.6% after (p<0.001) choledochotomy compared to 4.1% after ES.



Patients at risk	0 years	5 years	10 years
ES	16286	6499	2224
Choledochotomy	9892	6895	4034
ES and choledochotomy	637	338	150

Figure 9. *Time to first re-admission with intervention on the common bile duct after index admission (N=26815). Patients at risk = number of patients entering the time interval. ES = endoscopic sphincterotomy. The difference between choledochotomy versus ES is significant (p<0.001).*

Hospital stay

Length of hospital stay decreased at index admission for all patients with CBDS. Patients treated with ES had 5-6 days shorter LOS than patients treated with choledochotomy (Figure 10). During index admission, 10% of ES patients and 90% of choledochotomy patients underwent cholecystectomy.

During 3 years after index stays ES patients needed 3.72 days extra hospital stay with biliary diagnoses compared to 1.87 days for choledochotomy patients.

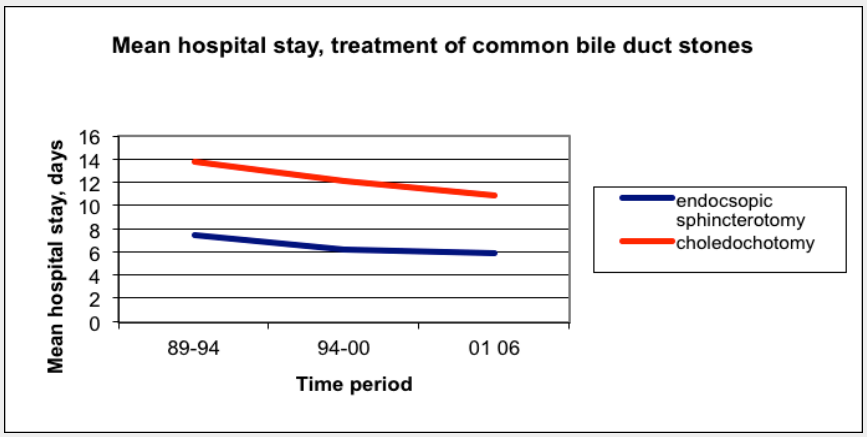


***Figure 10**. Hospital stay at index intervention for CBDS.*

Mortality

The total mortality for treatment of CBDS decreased significantly from 2.99 (2.62-3.38) in the first period to 2.08 (1.82-2.37), SMR (95% CI), in the last period. During the last time period, mortality 0-90 days as CFR, was 2.3% and 1.6% in patients treated with ES or choledochotomy, respectively. Adjusted for gender and age as SMR, it was 1.97 (1.70-2.28) and 2.60 (1.78-3.67), respectively.

Acute gallbladder disease

Hospital admissions and cholecystectomies for gallbladder disease.

A marked increase in hospital admissions for biliary disease, more pronounced for women than for men, more for elective than for emergency admissions is noticeable at the year of laparoscopic break-through in Sweden (Figure 11). There was a small but statistically significant rise in the proportion of emergency admissions from 48.5 to 54.4% (Table 6)

***Table 6**. Emergency and elective admissions for gallbladder disease from January 1st 1990 to December 31st 2004 in time periods.*

Time period	Emergency admissions	Elective admissions
1990-1994	35687 (48.5)	37841 (51.5)
1995-1999	43038 (52.0)	39796 (48.0)
2000-2004	45180 (54.4)	37866 (45.6)

p<0.001. Percent within brackets

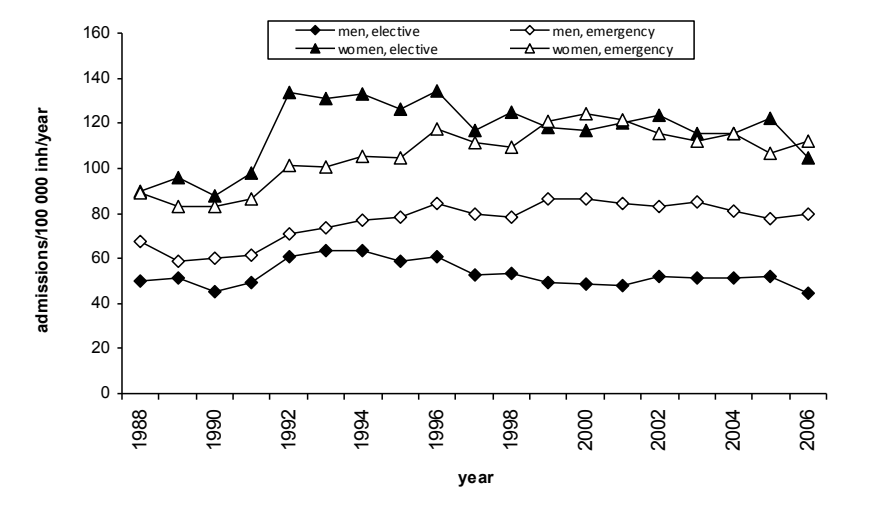


Figure 11. *Hospital admissions for gallbladder disease over time, grouped by gender and priority (emergency/elective). All patients had the main diagnosis cholecystitis or gall bladder stones.*

There was a rapid change from open to laparoscopic cholecystectomy 1992-1993, but this change in surgical technique was less pronounced in emergency cholecystectomy (Figure 12).

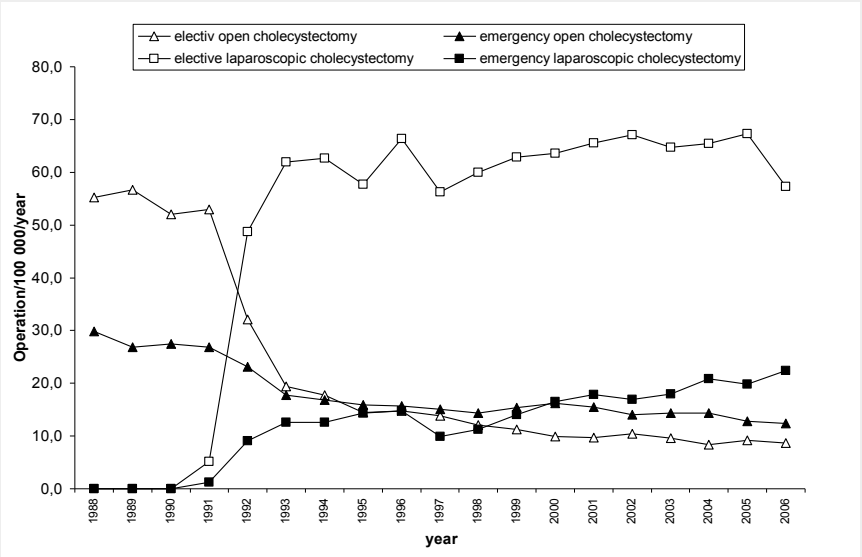


Figure 12*. Incidence of cholecystectomy operations over time grouped by operative technique and priority (emergency or elective). All patients had the main diagnosis gallbladder disease and were admitted between January 1st 1988 and December 31st 2006 in Sweden.*

In 2006, 36% of emergency cholecystectomies were performed as open procedures. From the first to the last time period, the relation between emergency and all cholecystectomies was unchanged, 29.5%-30.5%.

The acute gallbladder disease cohort

Of all patients admitted for acute gallbladder disease, 32.2% had a cholecystectomy during their index admission, whereas 20.3% were electively re-admitted and cholecystectomised within two years. A further 6.1% were operated at an emergency re-admission. The largest group, 41.4%, had no cholecystectomy within two years. Their mean age was close to 15 years older than the operated patients. There was little change between the three time periods, although a significant decline in cholecystectomy rate during index admission is noted in the second period (Figure 13).

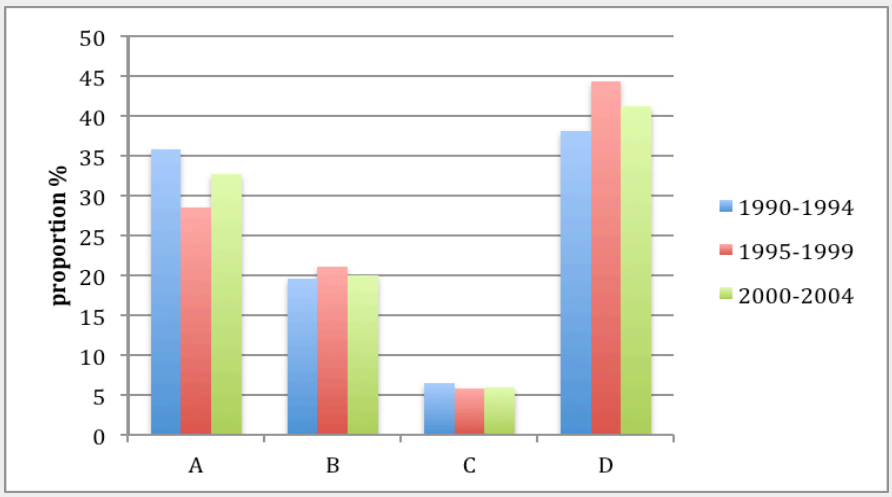


Figure 13*. Proportion in different time periods of patients in the four groups (A-D). All patients in this cohort had an emergency admission with the main diagnosis cholecystitis or gallbladder stones between January 1st 1988 and December 31st 2006 in Sweden. A= emergency cholecystectomy at index admission, B= elective cholecystectomy performed within two years after index admission, C= cholecystectomy performed in connection with a new emergency admission within two years after index admission, D= no cholecystectomy within two years after index admission.*

The median (CI 95%), time to emergency or elective re-admission with cholecystectomy was 34(32.0-36.0) days, and 87(85.6-88.4) days, respectively.

As a comparison of health care costs, we have calculated a mean per patient for total hospital stay for biliary disease from index admission with acute gallbladder disease up to two years. This is determined in each group of patients (Table 7). Patients with emergency re-admittance and cholecystectomy have 5 days longer mean LOS.

Table 7. *Proportion and mean of total length of hospital stay in the four groups (A-D). All patients had an emergency admission for the main diagnosis of cholecystitis or gallbladder stones between January 1st 1990 and December 31st 2004 in Sweden.*

Group	Patients	LOS Index	LOS Op	LOS No Op	LOS Total	LOS Mean	LOS Prop*
A	32291	226549		17923	244472	7.57	29.4
B	20357	70578	78607	24915	174100	8.55	20.9
C	6122	20705	46924	11840	79469	12.98	9.5
D	41588	211693		123142	334835	8.05	40.2
Total	100358	529525	125531	177820	832876	9.29	100.0

*A-Cholecystectomy at index admission. B-Elective cholecystectomy within two years. C-Emergency cholecystectomy within two years. D-No cholecystectomy within two years. Patients = Number of patients. LOS = Length of hospital stay in days. LOS Index = Accumulated LOS at index admission with or without cholecystectomy. LOS Op = Accumulated LOS at re-admission for biliary diagnosis with cholecystectomy within two years. LOS No op = Accumulated LOS at re-admissions for biliary diagnosis without cholecystectomy within two years. LOS Total = LOS Index + LOS Op + LOS No Op. LOS Mean = Mean total LOS. LOS Prop = Proportion of LOS. * = percent.*

Mortality 0-90 days (SMR) is increased threefold, but without time trend, and differences between age groups. Mortality is increased 91-365 days after index admission (SMR 1.8-2.0), also with no time trend or difference between age groups

Discussion

Strengths and weaknesses of research techniques used.

Our studies have utilised data from all Swedish hospitals from 1988 up to 2006 (2004 in two studies). Admissions with biliary diagnoses including acute pancreatitis are analysed concerning interventions for complicated gallstone and gallbladder disease. We have used hospital stay, length of stay, re-admissions/re-interventions and mortality as endpoints and aim to give an overall view on a population based level concerning treatment of complicated gallstone disease over more than a 15 year long period.

There are some limitations inherent in a retrospective study based upon nationwide databases. Completeness and coding quality must be accurate enough. For all records reported to NPR a data control is made, that codes for different variables that dates have valid values and that compulsory variables (personal identification number, hospital, and main diagnoses) are reported. Obvious incorrect data are corrected. In 2003, 0.9% of all diagnoses and 0.5% of acute somatic diagnoses were missing in hospital stays reported(20). In a study of validity of diagnoses in NPR the Diagnostic coding was compared to journal data from 900 hospital stays. Surgical clinics were more correct than medical clinics in this respect. The main diagnosis was judged wrong according to journal data in 6-8% concerning three digit level in ICD-9, depending on liberal or strict criteria(173). In a validation study in 2005 in the same register for the diagnosis of heart failure, journal data from 321 men showed the validity of primary diagnosis was 95%(174). A validation of the acute pancreatitis diagnosis in NPR found that 84% of patients with this diagnosis had a definitive acute pancreatitis and another 15% possibly acute pancreatitis as judged from medical records of 602 patients(175) The coding for operations seems at least just as valid as diagnosis coding(176). The Swedish national registry for quality assurance of gallstone surgery (GallRiks), compares in a report from 2009 the coverage of GallRiks and NPR concerning cholecystectomies. In 2007 and 2008, 3% of registrations in NPR were missing when compared to GallRiks. For some reason 11% of cholecystectomies were missing in 2009. There is a larger proportion of unregistered patients concerning ERCP in NPR, where 31-35% were missing during the same three years compared to GallRiks(177). However, the rate of missing registrations for ES is probably lower as ES is an invasive procedure, and procedure coding have a high validity(173). Furthermore, patients with ambulatory procedures are included in GallRiks, but not in NPR.

Acute pancreatitis

We have utilised nationwide data from all patients with FAAP in Sweden 1988-2003. The diagnostic validity of acute pancreatitis can be considered high. It is also important to differentiate first from recurrent attacks(178-180), which is accomplished in this audit. We found an incidence of FAAP of 33/100 000 inhabitants/year. This is comparable to previous studies from Scandinavia (179-181) and the US(113, 114). A lower incidence has been noted from UK and Holland(113, 182). We found an 18.5% increase in incidence from 1988-1992 to 1998-2003 (figures adjusted to Swedish population 1988-1992). This increase was statistically significant for women, but not for men. The same tendency concerning increasing incidence of FAAP has been noted by others(113, 114, 183). Of all patients with FAAP, 16.9% had at least one re-admission for acute pancreatitis within one year after index admission.

The incidence of FAAP is strongly related to age(114, 181, 184, 185). We noted a six-fold increase in age-standardised incidence from 0-49 years to 80 years and above. This parallels the increasing gallstone prevalence in higher ages. Interestingly, there is also a significant increase in incidence during the audit period for patients above 70 years of age. There are no data on changing gallstone prevalence in old age during the period covered by our audit. Changes in cholecystectomy incidence are probably too small to affect the incidence of acute pancreatitis in old age(186).

There are two important factors to consider in explaining the low rate of aetiological diagnoses in the register. First, they are based on secondary diagnoses which have lower validity compared to primary diagnoses(173, 174). Second, the responsible doctors may not have explored possible aetiologies with enough fervour. One suspicion is that only very obvious alcohol misuse has been identified. Small gallstones can easily be missed and the search is not complete after one single transabdominal ultrasound performed at late hours.

We found, like Gislason et al(187), a much higher mortality risk in alcohol-related FAAP compared to biliary FAAP. The difference may partly be a selection bias as alcohol overuse more likely is divulged and diagnosed in severe acute pancreatitis. Other reports state similar mortality rates for alcohol or biliary pancreatitis(113, 188). However, patients with alcohol pancreatitis are younger than those with biliary pancreatitis. The median difference is 16 years in our study. Patients with the two aetiological varieties of pancreatitis may have the same CFR, but significantly different SMR values since patients with alcohol pancreatitis are younger. SMR is in that respect a better indicator of the gravity of the disease. SMR 91-365 days after admission for FAAP provides information about the mortality risk when the influence of FAAP has subsided.

Higher SMR values for younger patients during this period indicate that they have a less healthy situation than older patients do. CFR is valuable in predicting the prognosis in the individual patient.

The total mortality as SMR decreased from 16.8 to 9.3 from the first to the last study period, which is a statistically significant and gratifying reduction. The corresponding decrease in CFR is less pronounced, from 8.2 to 6.2%, which reflects an increasing patient age.

The improved mortality could be caused by the retreat from a more aggressive surgical approach in the management of severe acute pancreatitis(179). Another improvement to be noticed in this audit is the modest but significant decrease in hospital stay.

Mild acute biliary pancreatitis

Of all patients with MABP, 10% had a cholecystectomy during the first admission, and another 10% an interval cholecystectomy within 30 days of first admission. Another 12% had ES without cholecystectomy within 30 days of first admission with MABP. Sixty-eight percent of the patients had no intervention for their MABP within 30 days.

Our register data are based on the combination of acute pancreatitis and gallstone diagnoses, both well known to doctors and accordingly we consider the presence of this combination of good validity. Ordinary severity classifications of acute pancreatitis like the Atlanta classification(189) is not possible to use. Instead, we used a proxy indicator as described above, which classifies 74% of biliary FAAP as mild. This is in accordance with the percentage expected from comparison with other studies based on the Atlanta classification(116). The cholecystectomy rate might be underestimated as we have no data on day-case surgery during the audit period, but ambulatory cholecystectomy was uncommon during the audit period, so this bias is unlikely to change the conclusions. For 2005, the first year of the register for day-case surgery, the rate of day-case surgery in Sweden was 13%(20).

Hospital stay for MABP with cholecystectomy at first admission was longer (7 days) compared to a first admission without cholecystectomy (4 days) followed by a re-admission and operation within 30 days. Early cholecystectomy seems well motivated as it makes re-admission unnecessary and is associated by just one convalescence period.

Patients initially treated with ES only comprised 12% of all MABP patients, and 31% of these had a later cholecystectomy within one year.

The 90-days mortality after MABP with early cholecystectomy did not deviate significantly from the expected mortality in the background

population. The groups with ES alone or with no biliary intervention during one month of first admission did not differ with respect to SMR from the early cholecystectomy groups. They had a higher CFR reflecting the older age of patients in these groups. The possibility of increased later mortality from these deviations from established guidelines remains to be investigated.

Common bile duct stones

Laparoscopic cholecystectomy has replaced open cholecystectomy, and endoscopic sphincterotomy superseded choledochotomy as the main therapeutic option for CBDS in Sweden. The transition from choledochotomy to ES has been gradual since the 1980s, and associated with an overall 28% increase in common bile duct interventions from 1989 to 2006.

Cholecystectomy rate during first admission for CBDS declined from 60% in 1990-1994 to 31% in 2001-2006. The risks for re-admission with any biliary diagnosis, with acute pancreatitis, and with new bile duct interventions were all higher after ES, compared to choledochotomy. SMR from index admission and 90 days onwards, declined from 1989-1994 through 2001-2006 for both ES and choledochotomy. SMR did not differ significantly between the two treatments during the latter part of the audit. The strength of our studies is that the databases are nationwide and cover a long period. It is a study of effectiveness, rather than of efficacy comprising hospitals and surgeons with all levels of experience and specialisation. Ambulatory procedures are omitted. The comparison between ES and choledochotomy is biased by the time difference; more choledochotomies were made early and more ES made later during the years of the audit. The effectiveness of most procedures improved with time during the 1990s, influenced by multimodal strategies to improve surgical outcomes(190).

We separated transcystic common bile duct exploration from choledochotomy as transcystic CBDS exploration can be regarded as a less traumatic intervention aiming at removing small CBDS(140)

To discuss the difference in hospital stay between ES and choledochotomy we have to consider that 90% of patients who underwent choledochotomy, also had a cholecystectomy, as compared to 10% of patients in the ES group.

Outcomes of RCTs indicate that cholecystectomy should be offered to patients whose gallbladders remain in situ after ES and common bile duct clearance(167). Early cholecystectomy during index admission (within 72 hours after ES) is preferable compared to delayed cholecystectomy (6-8 weeks after ES)(191). It is therefore, of great concern that cholecystectomy

performed during index admission in our audit declined from 60.0% to 30.1% from first to last six-year period.

The increased risk of acute pancreatitis following ES compared to choledochotomy is of interest, and when both ES and choledochotomy were done at the same admission the risk followed the ES curve.

SMR 0-90 days after index admission decreased over time for the entire study population and for patients treated with choledochotomy and ES analysed separately. The SMR difference between index admission with choledochotomy or with ES was small with overlapping 95% confidence intervals. This in spite of a nine-fold greater cholecystectomy rate at index stay with choledochotomy. It is of interest that the mortality risk fell drastically, and to a similar extent, for both choledochotomy and ERCP in the early 1990s in the US(134).

Acute cholecystitis

This population-based study reflects the actual treatment of acute gallbladder disease in all Swedish hospitals given by clinics and surgeons with varying experience and expertise. The signs and diagnose of acute gallbladder disease is usually straightforward with modern diagnostic tools widely available.

Emergency admission for acute gallbladder disease increased gradually during the audit period, and during the later part they were somewhat more common than elective admissions for cholecystolithiasis. Men were more often admitted emergently than women.

The number of acute cholecystectomies did not change drastically during the audit period, but the operative technique did gradually go from open to laparoscopic surgery. However, still in 2006, 1131/3172 (35.7%) of all emergency cholecystectomies were performed as open procedures for patients with acute gallbladder disease.

Of all patients with acute gallbladder disease 32.2% had a cholecystectomy at first admission, and 41.4% no cholecystectomy within two years. The differences between time periods were small, but a temporary decrease in 1995-1999, may have indicated a certain hesitation towards emergency cholecystectomy. Patients in the non-cholecystectomy group were more than 13 years older than patients in the other groups. Total length of hospital stay during two years including index stay, was similar for patients treated with cholecystectomy at index admission, elective cholecystectomy at a planned re-admission, or no cholecystectomy at all. Patients with emergency re-admittance had five days longer total hospital stay. SMR 0-90 and 91-365 days from index admission, did neither differ

between time periods, nor between different age groups. This is somewhat surprising as we noted a decreasing mortality in other areas of our audits.

Findings in relation to guidelines – do we do what we think we do?

Some of the guidelines have evolved during the audit period, as in fact predicted by evidence based medicine (EBM)(7) Clinicians need help in evaluating medical evidence, and guidelines are often elaborated in conjunction with consensus meetings. Notwithstanding, these are of varying quality. They should be scrutinised for level of evidence and grade of recommendation(192). The GRADE system has been developed both in order to make it easier to create better guidelines and for the clinician to evaluate these guidelines(193). But we always have also to consider the base of high quality knowledge, namely meta-analyses of RCTs if available. The quality of the RCTs are of importance and do vary(194). A pitfall in surgical RCTs, not often discussed, emanates from the surgeon him- or herself. He or she can have different experience in the interventions investigated, or have preconceived notions of which intervention is best. This may be a powerful bias on the outcomes measured. A remedy for this, is expertise based RCTs(195, 196). With this in mind, meta-analyses and guidelines are compared to our findings in the next section.

Acute pancreatitis and guidelines

We found the aetiological diagnosis of acute pancreatitis was missing at discharge to a great extent according to the NPR register. The finding of 68.4% of all FAAP patients lacked an aetiological diagnosis at index stay compares unfavourably with guidelines. The UK guidelines state that less than 20% of patients with acute pancreatitis should lack an aetiological diagnosis at discharge(119). Early diagnostic efforts in establishing the diagnosis of acute pancreatitis, its severity (and hence prognosis), and its aetiology, cannot be controversial. Gallstone disease must be actively hunted; one nightly transabdominal ultrasound is not enough!

In Sweden aetiologic primary diagnosis is now made easier with a new version the Swedish ICD-10 with specific aetiological codes for acute pancreatitis(20).

We found that there is a large group of patients with MABP, which are not treated according to guideline recommendations concerning cholecystectomy. In our survey 20% of all patients with MABP had a cholecystectomy within one month of the first attack of acute pancreatitis, and only half of these during index admission. With this diagnosis, an early

cholecystectomy is recommended(116, 119, 168, 197, 198). Early cholecystectomy shortens hospital stay according to one recent RCT(199) and observational studies(200). Delay of cholecystectomy can lead to unnecessary morbidity and re-admission for a new attack of biliary pancreatitis(201-203). This deviation from guidelines has been found common in previous studies(204-210). In our study, 12% of MABP patients had ES as initial treatment. ERCP as an initial intervention in any biliary pancreatitis without cholangitis is not warranted(211). A few days after the initiation of biliary pancreatitis, CBDS are present in less than 15% of patients, and CBD clearance (ES or surgery) is indicated in such cases(212). In our audit, patients with only ES had their initial treatment completed with a later cholecystectomy in 31% (within one year). In a Swedish study on 96 patients with gallstone pancreatitis, with high median age (74 years) and long observation time (median 84 months), the authors supported routine cholecystectomy in fit patients after endoscopic treatment of gallstone pancreatitis(213). This concurs with the recommendation in a meta-analysis for CBDS(167).

The possibility for adherence to UK guidelines in a regional upper gastrointestinal and HPB surgery service has been demonstrated by Mofidi et al(214) even in this respect. Of 359 patients with acute gallstone pancreatitis, 322 (89.7)% had a definitive treatment within two weeks from admission, 285 patients by cholecystectomy.

On the other hand, in our nationwide audit 44% of patients classified as MABP had no cholecystectomy within one year. It is unlikely that many of them were on a waiting list for cholecystectomy, so the actual treatment was expectancy in some form. To our knowledge, there are no long-term follow-up studies or other data on this category of patients, so evidence for expectancy is lacking. The 90-days mortality ratio (SMR) after index admission did not differ significantly between the four MABP groups in our audit. However, this should be interpreted with caution in lack of long-term morbidity and mortality data for patients with gallbladder in situ after an initial attack of acute biliary pancreatitis.

Common bile duct stones and guidelines

The British Society of Gastroenterology proposes treatment of CBDS by ES and stone extraction plus cholecystectomy, if the latter is not contraindicated. Laparoscopic bile duct exploration with cholecystectomy is an alternative(6). We found that more than 40% of Swedish patients treated for CBDS with ES still have their gallbladder in situ after two years. Current views support cholecystectomy in connection with removal of CBDS(167). What are the consequences of this discrepancy from guidelines?

Acute gallbladder disease and guidelines

As previously described a number of RCTs have demonstrated the efficacy of early cholecystectomy in acute cholecystitis(159). However, in one pragmatic RCT cost-utility of early and delayed (3 months) did not differ(215)

Our data show a 30% rate of cholecystectomies of patients admitted for acute gallbladder disease. The cholecystectomy in the emergency setting was more often a conventional open operation than a laparoscopic operation, as opposed to the elective setting. There are notably few data on the extent of cholecystectomy in patients with acute gallbladder disease. One study from England disclosed that around 15% of patients admitted for acute gallbladder disease underwent a cholecystectomy, of which over 30% were done as open procedures(171).

More than 40% of all patients in our study had no cholecystectomy within two years of initial admission with this diagnosis. Their mean age was more than 13 years older than the cholecystectomised patients, which suggests more co-morbidity. Nevertheless, there is limited evidence for expectancy in acute gallbladder disease. In a RCT by Vetrhus et al(216) comparing delayed cholecystectomy with watchful expectancy, the authors concluded that conservative (non-operative) treatment and observation of acute cholecystitis is an acceptable option and should at least be considered in elderly and frail patients. Only 64 patients were analysed, so the power to detect differences in outcomes was relatively weak.

The critical decision seems to be the choice between emergency cholecystectomy at first admission and watchful expectancy.

Gains and losses of endoscopic techniques

High quality data comparing surgery and endoscopic treatment of CBDS do not find any procedure related differences in mortality or morbidity(94). A remaining important issue is a comparison of long-term effects. Observational data indicates a higher rate of recurrent CBDS after ES(95, 217) than surgery with laparoscopic bile duct exploration(96, 218). Case series reporting open choledochotomy are older(219). Long-term recurrence rates in these reports are less than 1-3% for surgery, and 6-24% for ES, but these data are not based upon any RCTs.

Our observational nationwide register data demonstrate an increased risk for acute pancreatitis and increased need for re-interventions on the biliary ducts after ES compared to bile duct surgery, open or laparoscopic.

There is a need for new RCTs comparing ES and surgery to corroborate or refute earlier findings(94), as both endoscopy and surgery have been refined during the past decades. Modern minimal invasive procedures including SIC

are associated with quick recovery and short convalescence compared to ordinary open cholecystectomy. Primary closure of the CBD may be performed with short hospital stay in association with both small incision cholecystectomy(135) and laparoscopic cholecystectomy(139). The risks and benefits of T-tube drainage versus primary closure should be assessed in future randomised controlled trials(142)

Consequences for populations of increasing age.

Old age involves increasing gallstone prevalence, and an elevated risk for complicated gallstone disease(220). Age and male sex are also associated with an increased risk for difficult surgery. This leads to higher conversion rates in laparoscopic surgery(221). Young surgeons nowadays have limited experience in open biliary surgery(222, 223), resulting in increasing complication rates(134). This may ultimately lead to the paradox that older patients with more co-morbidities, are operated with traditional open cholecystectomy, by surgeons with little training in less traumatic open surgery, i. e. small incision cholecystectomy(224).

Conclusions

Mortality in first attack of acute pancreatitis decreased 1989 to 2004

Diagnostic accuracy in first attack of acute pancreatitis has been unsatisfactory.

Early cholecystectomy after first attack of mild acute biliary pancreatitis was not performed to a sufficient extent.

Endoscopic sphincterotomy compared to surgical choledochotomy is associated with more re-admissions with biliary disease, more re-admissions for re-interventions on the bile ducts, and an increased long-term risk for acute pancreatitis.

Without solid evidence, a large group of patients are treated conservatively during and after hospital stay for acute gallbladder disease.

Aside from a transition from open to laparoscopic surgery, the actual management of acute gallbladder disease was mainly unchanged from 1990 to 2004 in our audit.

Changes of practice necessary?
Centralisation of severe cases of acute pancreatitis after improved early prognostic measures should be discussed. More decisive definitive treatment of biliary pancreatitis is indicated.
It is desirable to develop and dissipate knowledge of choledocholithectomy. Both laparoscopic and small incision choledochotomy are valid alternatives to ES for CBDS.
Transcystic technique utilising the best available and modern instruments to remove CBDS during SIC may be explored.
Training young surgeons in open mini-invasive surgery leads to less traumatising open surgery when this is necessary.
Surgical acute clinics ought to have an organisation with ability to perform emergency cholecystectomy for acute gallbladder disease.

What else do we need to know – future studies
An update of register data for acute pancreatitis.
Long-term data for acute gallbladder disease
Long-term data for expectancy without cholecystectomy after MABP
Long-term data comparing ES and choledochotomy for CBDS.
Expertise based studies comparing T-tube or primary suture after choledochotomy.
New RCT comparing ES with mini-invasive techniques, including long-term follow up.

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