Cholecystectomy in perspective.

Risk factors of wound infection in open
and laparoscopic cholecystectomy.

Pieter Theodorus den Hoed

CHOLECYSTECTOMY IN PERSPECTIVE

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CHOLECYSTECTOMIE IN PERSPECTIEF

Risicofactoren voor wondinfectie na open
en laparoscopische cholecystectomie

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CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION

Cholecystectomy has been the accepted modality for treatment of patients with symptomatic gallstones. The purpose of cholecystectomy is the relief of symptoms and disability and the prevention of mortality. Although the mortality rate of the operation and the rate of complications following cholecystectomy are low, most patients still experience complaints because of discomfort, pain, long convalescence, disability and postoperative ileus.

The management of diseases of the gallbladder has undergone significant change during the last decade and clearly is still evolving. Recent years have seen the investigation and development of alternative methods for the management of cholecystolithiasis, including gall dissolution therapy[1], endoscopic and percutaneous methods of stone extraction[2,3], extracorporal shock-wave lithotripsy with or without adjuvant bile acid dissolution[4,5], the advocation of gallstone removal via a minilaparotomy[6] and the various techniques of laparoscopic cholecystectomy[7-9].

Laparoscopic cholecystectomy is at present the leading technique for the treatment of sympyomatic cholecystolithiasis in terms of reduction in postoperative morbidity and length of convalescence[10-13].

1.2 EPIDEMIOLOGY OF GALLBLADDER DISEASE

Gallstone disease presents a major clinical problem in the western society. Epidemiological studies demonstrate a prevalence of gallstones in Europe between 5 and 25%[14-16]. The prevalence increases with age and is higher in females and in obese people[17-20].

Bile consists of three specific constituents namely, bile acids, bile pigment and cholesterol. The second is poorly soluble and the last is almost insoluble in water. These substances are kept in aqueous solutions with the help of the emulsifying bile acids and fatty acids. Consequently, the bile is supersaturated with these compounds. In such an unstable solution, precipitation readily sets in. The causes of cholelithiasis appear well established. One is an increased concentration of one of the crucial substances in bile. Although the constitution of bile does not necessarily reflect that of the blood plasma, elevation of either plasma cholesterol or bilirubin may result in their increase in bile, with their subsequent precipitation given rise to stone formation. Hypercholesteremia is a metabolic phenomenon occuring in obesity, diabetes and pregnancy, and also in hypothyroidism and nephrosis, the first three of which have been said to appear relatively often in the histories of patients with gallstones. Cholesterol stones are firm and yellow-gray and have a granular surface, while on the cut surface glistening cholesterol crystals produce a radiating pattern. Even if these stones become large, they remain radiolucent. The incidence of pure cholesterol stones is relatively small, and in the greater percentage of cases some bilirubin or calcium-bilirubin is admixed.

Biliary stasis, brought on by spasm of the sphincter of Oddi, by faulty bladder emptying, by organic obstruction, by a stone in the cystic duct or by some malformations of the gallbladder is another instigating factor for stone formation. The stagnation of bile in the gallbladder leads to high concentrations of cholesterol and bile pigment because of excessive absorption of water and easily soluble salts. Precipitation under these circumstances leads to mixed stones, the most common type. They are of variable size, facetted if multiple, brown, and specially dark on their edges. On the cut surface a dark center is noted, surrounded by a glistening radiating layer which is frequently followed by a harder shell. These bilirubin-cholesterol stones contain sufficient calcium to make them opaque on X-ray examination. Sometimes the stones are small enough to appear as gravel.

The third important cause of stone formation is inflammation of the gallbladder. It results in an altered constitution of the bile. The inflamed gallbladder mucosa permits, in contrast to normal mucosa, absorption of bile acids with subsequent reduction of the solubility of cholesterol. Moreover, from the inflamed mucosa, especially if ulcerated, calcium salts diffuse into the bile in excessive amounts to add calcium bilirubinate to the developing cholesterol stone. The mixed stones in inflammation are rich in calcium and harder than other stones; they appear whiter and are distinctly radiopaque.

Pure cholesterol or bilirubin stones are rare. The vast majority of stones are mixed, quite independently of their pathogenesis, the mixture reflecting simultaneous or consecutive presence of several of the factors listed. Stones, originally pure, soon receive admixtures of other constituents. For this reason the cut surface of most stones shows a variegated picture, reflecting different layers of precipitation. Sometimes gallstones seem to form rapidly, possibly in a matter of weeks.

1.3 MICROBIOLOGY OF BILE

In the normal gallbladder, bile is generally sterile. In diseases of the gallbladder bile may be infected; the reported incidence of bacteria in the bile is variable, ranging from 8-42 %[21-24]. The incidence of bacteria increases in the presence of biliary tract pathology[25]. The incidence of bacteria in the bile in the presence of gallstones ranged from 11% for patients under 50 years to 17% in those over 70 years, and this relationship with age is seen over a wide range of patients with biliary disease. Keighley et al[22]. found bacteria in the bile in only 34% of the cases of empyema of the gallbladder, although this incidence may have been decreased by previous antibiotic treatment. There is an interesting difference in the presence of micro-organism between patients undergoing cholecystectomy for acute cholecystitis in the convalescent phase (48%) and those undergoing emergency cholecystectomy (82%).

Infected bile is usually colonized by more than one organism. The more complex the pathology the greater the chance of mixed infections. In approximately 45% of the patients with infected bile anaerobes are present, nearly always as a part of a mixed infection[26]. The most frequently occuring aerobes are Escherichia coli, Klebsiella species and Streptococcus faecalis, whereas Bacteroides fragilis and other Bacteroides species form the largest genus of anaerobics[27,28].

Introduction of foreign bodies, such as tubes, into the biliary tract encourages modification of the normal bacterial spectrum[29]. Exogenous T-tube infection may represent an important clinical risk[30].

1.4 THE ROLE OF ANTIBIOTICS IN BILIARY TRACT SURGERY

Perioperative antibiotics may be given either prophylactically or therapeutically. Therapeutic antibiotics are given when inflammation or pus is encountered at surgery and are administered to treat an established infection. They have the additional benefit of reducing the likelihood of a wound infection. Prophylactic antibiotics are given when there is a risk of contamination of the wound at surgery. The aim is to prevent a wound infection and to reduce the risk of the development of deep-seated infection, such as abscess or systemic sepsis. The most important determinant factor in postoperative wound infections is the presence of viable bacteria in the surgical field at the time of wound closure[31]. Therefore antibiotics should be administered sufficiently early to allow adequate tissue levels to be achieved at the time of closure. In most circumstances the antibiotic should be given on induction of anaesthesia and before contamination occurs. A single dose is probably sufficient and the antibiotic should not be continued for more than 16 to 24 hours following surgery as it does not enter the wound once it is sealed with clot and fibrin[32].

Antibiotic treatment is necessary in acute cholecystitis. Parenteral antibiotics should be commenced immediately, preferably based upon the known bacterial flora in the population concerned. For this it is important for clinicians to be aware of local variations in the bacterial flora of the gallbladder bile, which means that bile must be sampled with every biliary procedure.

Four strategies for the use of antibiotics in elective cholecystectomy can be defined. Firstly, no antibiotics for any case. This policy has been abandoned by almost all surgeons. Secondly, antibiotics only for patients who fall into established "high-risk" categories. One set of criteria for this high-risk category was established by Keighley et al.[22] and is widely used:

- Age greater than 60 years
- Recent cholangitis
- Recent acute cholecystitis
- Previous biliary surgery
- Current of recent history of jaundice
- Choledocholithiasis
- Emergency surgery

These categories delineate patients with an increased possibility of bacteria in the bile, who are most at risk for postoperative wound infections and other septic complications. Most can be categorized preoperatively, however common bile duct stones are sometimes found peroperatively. A third option is antibiotics given based on intraoperative Gram's stain. This originally was proposed as a more rational and rigorous method of selecting patients as candidates for antibiotic therapy, but this methodology has been almost universally abandoned. One randomized, controlled study[33] demonstrated that there were both false positives and false negatives for the intraoperative Gram's stain, and that the postoperative infection complication rate was unacceptably high, even in patients who received antibiotics on the basis of a positive Gram's stain. Fourth option is the use of antibiotics in all patients. The use of a single dose or two doses of antibiotic would appear to have little adverse effect on the ecology or economy and side effect reactions to antibiotics are infrequent and generally mild.

1.5 AIMS OF THE STUDY

Open cholecystectomy, now being performed for more than 100 years[34], has been an effective method of treating gallstone disease and has demonstrated an acceptable low morbidity and a minimal mortality, with a variation from 0 to 0.8 percent[35-39]. Thus open cholecystectomy represents an acceptable risk-benefit ratio for patients and until recently has been regarded as "the gold standard" against which new therapies are compared[40].

Laparoscopic cholecystectomy is a method of removing the gallbladder through four small incisions using an endoscopic technique. This approach varies in many respects from open cholecystectomy. The goal for both techniques is identical: a safe removal of the gallbladder with low mortality, little morbidity and early recovery. Comparison between open and laparoscopic cholecystectomy can be made in many ways including indication, contraindication, risk factors, equipment, technique, complications, outcome, results, benefits to the patient and surgeon, costs, training and credentialing.

It has been suggested that unbiased randomized trials comparing laparoscopic and open cholecystectomy are impossible, because nowadays a patient would not accept an open cholecystectomy when the minimal access technique is available[41]. Data from recent series of elective open cholecystectomy (i.e., just before the era of laparoscopic cholecystectomy) are critical for comparison when evaluating alternatives to open cholecystectomy. Comparisons between laparoscopic and open cholecystectomy should not be made with outdated historic series of open cholecystectomy, but with the results that were attainable in the latest period before it became superseded by laparoscopic cholecystectomy[42,43].

In 1989 this study was initiated to determine the effect of a single dose amoxycillin/clavulanic acid as infection prophylaxis in open cholecystectomy. However with the introduction of laparoscopic cholecystectomy the aims were extended and the particular role of laparoscopic cholecystectomy in the whole spectrum of treatment modalities for symptomatic cholelithiasis was evaluated.

The aims of the study were:

- To determine the results of open cholecystectomy, by means of a retrospective analysis in a teaching and a non-teaching hospital. (Chapter 3)
- To determine the effect of a single dose amoxycillin/clavulanic acid as infection

prophylaxis in open and laparoscopic cholecystectomy. (Chapter 4)

- To analyse the indications, details of practice, risk factors, complications, outcome and results of the patients treated for gallstone disease after introduction of the laparoscopic cholecystectomy in a district general hospital. (Chapter 5)
- To compare the results of open and laparoscopic cholecystectomy. (Chapter 6)
- To define a group that is at "high risk" of developing postoperative wound infection after open (Chapter 4) or laparoscopic cholecystectomy. (Chapter 7)
- To assess the bacteriological data of bile cultures after laparoscopic and open gallbladder surgery. (Chapter 8)
- To analyse the risk factors for conversion from laparoscopic to open cholecystectomy. (Chapter 9)
- To determine retrospectively the results, complication rate and mortality in patients who have undergone open surgical common bile duct exploration in the last eight years. (Chapter 10)

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CHAPTER 2

REVIEW OF THE LITERATURE

2.1 TREATMENT MODALITIES OF GALLBLADDER DISEASE

2.1.1 History of gallbladder disease and cholecystectomy

The gallbladder and its contained concretions were recognized for centuries before the birth of Christ. The sinister complications and high mortality of gallbladder disease were well-known. Anatomic knowledge of the liver, bile ducts and gallbladder as demonstrated by clay models of sheep livers made by the Babylonians dated from 2,000 B.C.[1]. The Babylonians considered the liver to be the seat of all life. Gallstones were found in the mummy of the Egyptian priestess Amen, circa 1500 B.C. The anatomic knowledge of Hippocrates, 460 B.C., was based on observations made on slaughtered and sacrificed animals. He first recognized the esophagus, the stomach and the liver[2]. Aristotelian anatomy described the liver and gallbladder, which was noted to be attached to the liver and was considered to contain bile. Alexander (525-606), a Greek physician, described concretions within the bile ducts[3]. Nearly 400 years elapsed before mention of gallstones again appeared in the medical literature, namely by Rhazes (841-921), a Persian, who described gallstones in an ox[3].

Surgical treatment of cholecystolithiasis was first described in the 17th century. Johannus Jaenis performed the first cholecystolithotomy in 1673[4]. Jean Louis Petit, a French surgeon, in 1743 introduced many new surgical concepts and described that the gallbladder can be opened after an abscess had formed in it and had become adherent to the abdominal wall. Richter (1798) made the logical suggestion, that the gallbladder might be punctered with a pointed tube. In 1867 John Bobbs performed the first elective cholecystotomy for a hydrops of the gallbladder, which he reported on The Transactions of the Indiana State Society in 1868[5]. The first cholecysto-enterostomy was performed by von Winiwarter, a pupil of Billroth, in 1880. This would prevent the biliary fistula and would also overcome the complication of recurrent obstruction caused by common bile duct stones. With further experience Langenbuch (1846-1901) performed the first cholecystectomy in a patient in 1882[6]. Ludwig Courvoisier (1843-1918) made numerous contributions to the understanding of diseases of the biliary tract. In 1890 he was the first to remove a stone from the common bile duct[7].

2.1.2 Laparoscopic cholecystectomy

Laparoscopy was first performed almost 90 years ago by Kelling[8] who utilized a cystoscope and thus was able to view the intra-abdominal organs of the dog. He applied the name "celioscopy" to this procedure. Ott used a speculum and with the aid of a mirror was similarly able to visualize the peritoneal contents[9]. Many other authors contributed to the development of this new technique. Jacobaeus, a Swedisch physician, applied the same technique to humans and, at this time, applied the name "laparoscopy"[10]. The first known textbook, in which the procedure was titled "laparothoracoscopy" was published by Korbsch in 1927 in Munich, Germany. Most of these early pioneers utilized instruments which had been developed for cystoscopy. Kalk's contribution is especially pertinent to the subject of diagnostic laparoscopy, because he developed the multiple trocar system, together with numerous instruments[11]. Despite the efforts of these early investigators, in only a few centers laparoscopic procedures were taken up by surgeons. It was only with the advent of laparoscopic cholecystectomy that the general surgeon suddenly became interested in other indications for laparoscopy.

Two years after the introduction of laparoscopic cholecystectomy the first three large series were reported in the literature[12-14]. First there was "the European experience with laparoscopic cholecystectomy" reported by A. Cuschieri[12]. He described a retrospective study of 7 European centers involving 20 surgeons who undertook 1236 laparoscopic cholecystectomies. The procedure was completed in 1191 patients. Conversion to open cholecystectomy was necessary in 45 (3.6%) patients. There were no deaths reported, and the total postoperative complication rate was 1.6% (20 of 1203), with serious complications in 9 patients requiring laparotomy. Bile duct damage was reported in 4 patients. Cushieri concluded that despite these problems laparoscopic cholecystectomy is a well established surgical procedure. There have been few instances in the history of surgical practice where the benefits of a procedure became so clear in such a short time spare.

A second, prospective study describing 500 laparoscopic cholecystectomies, was published by C.R. Voyles[13]. The laparoscopic procedure was completed in 95% of the patients. There was no mortality or bile duct injury. He concluded that laparoscopic cholecystectomy was a safe procedure in the treatment of gallbladder disease.

The Southern Surgeons Club described 1518 laparoscopic cholecystectomies in a prospective analysis, in order to evaluate the safety of this procedure[14]. In 72 patients (4.7%) the operation had to be converted to a open cholecystectomy. In total 82 complications occurred in 78 patients (5.1%); this percentage matches the complication rates reported for open cholecystectomy[15-17]. Their conclusion is that the results of laparoscopic cholecystectomy compare favorably with those of open cholecystectomy with respect to mortality, complications and length of hospital stay. A slightly higher incidence of biliary tract injury in the laparoscopic procedure is probably offset by the low incidence of other complications. Furthermore it is possibly caused by the inexperience of most surgeons starting endoscopic procedures.

Presently, laparoscopic cholecystectomy has clearly become the treatment of choice for patients with symptomatic cholecystolithiasis[18]. With the enormous experience surgeons are acquiring in laparoscopic cholecystectomy worldwide, contraindications to a laparoscopic approach are few. Some experienced surgeons recommend a case-by-case evaluation for determination of the indications for laparoscopic surgery[19].

2.1.3 Laparoscopic versus open cholecystectomy

In the literature there are no large randomized controlled trials concerning open versus laparoscopic cholecystectomy. There are a few exceptions, however these studies are based on trials with a high rate of withdrawal after randomisation, a selection bias and a difficult patient recruitment[20-23]. Neugebauer, Troidl, Spangenberger et al.[24] considered to use a randomized trial to assess the value of laparoscopic cholecystectomy. However, the advantages and disadvantages for the timing of such a trial were in favour of not starting such a trial until there was a great experience in laparoscopic surgery. For this reason they started an observational study to demonstrate that the laparoscopic procedure proved to be as safe and feasible to use as the conventional method. They proved that there were strong benefits in the laparoscopic group in terms of quicker recovery, less pain, less discomfort, and a reduction of hospitalization time. Nowadays, the planning of a randomized controlled study will place ethical constraints with the patients as well with the surgeons. Currently, comprehensive surveillance and monitoring of laparoscopic cholecystectomy is the only realistic method to assess the impact of this technique.

Despite the lack of large prospective, randomized studies between laparoscopic and open cholecystectomy, most reports described in the literature demonstrate the superiority, or at least the equivalence, of the laparoscopic procedure[14,25-27]. The overall morbidity and mortality after laparoscopic cholecystectomy are similar to the reported experience with open cholecystectomy. The overall morbidity after laparoscopic cholecystectomy ranges from 1% to 5.1%, with major complications occurring in 0.7% to 2% of patients and minor complications in 4%[12,14,25,28-31]. Operative mortality following laparoscopic cholecystectomy appears to be low, ranging from 0% till 0.1%[12,14,25,28-32]. These results compare well with the results reported from open cholecystectomy[33-36]. In fact, the mortality of less than 0.1% appears to be better than the 0%-1.5% mortality rate following open cholecystectomy[33,34,37-40]. However this difference may be caused by the early selection bias toward elective patients for laparoscopic cholecystectomy.

2.1.4 Extracorporeal shock wave lithotripsy

Extracorporeal shock wave lithotripsy (ESWL) was developed by Dornier, a German aircraft manufacturer, in the early 1980s, as the result of their investigation into the causes of structural damage to aircraft, which was found to be due to shock waves. Shock waves are high-energy acoustic presssure waves that have a duration of less than a microsecond and an amplitude of 100 to 600 Bar. They are generated within a water medium and focused so that they converge at a cigar-shaped focal zone in which 50% of their energy is concentrated. When the water medium is coupled to the skin of man, shock waves pass through tissue without producing damage and cause fragmentation of stones positioned within the focal zone. Dornier first applied shock wave technology to the development of the kidney lithotriptor[41]. After the good results with ESWL in the treatment of kidney stones, research was started into the possible application of ESWL for gallbladder stones[42]. In 1986 Sauerbruch[43] reported the first clinical results with ESWL for gallbladder stones. Since then many manufacturers have developed and tested lithotriptors for biliary applications[44-48]. The efficacy of ESWL is closely related to the size, number and composition of the gallstones. The best results are obtained in single, radiolucent gallstones which are not larger than 2 cm in diameter[49,50]. In a described patient population (i.e. single <2 cm cholesterol stone) ESWL in combination with oral bile acid therapy is successful in 80-90 % of the cases after approximately one year. A similar success rate has been achieved with 2 - 3 gallstones if their combined diameters does not exceed 2 cm[49]. However, preference is given to the selection of single gallstones for ESWL, because the recurrence rate in this patient population is significantly lower than in multiple gallstones. Sackman[51] described a stone recurrence of 20% in 4 years.

ESWL has proven to be exceedingly safe. No mortality attributable to gallstone ESWL has been reported in the literature. The incidence of complications is very low. Complications of the ESWL are petechiae, haematuria and biliary pain[50]. Acute pancreatitis occurs only in 1-2 % of the patients post ESWL. Acute cholecystitis and the need for emergency surgery are even rarer after lithotripsy. In most centers, ESWL is an outpatient procedure.

ESWL has a clinically not yet fully realized potential as an important procedure in the management of selected symptomatic gallstone patients who either refuse surgery or want to try medical treatment before considering an operation. Since ESWL is most successful in radiolucent, single, <2 cm gallbladder stones, approximately 10% of all patients with biliary symptoms can be estimated to benefit from this procedure. ESWL is, therefore, most effectively used in regional gallstone treatment centers, which offers both surgery and medical alternative treatments, including ESWL and oral bile acid dissolution therapy.

2.1.5 ESWL versus laparoscopic cholecystectomy

ESWL, if performed in a described selected patient population, is successful in almost all patients. It can be carried out on an outpatient basis and has proven to be exceedingly safe. The mortality and the rate of complications appear to be lower than those of laparoscopic cholecystectomy. ESWL is cosmetically highly satisfactory, since it produces no scars.

A drawback of ESWL lies in the limited number of patients in which excellent results can be expected and the potential for gallstone recurrence with the necessity of reinstitution of oral bile acid therapy or possible repeat ESWL.

2.1.6 Laparoscopic versus mini-cholecystectomy

Laparoscopic cholecystectomy has gained wide acceptance for treatment of cholelithiasis in preference to open cholecystectomy, however little is known about the comparison between laparoscopic and mini-cholecystectomy. In 1992 Barkun[20] described a randomized controled trial of laparoscopic versus mini-cholecystectomy. This is an important study as it represents one of the very few prospective randomized trials on laparoscopic cholecystectomy. The authors compared laparoscopic cholecystectomy with mini-cholecystectomy in 70 patients, none of whom were suspected of having common duct stones. The primary endpoints of the study were mean hospital stay, duration of convalescence, and rate of return to normal activities. All showed statistically significant advantages of laparoscopic over mini-cholecystectomy. There was no difference in postoperative pain. The operating time for the laparoscopic approach was longer. This randomised trial showed the superior effectiveness of laparoscopic cholecystectomy over mini-cholecystectomy in treating cholecystolithiasis. McMahon[23] in 1994 also performed a randomized trial between laparoscopic cholecystectomy and minilaparotomy cholecystectomy. He also described a statistical significant difference in postoperative pain, hospital stay, convalescence and operating time in favour of the laparoscopic approach.

However, Majeed et al[52] concluded from their prospective randomized trial that laparoscopic cholecystectomy takes longer to do than small-incision cholecystectomy and does not have any significant advantages in' terms of hospital stay or postoperative recovery.

2.2 INDICATIONS AND CONTRAINDICATIONS

The generally accepted indications for laparoscopic cholecystectomy are the same as those for the open procedure, i.e. gallstones that cause symptoms. It is difficult to assess whether surgeons have broadened the indications for laparoscopic compared to open cholecystectomy. Debate will continue about whether a prophylactic laparoscopic operation is indicated for asymptomatic gallstones[53,54].

The list of generally agreed absolute contraindications has diminished to the patient unfit for general anaesthesia, pregnancy, acute cholangitis, septic peritonitis and severe bleeding disorders (portal hypertension)[26,55-57]. Patients who are not considered candidates for open cholecystectomy due to coexisting medical illness or poor prognosis should not routinely be considered candidates for laparoscopic cholecystectomy, because conversion from laparoscopic to open cholecystectomy is always a possibility.

History of upper abdominal surgery, choledocholithiasis, minor bleeding disorders, known abdominal malignancy and advanced liver disease are relative contraindications[55,57-59]. Patients with one or more of the relative contraindications should be evaluated on a case-by-case basis. The experience of the operative team is perhaps the most important factor. Many patients we would not consider candidates early in our experience will now routinely undergo laparoscopic cholecystectomy.

Considerations for conversion from the laparoscopic procedure to the open cholecystectomy may include gangrene of the gallbladder, impacted common bile duct stones, excessive adhesions, unsuspected pathology, excessive bleeding and an inability of the surgeon to identify the regional anatomy.

2.3 RISK FACTORS

The risk of postoperative complications arising from pre-existing conditions is still uncertain for open as well as for laparoscopic cholecystectomy. Age[60,61], sex, obesity, diabetes[62-65], cardiovascular diseases, history of abdominal disease, immunological disorders (i.e. patients were considered to be immunodeficient if they had cancer, or if they were treated by radiotherapy, corticosteroid therapy or chemotherapeutic agents), liver disease[66] as well as common bile duct exploration[67], occasionally have been incriminated as risk factors.

A number of risk factors are frequently quoted as being associated with an increased risk of postoperative infection. These include age, length of preoperative stay, diabetes, concurrent disease or immunosuppression, duration of surgery, grade of surgeon and obesity. The relative importance of these risk factors is unclear. Each may render the patient more susceptible to a wound infection, but their influence is still dependent upon the degree of endogenous and exogenous contamination encountered at the time of surgery.

It has been suggested that elderly patients have a higher proportion of contaminated operations, and that at the time of surgery the degree of contamination is greater[68], though this has not been confirmed when the type of operation has been accounted for[69]. Little can be done about concurrent disease at operation. Attention should be paid to patient preparation and aseptic technique in all operations.

2.4 COMPLICATIONS

2.4.1 Complications of laparoscopy

Complications associated with creation of the initial pneumoperitoneum are the most frequent. These include subcutaneous emphysema, mediastinal emphysema, pneumothorax, bleeding from the omentum or abdominal wall, gastrointestinal tract perforation, solid visceral injury (spleen or liver), and cardiac arrhythmia.

Injury has also been reported to occur as the trocar is introduced prior to insertion of the laparoscope. Such injuries have included bleeding from abdominal wall vessels or retroperitoneal vascular structures, gastrointestinal tract perforation, hepatic and splenic tears, avulsions or adhesions, omental disruption, and hernia at the trocar insertion site.

Severe hemorrhage from trocar injury to a major portal or retroperitoneal vessel has been reported to occur in only 0.25% of all laparoscopic cholecystectomies. The most common cause of hemorrhage remains injury to the cystic artery and its branches[12,29]. Other sources of bleeding during laparoscopic cholecystectomy include bleeding from the gallbladder fossa or as a result of adhesiolysis[13,14,25,29,70].

Aside from biliary tract and vascular injuries, viscera that have been reported to be damaged during laparoscopic cholecystectomy include the stomach, duodenum, small intestine, colon, liver, and less commonly, diaphragm, mesentery, kidney, bladder, uterus and ovary[12,14,25,28-31]. Deziel reported a bowel injury rate of 0.14% with an overall incidence of visceral injury to be 0.4%[29]. Other large series reporting on laparoscopic cholecystectomy indicate a similar incidence of visceral injury, in the range of 0.1% to 0.4%[14,15,29-32].

There appear to be no associated major vascular injuries or abdominal visceral injuries, except bile duct injuries, described in several large series involving conventional cholecystectomy[33-35]. These increased incidence of visceral injuries may be unique to laparoscopic surgery as a whole.

2.4.2 Complications of cholecystectomy

All of the complications described with diagnostic laparoscopy (Chapter 2.4.1) may occur with the performance of laparoscopic cholecystectomy. In addition, there are complications that are specifically associated with cholecystectomy. These problems are the same that may occur with the open cholecystectomy, although the frequency may differ. Such complications include hemorrhage, bile duct injury, overlooked bile duct stones, bile leakage, perihepatic collections and infection.

Perforation of the gallbladder itself, although not usually significant during the performance of open cholecystectomy, may preclude the successful completion of the laparoscopic approach.

Severe adhesions, inflammations surrounding the gallbladder, and variations in biliary anatomy that render the laparoscopic approach difficult or dangerous may lead the operator to convert the procedure to the open method. Such conversion prior to an injury should not be deemed a failure or complication, but rather a necessary occurence designed to preclude injury to the patient.

2.4.2.1 Bile duct injury

A complication of low frequency, always very serious and with some mortality and a high morbidity, is accidentical lesion of the common bile duct, which has been called "the most catastrophic complication of cholecystectomy". Iatrogenic injury is the most common cause of benign stricture of the extrahepatic bile duct. Data from retrospective series estimate that approximately 0.5% of patients undergoing cholecystectomy sustain a common bile duct injury[71-73]. In laparoscopic cholecystectomy the incidence of bile duct injury seems to be higher compared to the open cholecystectomy[14,26,74,75]. Common bile duct injuries after laparoscopic cholecystectomy are repored to occur between 0.2% and 1%[14,29,76-80].

2.4.2.2 Wound infection

Surgical infection is a major cause of postoperative morbidity and, on ocassion, mortality. It has been estimated that a wound infection will delay the discharge of a patient by 9 - 10 days[81,82].

There is a wide variation in the definition of wound infection in literature and sometimes no definition is given at all. The generally accepted definition of a wound infection is that of the National Research Council which defines infection as "a break of skin or mucous membrane, due to surgery, burns or trauma, which is discharging pus"[83]. However, the need to see a purulent discharge may result in an artificially low rate of infections. Others have taken the presence of a positive culture, together with discharge, as evidence of an infection[84], while some believe that any discharge is an infection[85].

Wound infection can be divided into primary, in which the first discharge is pus, and secondary, in which a serous or other discharge becomes contaminated and colonized by bacteria from an endogenous or exogenous source. Wound infection may be early when it appears within a few days of surgery, or late when it does not appear for up to three weeks after surgery. More than a third of wound infections present late, and any assessment therefore must include follow-up beyond this time[68]. This invariably means that audit must include some form of community follow-up or surveillance[81].

The cause of postoperative wound infection is multifactorial, i.e. exogenous or endogenous. Endogenous contamination of a wound, caused by opening of infected viscera, is the most frequently occurring cause of wound infections in abdominal operations[86]. In biliary tract surgery endogenous contamination is mainly due to infected bile[87]. Exogenous sources include the patient's or operating team's skin and nose, the operating room air or the surgical instruments.

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CHAPTER 3

RESULTS OF OPEN CHOLECYSTECTOMY: A RETROSPECTIVE ANALYSIS IN A TEACHING AND A NON-TEACHING HOSPITAL.

ABSTRACT

In this study clinical records of patients, who underwent a cholecystectomy in the Ikazia Hospital or the Haven Hospital, between 16-12-1986 and 30-05-1989 were scored retrospectively. The records of 663 patients were reviewed. Four patients had to be excluded.

The aim of this study was to determine the results in patients undergoing open surgery for symptomatic bile stones in a teaching and a non-teaching hospital. Endpoint is the percentage of per- and postoperative complications, especially postoperative wound infections.

Fourhundred sixty-five patients (70.6%) were operated at the Ikazia Hospital and 194 (29.4%) at the Haven Hospital. The mean age for the whole serie was 56.2 years (range 18.8 - 92.5). Patients operated at the Ikazia Hospital were significantly ($p=0.007$) older than at the Haven Hospital. As to patient differences the patients in the Ikazia were more at risk.

There were significant differences in surgical procedures between both hospitals. At the Ikazia Hospital more common bile duct explorations were done ($p<0.0001$) and more non-biliary interventions ($p<0.002$) next to the cholecystectomy were performed.

Comparing the two hospitals substantial differences in hospital policies were found. Most profound were differences in methods of standard versus non standard use of drains, bandage versus open treatment of the surgical wounds and the use of antibiotics. There were no significant differences in complications and infection rate between both hospitals.

Of the whole group the incidence of major wound infections was 3.1%. The other postoperative infections were pulmonary infection (2.6%), sepsis (2.0%) and urinary tract infection (1.8%) were the most frequently reported.

From 558 bile cultures taken from gallbladder and common bile duct 235 (42.1%) were positive. The most common organism cultured in bile was Escherichia coli. There was no relationship between the positive bile cultures and the cultures of the wound smear.

In this study 66.1% had one or more specific risk factors for the development of postoperative wound infection, this taken together with the high incidence of positive bile cultures justifies the use of antibiotic prophylaxis in biliary surgery.

3.1 INTRODUCTION

Since the advent of cholecystectomy approximately 100 years ago, mortality[1,2] and morbidity have decreased with safer surgery, anaesthesia, antibiotics and increasingly sophisticated investigation. There is an increase in the number of operations for gallstones[3]. Surgery is reserved for the symptomatic patient. Since bile stone dissolution is only successful in certain patients and recurrence occurs in some patients after cessation of therapy[4], cholecystectomy will remain a frequently performed procedure. Risk factors related to this operation have been defined[5-10].

The aim of this study was to determine retrospectively the results in patients undergoing open surgery for symptomatic bile stones in a teaching and a non-teaching hospital. Endpoint fot this study is the percentage of per- and postoperative complications, especially postoperative wound infections.

3.2 PATIENTS AND METHODS

Between December 1986 and May 1989, a group of eight surgeons performed 663 operations with a primary diagnosis of inflammatory or calculous disease of the gallbladder. Excluded from the series were patients younger than 18 years. Data were recovered from the records of patients operated on in the Haven Hospital, a non teaching, and in the Ikazia Hospital, a teaching hospital, both in Rotterdam, the Netherlands.

The data were analyzed for various factors related to indications and contraindications, treatment technique, length of hospitalization, risk factors and complications. The subgroups were compared for hospital.

Admissions were subdivided into an emergency group and an elective group, which were defined as follows. Emergency admissions were those patients admitted acutely and who either underwent immediate laparotomy or were operated on shortly after admission because of clinical deterioration. The elective admission group were those patients investigated in the outpatient department, followed by elective surgery.

Mortality is defined as the number of patients dying during hospitalization for surgery by the number of operated patients, irrespective of the duration of hospitalization or cause of death.

Morbidity is defined as the number of patients with one or more complications, devided by the number of operated patients.

The wound infections are categorised in three groups namely: major, minor and no wound infection. Major wound infections include all postoperative infections registrated under code 998.5 of the classification of diseases. These include wound abscess, intra-abdominal or subphrenic abscess, as well as sepsis. Erythema and/or serous exudate only are defined as minor.

All histopathology was performed by a single group of pathologists.

Statistical analysis was performed using either one-way analysis of variance for comparison, Chi square for assessing significance of observed versus expected values, or linear regression for correlation as appropriate. Significance was defined as $p < 0.05$.

3.3 RESULTS

The records of 663 patients were reviewed. Fourhundred sixty-five (70.6%) were operated at the Ikazia Hospital and 194 (29.4%) at the Haven Hospital. In both clinics two patients (0.6%) were excluded. Three patients were excluded because they were younger than 18 years. One patient was excluded because his data were unavailable for review. There were 659 (99.4%) patients included in this investigation.

3.3.1 Subgroup comparison for hospital

3.3.1.1 Demographic characteristics

The mean age for the whole serie was 56.2 years (range 18.8 - 92.5). Patients operated at the Ikazia Hospital were significantly ($p=0.007$) older than at the Haven Hospital. Females accounted for the majority of patients in both hospitals, 153 at the Haven Hospital and 325 at the Ikazia Hospital. There were no significant differences in height and weight of the patients between both hospitals. There was a significant difference ($p=0.004$) in hospital stay between both hospitals. Patients stayed 12 days at the Haven versus 15 days at the Ikazia Hospital. Table 3.01 shows comparisons on demographic characteristics controlled for hospital.

Table 3.01: Comparisons on demographic characteristics controlled for hospital.

	TOTAL	MALES	FEMALES
HAVEN	194 (29.4%)	41 (21.1%)	153 (78.9%)
IKAZIA	465 (70.6%)	140 (30.1%)	325 (69.9%)
(Chi square : X2=5.53 df=1; p=0.018: **S.**)			

	TOTAL	HAVEN	IKAZIA
Age Mean	56.2	53.6	57.2
SD	15.6	16.1	15.3
Range	18.8-92.5	18.7-89.7	20.5-92.5
(Oneway : F=7.40: df=1: p=0.007: **S.**)			
Height (cm)			
Mean	167.6	166.9	167.8
SD	8.4	7.7	8.6
Range	144-194	149-187	144-194
(Oneway : F=1.47; df=1; p=0.226: **N.S.**)			
Weight (kg)			
Mean	73.1	72.3	73.5
SD	12.5	11.5	12.8
Range	40-144	47-108	40-144
(Oneway : F=1.04; df=1; p=0.306: **N.S.**)			
Days in hospital			
Mean	14.1	12.1	15.0
SD	11.6	8.8	12.4
Range	4-110	4-68	6-110
(Oneway : F=8.50; df=1; p=0.004: **S.**)			

3.3.1.2 Medical information on trial admission

The mean temperature at trial admission was 37.0° Celsius, with a range from 34.5 till 40.1. Temperature at trial admission showed no significant difference between both hospitals. In Table 3.02 the comparison for hospital is listed.

Table 3.02: Temperature at trial admission.

		TOTAL 659	HAVEN 194	IKAZIA 465
Temperature	mean	37.0	37.2	36.9
	SD	0.71	0.60	0.73
	range	34.5-40.1	35.8-40.10	34.5-40.1

Of the 659 patients reviewed 305 (46.4%) had no history of other disease; 245 (37.3%) had a single and 107 (16.3%) multiple other diseases. In two patients review was not available. The greatest incidence had hypertension (12.0%), followed by gastrointestinal diseases (11.7%), other cardiovasculair diseases (11.1%) and cancer (7.3%). Significantly (p=0.02) more patients at the Ikazia Hospital had a medical history of cancer.

Table 3.03: Medical history, general risk factors.

	TOTAL 659 (100%)	HAVEN 194 (100%)	IKAZIA 465 (100%)	P-value
None	305 (46.4%)	94 (48.5%)	211 (45.5%)	N.S. (0.493)
Single disease	245 (37.3%)	75 (38.7%)	170 (36.7%)	N.S. (0.658)
Multiple diseases	107 (16.3%)	25 (12.9%)	82 (17.7%)	N.S. (0.134)
Missing	2	0	2	
<u>Specified:</u>				
Diabetes mellitus	27 (4.1%)	8 (4.1%)	19 (4.1%)	N.S. (0.999)
Hypertension	79 (12.0%)	18 (8.9%)	61 (13.2%)	N.S. (0.189)
Cardiovasc.: other	73 (11.1%)	16 (8.2%)	57 (12.3%)	N.S. (0.137)
Gastrointestinal	77 (11.7%)	24 (12.4%)	53 (11.4%)	N.S. (0.790)
Cancer	48 (7.3%)	7 (3.6%)	41 (8.9%)	= **0.02**
Liver disease	10 (1.5%)	4 (2.1%)	6 (1.3%)	N.S. (0.490)
COPD	31 (4.7%)	7 (3.6%)	24 (5.2%)	N.S. (0.429)
Drugs/alcohol abuse	5 (0.8%)	0	5 (1.1%)	N.S. (0.328)
Others	87 (13.2%)	30 (15.5%)	57 (12.3%)	N.S. (0.322)

Of the 659 patients reviewed 223 (33.9%) had no specific risk. Two hundred sixty nine (40.9%) had a single risk factor and 166 (25.2%) had multiple risk factors. From one patient the data were not available. The risk factor with the greatest incidence was age > 60 years (43.7%), followed by history of abdominal disease (29.3%). Significantly (p=0.04) more patients with obstructive jaundice as risk factor were operated at the Ikazia Hospital. The other specific risk factors showed no significant difference between both hospitals. Table 3.04 shows a specific list of risk factors. Comparison of the specific risk factors between men and women showed significantly more (p=0.0001) acute cholecystitis in men. The other specific risk factors showed no difference between men and women.

Table 3.04: Specific risk factors.

	TOTAL 659 (100%)	HAVEN 194 (100%)	IKAZIA 465 (100%)	P-value
None	223 (33.9%)	72 (37.1%)	151 (32.5%)	N.S. (0.278)
Single risk	269 (40.9%)	77 (39.7%)	192 (41.3%)	N.S. (0.728)
Multiple risk	166 (25.2%)	45 (23.2%)	121 (26.0%)	N.S. (0.491)
Missing	1		1	
<u>Specified:</u>				
Age > 60 years	288 (43.7%)	74 (38.1%)	214 (46.1%)	N.S. (0.070)
History of abd.	193 (29.3%)	60 (30.9%)	133 (41.3%)	N.S. (0.573)
Both: >60 + abd.	98 (14.9%)	25 (12.9%)	73 (15.6%)	N.S. (0.401)
Acute cholecystitis	66 (10.0%)	22 (11.3%)	44 (9.5%)	N.S. (0.478)
Obstructive jaundice	45 (6.8%)	7 (3.6%)	38 (8.2%)	**= 0.04**
Acute pancreatitis	9 (1.4%)	2 (1.0%)	7 (1.5%)	N.S. (0.733)
Preoperative sepsis	2 (0.3%)	0	2 (0.4%)	N.S. (0.583)
Preoperative ERCP	15 (2.3%)	3 (1.5%)	12 (2.6%)	N.S. (0.570)

3.3.1.3 Preoperative investigations and diagnosis

The departments or Radiology of both hospitals were of great help in diagnosing gallbladder diseases (Table 3.05). The diagnosis was based on ultrasound examination alone in 405 (62.9%) patients, on oral cholecystography in 18 (3.0%) patients and on i.v. cholangiography in 14 (2.2%) patients. Oral cholecystography was used more often by the radiologists at the Haven Hospital. Results of radiology are shown in Table 3.06. From the 659 patients reviewed 489 (74.1%) patients had cholecystolithiasis as preoperative diagnosis, 54 (8.2%) in combination with common bile duct stones, 66 (10.0%) patients had cholecystitis as preoperative diagnosis, 7 (1.1%) accompanied with common bile duct stones. There was a significant difference in preoperative diagnosis. In the Ikazia Hospital more common bile duct stones were diagnosed (Table 3.07).

Table 3.05: Radiology.

	TOTAL 659 (100%)	HAVEN 194 (100%)	IKAZIA 465 (100%)	P-value
Ultrasonography	405 (62.9%)	112 (60.2%)	293 (64.0%)	N.S. (0.219)
Oral cholecystography	18 (3.0%)	13 (7.0%)	5 (1.1%)	**< 0.0002**
IV cholangiography	14 (2.2%)	3 (1.6%)	11 (2.4%)	N.S. (0.573)
Others	13 (2.0%)	6 (3.2%)	7 (1.5%)	N.S. (0.218)
Combinations	182 (28.3%)	49 (26.3%)	135 (29.5%)	N.S. (0.342)
Not done	12 (1.9%)	3 (1.6%)	9 (2.0%)	N.S. (1.000)
Missing data	15	8	7	

Table 3.06: Results radiology (GB = gallbladder).

	TOTAL 659 (100%)	HAVEN 194 (100%)	IKAZIA 465 (100%)	P-value
Bile stones	457 (71.1%)	138 (74.2%)	319 (69.7%)	N.S. (0.578)
Non-imaging GB	9 (1.4%)	4 (2.2%)	5 (1.1%)	N.S. (0.460)
Thick GB wall	1 (0.2%)	0	1 (0.2%)	N.S. (0.999)
Suspect bile stones	3 (0.5%)	3 (0.6%)	0	**= 0.025**
Others	22 (3.4%)	5 (2.7%)	17 (3.7%)	N.S. (0.635)
Normal GB	6 (0.9%)	2 (1.1%)	4 (0.9%)	N.S. (1.000)
Combinations	133 (20.7%)	34 (18.3%)	99 (21.6%)	N.S. (0.288)
Not done	12 (1.9%)	3 (1.6%)	9 (2.0%)	N.S. (1.000)
Missing data	16	8	8	

Table 3.07: Preoperative diagnosis.

	TOTAL 659 (100%)	HAVEN 194 (100%)	IKAZIA 465 (100%)	P-value
Cholecystolithiasis	435 (65.9%)	144 (74.2%)	291 (62.4%)	**< 0.004**
+ choledocholithiasis	(54; 8.2%)	(2; 1.0%)	(52; 11.2%)	**< 0.0001**
Cholecystitis	66 (10.0%)	24 (12.4%)	42 (9.0%)	N.S. (0.201)
+ choledocholithiasis	(7; 1.1%)	(1; 0.5%)	(6; 1.3%)	N.S. (0.679)
Choledocholithiasis	5 (0.8%)	0	5 (1.1%)	N.S. (0.328)
Others	35 (5.3%)	8 (4.1%)	27 (5.8%)	N.S. (0.448)
Combinations	118 (17.9%)	18 (9.3%)	100 (21.5%)	**= 0.001**

3.3.1.4 Surgical findings

All operations were performed under general anaesthesia regardless of patient age or condition. One hundred and sixty five (25.0%) patients were operated acutely and 494 (75.0%) electively. Significantly more emergency procedures were performed at the Ikazia Hospital (Table 3.08). The mean time of surgery showed no significant difference between both hospitals. Almost all operations (89.2%) were carried out by way of a right subcostal incision. Surgeons at the Ikazia Hospital made significantly more median incisions (Table 3.09). Cholecystectomy was completed at the primary operation. Common duct exploration was carried out for the usual indications such as a history of jaundice, elevated liver functions tests, an elevated serum amylase level or a common duct diameter greater than 10 mm. The procedures performed are shown in Table 3.10. There were great significant differences in surgical procedures between both hospitals. At the Ikazia Hospital more common bile duct explorations were done ($p<0.0001$). More non-biliary interventions ($p<0.002$) next to the cholecystectomy were performed at the Ikazia Hospital.

Of the 659 patients 592 (90.2%) had bilestones and 75 (11.4%) had stones in the common bile duct. In 65 (9.8%) patients an infiltrate of the gallbladder was found. The surgical findings are shown in Table 3.11. Significantly more common bile duct stones were found in patients operated at the Ikazia Hospital. Infiltrate and/or gangrene of the gallbladder were found in the Haven Hospital.

Table 3.08: Operation circumstances and duration of surgery.

	TOTAL 659 (100%)	HAVEN 194 (100%)	IKAZIA 465 (100%)	P-value
Acute	165 (25.0%)	38 (19.6%)	127 (27.3%)	**= 0.038**
Elective	494 (75.0%)	156 (80.4%)	338 (72.7%)	
Time surgery (hh:mm)				
Mean	1:06	1:02	1:07	
Median	:60	:60	:55	
SD	:36	:22	:41	
Range	:20-5:08	:25-3:20	:20-5:08	

Table 3.09: Incision.

	TOTAL 659 (100%)	HAVEN 194 (100%)	IKAZIA 465 (100%)	P-value
Right subcostal	586 (89.2%)	182 (94.3%)	404 (87.0%)	**= 0.009**
Other subcostal	22 (3.3%)	3 (1.6%)	19 (4.1%)	N.S. (0.103)
Median incision	49 (7.5%)	8 (4.1%)	41 (8.8%)	**= 0.035**
Missing data	2	1	1	

Table 3.10: Surgical procedures.

	TOTAL 659 (100%)	HAVEN 194 (100%)	IKAZIA 465 (100%)	P-value
Subserosal cholecystectomy	414 (62.9%)	152 (78.8%)	262 (56.3%)	**< 0.0001**
+ CBD exploration	127 (19.3%)	14 (7.3%)	113 (24.3%)	**< 0.0001**
+ other intervention	107 (16.2%)	18 (9.3%)	89 (19.1%)	**< 0.002**
Non-sub. cholecystectomy	7 (1.1%)	6 (3.1%)	1 (0.2%)	**= 0.003**
Partial cholecystectomy	3 (0.5%)	3 (1.6%)	0	**= 0.025**
Missing data	1	1	-	

Table 3.11: Surgical findings

	TOTAL 659 (100%)	HAVEN 194 (100%)	IKAZIA 465 (100%)	P-value
Bilestones only	398 (60.7%)	127 (65.8%)	271 (58.4%)	N.S. (0.096)
Bilestones + others	194 (29.6%)	49 (25.4%)	145 (31.3%)	N.S. (0.134)
Others, no stones	64 (9.7%)	17 (8.8%)	47 (10.1%)	N.S. (0.666)
Missing	3	1	2	
Specified:				
Bilestones	592 (90.2%)	176 (91.2%)	416 (89.7%)	N.S. (0.673)
CBD stones	75 (11.4%)	4 (2.1%)	71 (15.3%)	**< 0.0001**
Infiltrate	65 (9.8%)	23 (11.9%)	42 (9.1%)	N.S. (0.315)
Empyema	21 (3.2%)	11 (5.7%)	10 (2.2%)	= **0.026**
Gangrene	13 (2.0%)	8 (4.1%)	5 (1.1%)	= **0.025**
Perforation	9 (1.4%)	2 (1.0%)	7 (1.5%)	N.S. (0.733)
Hydrops	44 (6.7%)	7 (6.3%)	37 (7.9%)	N.S. (0.056)
No abnormalities	15 (2.3%)	3 (1.6%)	12 (2.9%)	N.S. (0.570)

Fivehundred sixty-nine (86.3%) patients were operated without surgical complications. In 6 (0.9%) patients there was an accidental lesion of the common bile duct. The other complications during surgery are shown in Table 3.12.

Table 3.12: Peroperative complications.

	TOTAL 659 (100%)	HAVEN 194 (100%)	IKAZIA 465 (100%)	P-value
None	569 (86.3%)	167 (86.1%)	402 (86.5%)	N.S. (0.275)
Damage to liverbed	31 (4.7%)	10 (5.2%)	21 (4.7%)	N.S. (0.264)
Unspecified bleeding	6 (0.9%)	4 (2.1%)	2 (0.4%)	N.S. (0.06)
Multiple adhesions	24 (3.6%)	6 (3.1%)	18 (3.9%)	N.S. (0.660)
Accidental CBD lesion	6 (0.9%)	3 (1.6%)	3 (0.6%)	N.S. (0.366)
Other	21 (3.2%)	3 (1.6%)	18 (3.9%)	N.S. (0.147)
Missing data	2	1	1	

Peroperative differences were seen in the use of drains and abdominal washing. The results are shown in Table 3.13. Abdominal washing with saline was performed in 19.8% of the patients operated at the Ikazia Hospital. In almost all patients at the Ikazia Hospital a drain was used. T-tubes were more used because more common bile duct explorations were done.

In 49 patients (10.6%) operated at the Ikazia Hospital the wound was washed with a betadin solution. Surgeons at the other hospital didn't use this technique.

Table 3.13: Factors concerning wound assessment.

	TOTAL 659 (100%)	HAVEN 194 (100%)	IKAZIA 465 (100%)	P-value
Abdominal washing				
No	499 (84.1%)	171 (95.5%)	328 (79.3%)	**< 0.0001**
Saline	90 (15.2%)	8 (4.5%)	82 (19.8%)	**< 0.0001**
Other	4 (0.7%)	0	4 (1.0%)	N.S. (0.322)
Missing data	66	15	51	
Drains:				
None	167 (25.3%)	152 (78.4%)	15 (3.2%)	
T-tube only	3 (0.5%)	1 (0.5%)	2 (0.4%)	N.S. (0.999)
Wound drain only	351 (53.3%)	30 (15.5%)	321 (69.1%)	
Both	138 (20.9%)	11 (5.7%)	127 (27.3%)	**< 0.0001**
Other drains	42 (6.4%)	6 (3.1%)	36 (7.7%)	**= 0.023**

3.3.1.5 Postoperative information

Postoperatively differences in wound management between the hospitals were seen. Fourhundred eighty-seven (74.0%) patients had the wound covered by a dry bandage, 171 (26.0%) wounds were treated in an open fashion. At the Ikazia Hospital almost all patients had a bandage in contrast to the Haven Hospital where most wounds were treated open. In 24 (3.6%) patients extra wound treatment was necessary because of a wound infection. The extra treatments are shown in Table 3.14.

Table 3.14: Wound treatment.

	TOTAL 659 (100%)	HAVEN 194 (100%)	IKAZIA 465 (100%)	P-value
Open	171 (26.0%)	170 (87.6%)	1 (0.2%)	
Dry bandage	487 (74.0%)	24 (12.4%)	463 (99.8%)	
Missing data	1		1	
Extra wound treatment:				
No	632 (96.4%)	185 (95.4%)	448 (96.8%)	N.S. (0.494)
Yes	24 (3.6%)	9 (4.6%)	15 (3.2%)	
Missing data	3	0	3	
Specified:				
Drainage of pus	9 (1.4%)	4 (2.1%)	5 (1.1%)	N.S. (0.678)
Woundcleaning	9 (1.4%)	6 (3.1%)	3 (0.6%)	**= 0.03**
Stitches removed	2 (0.3%)	1 (0.5%)	1 (0.2%)	N.S. (0.999)
Wet bandage	5 (0.8%)	1 (0.5%)	4 (0.9%)	N.S. (0.664)
Eusol in wound	7 (1.1%)	0	7 (1.5%)	**= 0.02**
Antibiotics in wound	2 (0.2%)	1 (0.5%)	1 (0.2%)	N.S. (0.999)

Fivehundred and two (76.2%) patients had no postoperative temperature elevation. Comparing temperature elevation between both hospitals significant difference (p=0.006) was seen in teperature elevation caused by a pulmonary infection. In 54 (8.2%) patients the cause of the temperature elevation was uncertain, and in 52 (7.9%) no reason was given. The causes of temperature elevation are given in Table 3.15.

Table 3.15: Post-operative temperature elevation.

	TOTAL 659 (100%)	HAVEN 194 (100%)	IKAZIA 465 (100%)	P-value
No	502 (76.2%)	142 (73.2%)	360 (77.5%)	N.S. (0.269)
Wound infection	5 (0.8%)	2 (1.0%)	3 (0.6%)	N.S. (0.634)
Pulmonary infection	14 (2.1%)	9 (4.6%)	5 (1.1%)	= **0.006**
Bile leakage	2 (0.3%)	0	2 (0.4%)	N.S. (0.583)
Pancreatitis	6 (0.9%)	1 (0.5%)	5 (1.1%)	N.S. (0.615)
Other (infections)	24 (3.6%)	8 (4.1%)	16 (3.4%)	N.S. (0.819)
Cause is uncertain	54 (8.2%)	24 (12.4%)	30 (6.4%)	= **0.018**
No reason given	52 (7.9%)	8 (4.1%)	44 (9.4%)	= **0.018**

Fivehundred sixty-two (85.3%) patients were operated without post-operative complications. Five (0.8%) patients developed a wound haematoma, 8 (1.5%) had a bleeding and 16 (2.4%) had to be reoperated. In 13 (2.0%) of these reoperated patients there was a suspicion of retained common bile duct stones. There were no significant differences in postoperative complications between both hospitals.

Table 3.16: Postoperative complications.

	TOTAL 659 (100%)	HAVEN 194 (100%)	IKAZIA 465 (100%)	P-value
None	562 (85.3%)	167 (86.1%)	395 (85.0%)	N.S. (0.720)
Wound haematoma	5 (0.8%)	2 (1.0%)	3 (0.6%)	N.S. (0.624)
Haemorrhage	8 (1.5%)	5 (2.6%)	3 (0.6%)	N.S. (0.052)
Reoperation	16 (2.4%)	2 (1.0%)	14 (3.0%)	N.S. (0.169)
Bile leakage	1 (0.2%)	1 (0.5%)	0	N.S. (0.294)
Other	84 (12.7%)	20 (10.3%)	64 (13.7%)	N.S. (0.250)

No significant differences in postoperative infections between both hospitals were diagnosed. The greatest incidence had pulmonary infections (2.6%). The postoperative infections are listed in Table 3.17.

Table 3.17: Postoperative infections.

	TOTAL 659 (100%)	HAVEN 194 (100%)	IKAZIA 465 (100%)	P-value
None	594 (90.3%)	173 (89.2%)	421 (90.7%)	N.S. (0.670)
Urinary tract infection	12 (1.8%)	3 (1.5%)	9 (1.9%)	N.S. (1.000)
Sepsis	13 (2.0%)	4 (2.1%)	9 (1.9%)	N.S. (1.000)
Pulmonary infection	17 (2.6%)	9 (4.6%)	8 (1.7%)	N.S. (0.054)
Various infections	17 (2.6%)	3 (1.5%)	14 (3.0%)	N.S. (0.419)
Other	5 (0.8%)	2 (1.0%)	3 (0.6%)	N.S. (0.634)
Missing data	1	-	1	

Table 3.18 shows the histopathological diagnoses. The majority of patients had chronic cholecystitis (77.6%). Histologically normal gallbladders without evidence of inflammation were removed from 15 patients (2.3%). Significantly more gallbladders with a histopathological diagnosis of acute inflammation were found at the Ikazia Hospital, while chronic active inflammation was found more frequently at the Haven Hospital.

Table 3.18: Histopathological diagnosis.

	TOTAL 659 (100%)	HAVEN 194 (100%)	IKAZIA 465 (100%)	P-value
Chronic inflammation	509 (77.6%)	159 (82.8%)	350 (75.6%)	N.S. (0.066)
Chronic active inflammation	49 (7.5%)	21 (10.9%)	28 (6.0%)	= **0.049**
Acute inflammation	44 (6.7%)	7 (3.6%)	37 (8.0%)	= **0.041**
No sign of inflammation	15 (2.3%)	0	15 (3.2%)	= **0.008**
Carcinoma	5 (0.8%)	3 (1.6%)	2 (0.4%)	N.S. (0.154)
Others/combinations	31 (4.7%)	0	31 (6.7%)	< **0.0001**
Missing data	6	4	2	

The postoperative deaths are shown in Table 3.19. The mortality rate was 0.9%. There was no significant difference between both hospitals in mortality rate. The surgical related deaths were due to pancreatitis.

Table 3.19: Postoperative deaths.

	TOTAL 659 (100%)	HAVEN 194 (100%)	IKAZIA 465 (100%)	P-value
No	653 (99.1%)	193 (99.5%)	460 (98.9%)	N.S. (0.676)
Yes	6 (0.9%)	1 (0.5%)	5 (1.1%)	
specified:				
Hemorrhage	1	0	1	
Lung embolism	1	1	0	
Heart failure	1	0	1	
Respiratory failure	1	0	1	
Pancreatitis	1	0	1	
Pancancreatitis/pneumonia	1	0	1	

3.3.1.6 Follow-up information

Fivehundred fourty-nine (84.7%) patients visited the outpatient department. Only 107 patients (56.3%) operated at the Haven Hospital were seen at the outpatient department versus 442 patients (96.5%) at the Ikazia (Table 3.20).

Tabel 3.20: Follow-up.

	TOTAL 659 (100%)	HAVEN 194 (100%)	IKAZIA 465 (100%)	P-value
No	93 (14.4%)	82 (43.2%)	11 (2.4%)	**< 0.0001**
Yes	549 (84.7%)	107 (56.3%)	442 (96.5%)	
Patients died	6 (0.9%)	1 (0.5%)	5 (1.1%)	N.S. (0.676)
Missing data	11	4	7	

Of the 549 patients seen at the outpatient department 395 (72.1%) had no complaints. Thirty-eight (6.9%) patients complained about woundpain and 16 (2.9%) had abdominal pain. There were no significant differences between both hospitals (Table 3.21).

Table 3.21: Outpatient department parameters.

	TOTAL 659 (100%)	HAVEN 194 (100%)	IKAZIA 465 (100%)	P-value
No complaints	395 (72.1)	76 (71.7%)	319 (72.2%)	N.S. (0.811)
Woundpain	38 (6.9%)	7 (6.6%)	31 (7.0%)	N.S. (0.999)
Abdominal pain	16 (2.9%)	3 (2.8%)	13 (2.9%)	N.S. (1.000)
Others	100 (18.2%)	21 (19.6%)	79 (17.8%)	N.S. (0.676)
Missing data	110	87	23	

3.3.2 Antimicrobial therapy

There was a large variation in the use of antimicrobial agents (Table 3.22). Threehundred ninety-six (60.3%) patients received no antibiotics. The mostly used antimicrobial agents were the combination of gentamicin and ampicillin (15.1%) or gentamicin in combination with metronidazole (6.0%). Great differences were observed in antimicrobial therapy between the hospitals. Also the duration of antimicrobial therapy showed a wide variation (Table 3.23). Fifty- nine (9.0%) patients received a single-dose prophylaxis. Onehundred fifteen (17.6%) patients received multiple-dose regimens during one day, and fifty-six (8.6%) received antibiotics for more than 24 hours postoperatively.
In two of the 659 patients topical amplicox powder was used to prevent wound infection.

Table 3.22: Antimicrobial agents.

	TOTAL 659 (100%)	HAVEN 194 (100%)	IKAZIA 465 (100%)	P-value
None	396 (60.3%)	143 (74.1%)	253 (54.6%)	**< 0.0001**
Gentamicin (genta)	2 (0.3%)	0	2 (0.4%)	N.S. (0.545)
Genta + Metronidazol	39 (6.0%)	2 (1.0%)	37 (8.0%)	**= 0.0002**
Genta + Ampicillin	99 (15.1%)	0	99 (21.3%)	**< 0.0001**
Genta + Amoxycillin	9 (1.4%)	1 (0.5%)	8 (1.7%)	N.S. (0.294)
Genta + Augmentin	7 (1.1%)	0	7 (1.5%)	N.S. (0.111)
Genta + Erythromycin	1 (0.2%)	0	1 (0.2%)	N.S. (0.999)
Metronidazol	1 (0.2%)	1 (0.5%)	0	N.S. (0.294)
Metronidazol + Amoxycillin	1 (0.2%)	0	1 (0.2%)	N.S. (0.999)
Ampicillin	2 (0.3%)	0	2 (0.4%)	N.S. (0.545)
Amoxycillin	1 (0.2%)	0	1 (0.2%)	N.S. (0.999)
Augmentin	8 (1.2%)	0	8 (1.7%)	N.S. (0.112)
Cotrimoxazol	4 (0.6%)	4 (2.1%)	0	**= 0.007**
Erythromycin	2 (0.3%)	0	2 (0.4%)	N.S. (0.545)
Others	81 (12.3%)	42 (21.8%)	39 (8.4%)	
Missing data	2	1	1	

Table 3.23: Duration of antimicrobial therapy.

	TOTAL 659 (100%)	HAVEN 194 (100%)	IKAZIA 465 (100%)	P-value
Variable	396 (60.6%)	143 (74.1%)	253 (55.1%)	**< 0.0001**
Once during operation	59 (9.0%)	10 (5.2%)	49 (10.6%)	**= 0.025**
One day	115 (17.6%)	12 (6.2%)	103 (22.3%)	**< 0.0001**
Several days	56 (8.6%)	23 (11.9%)	33 (7.2%)	N.S. (0.064)
Day before operation	25 (3.8%)	3 (1.6%)	22 (4.8%)	**= 0.048**
Begining/end operation	2 (0.3%)	2 (1.0%)	0	N.S. (0.086)
Missing data	6	1	5	

3.3.3 Wound infections

Wound assessment based on status reports were categorised into three groups namely: "no wound infection", "minor" and "major".

A total of 81 wound infections of some sort was reported. Details are given in Table 3.24. During the hospital period 10 were rated as minor, while 20 were rated as major wound infection. Fistula and purulent discharge along the T-tube with a good healing of the wound were rated as minor. At the outpatient department 36 were rated as minor, while 15 were rated as major wound infection.

Table 3.24: Ratings woundhealing.

During hospital period:		
Uncomplicated	-	621 (95.4%)
Infiltrate	+	3 (0.5%)
Hematoma	#	1 (0.2%)
Erythema	#	3 (0.5%)
Exudate	#	2 (0.3%)
Purulence (T-tube)	#	3 (0.5%)
Infection drain hole	+	1 (0.2%)
Fistula	#	1 (0.2%)
Wound infection	+	16 (2.5%)
Missing		8
Outpatient department:		
Good healing	-	493 (75.6%)
Disturbed healing	#	2 (0.3%)
Scar separation	#	8 (1.3%)
Exudate	#	19 (2.9%)
Infiltrate	+	4 (0.6%)
Fluid under scar	#	2 (0.3%)
Erythema	#	1 (0.2%)
Purulence	+	5 (0.8%)
Bile fistula	-	1 (0.2%)
Hernia cicatricalis	-	1 (0.2%)
Haematoma	#	1 (0.2%)
Wound open; no inflammation	#	3 (0.5%)
Wound partially infected	+	2 (0.3%)
Wound infection	+	4 (0.6%)
Missing		8

Note:
- = rated as "no wound infection"
= rated as "minor wound infection"
+ = rated as "major wound infection"

The rating system described here leads to in-hospital wound infection percentage of 3.1% (20/651). Assessment of wound infection (in-hospital according to status) controlled for gender and hospital is shown in Table 3.25.

For the outpatient department assessments the wound infection percentage is 2.7% (15/546). However, 105 patients had no appointment at the outpatient department; it mainly concerned patients operated at the Haven Hospital. The assessments of wound infection (Outpatient department according to status) controlled for gender and hospital are shown in Table 3.26. There was no significant difference in wound infections between men and women and between both hospitals.

Table 3.25: Assessments of wound infection (in-hospital according to status) controlled for gender and hospital.

N = 651	MALES	FEMALES	P-value
No wound infection	165 (93.8%)	456 (96.0%)	N.S. (0.291)
Minor	3 (1.7%)	7 (1.5%)	N.S. (0.999)
Major	8 (4.5%)	12 (2.5%)	N.S. (0.203)
N = 651	**HAVEN**	**IKAZIA**	**P-value**
No wound infection	181 (93.3%)	440 (96.3%)	N.S (0.150)
Minor	4 (2.1%)	6 (1.3%)	N.S. (0.494)
Major	9 (4.6%)	11 (2.4%)	N.S. (0.140)
Missing: 8			

Table 3.26: Assessments of wound infection (Outpatient department according to status) controlled for gender and hospital.

N = 651	MALES	FEMALES	P-value
Unknown	(20)	(85)	
No wound infection	141 (88.7%)	354 (91.5%)	N.S. (0.332)
Minor	12 (7.5%)	24 (6.2%)	N.S. (0.571)
Major	6 (3.8%)	9 (2.3%)	N.S. (0.389)
N = 651	**HAVEN**	**IKAZIA**	
Unknown	(85)	(20)	
No wound infection	99 (95.2%)	396 (89.6%)	N.S. (0.09)
Minor	4 (3.8%)	32 (7.2%)	N.S. (0.273)
Major	1 (1.0%)	14 (3.2%)	N.S. (0.323)
Missing: 8			

In the hospital 20 wound infections were diagnosed, while at the outpatient department 15 wound infections were diagnosed.
There is no relationship between the wound infections in the hospital and the wound infections at the outpatient department (Table 3.27).

Table 3.27: Relationship between wound infections in the hospital and at the outpatient department.

In-hospital		Outpatient department	
Minor	10	No wound infection	4
		Minor	1
		Major	1
		Unknown	4
Major	20	No wound infection	11
		Minor	4
		Major	4
		Unknown	1

Also 20 patients developed a wound infection (in-hospital). The predominant organisms in the woundsmear were Escherichia coli (6 isolates), Staphylococcus aureus (3 isolates), Pseudomonas aeruginosa (2 isolates), Clostridium welchii (2 isolates) and Enterococcus spp., Morganella and Proteus mirablis (1 isolate). From one woundsmear four organisms were isolated namely Klebsiella spp., Morganella, Enterococcus spp. and Pseudomonas. From 10 patients the woundsmear was missing.
There was no relationship between the peroperative bile cultures and the woundsmears (Table 3.28).

Table 3.28: Micro-organism found in patients with wound infection
In three patients all cultures were missing.

Peroperative bile culture	Woundsmear
- Missing	Staphylococcus aureus Pseudomonas aeruginosa
- Staphylococcus aureus	Staphylococcus aureus Escherichia coli
- Missing	Escherichia coli
- Clostridium welchii	Clostridium welchii Escherichia coli
- Missing	Clostridium welchii Escherichia coli
- Escherichia coli	Escherichia coli
- Escherichia coli	Missing
- Viridans streptococci	Missing
- Escherichia coli	Missing
- Sterile	Missing
- Sterile	Missing
- Escherichia coli	Faecal flora
- Sterile	Sepsis by Staphylococcus aureus
- Sterile	Missing
- Missing	Klebsiella spp., Morganella Enterococcus spp., Pseudomonas
- Escherichia coli	missing
- Sterile	Proteus mirablis Escherichia coli

3.3.4 Bacteriology

From 659 patients a total of 1281 culture specimens were obtained, a mean of two cultures (1.94) per patient. Cultures were positive (i.e. micro-organism(s) detected) in 64.3% (823/1281) and negative in 35.7% (457/1281). Most cultures were taken per-operatively (585) and post-operatively (565). Per-operatively 558 cultures were taken from the gallbladder and/or common bile duct, which in 235 (42.1%) were positive (Table 3.29).
The predominant aerobic organisms were Escherichia coli (93 isolates), Streptococcus spp. (42 isolates), Klebsiella spp. (34 isolates) and Staphylococcus spp. (2 isolates). The predominant anaerobic bacteria were Clostridium (21 isolates) and Bacteroides spp. (3 isolates).

Table 3.29: Survey of bacteriological cultures.

N = 1281	NEGATIVE 457 (35.7%)	POSITIVE 823 (64.3%)
Time culture taken		
Pre-operative	43 (9.4%)	80 (9.7%)
Per-operative	337 (73.7%)	250 (30.4%)
Post-operative	76 (16.6%)	489 (59.4%)
Outpatient department	1 (0.2%)	4 (0.5%)
Sources		
Bile gallbladder	317 (69.4%)	222 (27.0%)
Bile common bile duct	6 (1.3%)	13 (1.6%)
Bile T-tube	2 (0.4%)	40 (4.9%)
Tip T-tube	0	6 (0.7%)
Tip W-drain	0	2 (0.2%)
Urine (midstream)	2 (0.4%)	43 (5.2%)
Urine (catheter)	1 (0.2%)	150 (18.2%)
Blood	102 (22.3%)	26 (3.2%)
Sputum	1 (0.2%)	116 (14.1%)
Wound smear	0	58 (7.0%)
Others	26 (5.7%)	139 (16.9%)
Missing: 1		

Table 3.30: Micro-organisms in operative bile cultures from gallbladder and common bile duct in 659 patients.

N=558	TOTAL
No micro-organisms cultured	323
Gram-negative	
Escherichia coli	93
Klebsiella spp.	34
Enterobacter spp.	11
Citrobacter freundii	6
Proteus spp.	2
Aeromonas hydrophila	2
Gram-positive	
Streptococcus spp.	42
Enterococcus spp.	7
Staphylococcus epidermidis	1
Staphylococcus aureus	1
Coryneforms (diphteroids)	1
Anaerobic	
Clostridium welchii	21
Bacteroides spp.	3
Mixed flora	1
Fungi	
Candida spp.	3
Other organisms	7

3.4 DISCUSSION

In this part of the study clinical records of patients, who underwent a cholecystectomy between 16-12-1986 and 30-05-1989 were scored retrospectively. The records of 663 patients were reviewed. Four patients had to be excluded, three because they were younger than 18 years. The data were analysed after stratification for hospital of admission.

Substantial differences in hospital policies were found. Most profound were differences in methods of standard versus non standard use of drains and bandage versus open treatment of the surgical wound (resp. Ikazia vs. Haven). As to patient differences, more at risk patients were seen in the Ikazia Hospital. Significantly more patients with obstructive jaundice were operated at the Ikazia Hospital. They were on average 3.6 years older. However there was no significant difference between the hospitals in percentage of patients aged > 60 years. As to preoperative diagnosis significantly more common bile duct stones were found at the Ikazia Hospital. More cholecystectomies with common bile duct exploration and other interventions were done and antibiotics were used more often (45.4% vs. 25.9%). Histopathological investigation showed significantly more acute inflammation at the Ikazia. Despite the differences in hospital policies no significant differences were found in postoperative complications and infections.

Endpoint of this study was the percentage of per- and postoperative complications and infections in the whole series. Peroperatively the complication rate was low. The incidence of common bile duct lesion was 0.9%.

Wound infections were reported during hospital stay and at the outpatient department. A total of 81 wound infections in some degree was reported. The incidence of in-hospital major wound infections was 3.1%. Four patients had a wound infection in the hospital that was still present at the outpatient department. Especially at the outpatient department many patients had wound problems; of the 546 who were seen at the outpatient department 51 patients (9.3%) had disturbance of healing to some degree.

The other postoperative infections were pulmonary infection (2.6%), sepsis (2.0%) and urinary tract infection (1.8%) were the most frequently reported. In 17 patients (2.6%) a combination of infections was observed.

Other postoperative complications were haemorrhage (1.5%), reoperation (2.4%) and bile leakage (0.2%). In 13 patients reoperation was performed because of retained common bile duct stones.

It is accepted that wound infections are usually caused by biliary micro-organisms[11-13]. The most common organism cultured in bile was Escherichia coli. On the other hand, we found that Staphylococcus were uncommon in bile; this finding has been reported by other investigators[14-16]. In three patients the same micro-organisms were found in the bile cultures as in the cultures of the wound smear. In the other 17 patients (with major wound infections during hospital stay) this was not assessable.

Whether or not all patients undergoing cholecystectomy should receive antibiotic prophylaxis, remains controversial. It is generally accepted that patients undergoing biliary tract surgery are at higher risk for developing postoperative sepsis if bacteria are present in their bile at the time of operation[13,14,17-19]. In this study peroperative bile cultures from gallbladder and common bile duct were positive in 42.1%. The incidence of bile colonization in low risk patients lies within the range of 8-19 percent[13,18-20] and in high risk patients within the range of 30-45 percent[13,21,22]. Although antibiotic prophylaxis may not be essential in patients without risk factors undergoing biliary tract surgery, a beneficial effect has been reported in other clean operations[23].

In this study 66.1% had one or more specific risk factors for the development of postoperative wound infection or other septic complications and this taken together with the high incidence of positive bile cultures, justifies the use of antibiotic prophylaxis in biliary surgery.

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CHAPTER 4

ANALYSIS OF RISK OF WOUND INFECTION FOLLOWING OPEN BILIARY SURGERY IN PATIENTS RECEIVING AMOXYCILLIN/CLAVULANIC ACID PROPHYLAXIS

ABSTRACT

In this prospective study 407 patients were eligible for infection prophylaxis during biliary surgery, both in the Ikazia and the Haven Hospital. The inclusion criteria were met by 297 (73%) patients leaving 110 (27%) to be excluded.

The aim of this prospective study was to determine the effect of a single dose of amoxycillin/clavulanic acid on per- and postoperative infections in open cholecystectomy. Endpoint was the percentage of complications, especially postoperative wound infections, in different risk groups.

Patients undergoing a open cholecystectomy were enrolled in the study. All patients were treated prophylactically with a single dose of amoxycillin/clavulanic acid. Subgroup stratification was done for hospital of admission. In the Ikazia Hospital a cholecystectomy was performed more often in combination with a common bile duct exploration. Hospital policies were also different regarding abdominal washing and washing of the wound, which were done more often in the Ikazia Hospital. Drains were used routinely in the Ikazia Hospital.

The incidence of major wound infections in the whole group was 5.1% and of minor wound infections 10.1%. Significant risk factors for the development of wound infection were age > 60 years ($p=0.05$), emergency procedure ($p=0.022$), preoperative ERCP ($p=0.03$), common bile duct stones ($p=0.012$), common bile duct exploration ($p<0.001$), duration of the operation ($p=0.014$), closed versus the open woundtreatment ($p=0.021$), drains ($p=0.004$) and bile leakage ($p=0.0125$). Other infections reported were urinary tract infections (1.3%), pulmonary infections (0.7%), sepsis (0.7%) and peritonitis (0.3%). In this prospective study there was no mortality.

In 79.9% no micro-organisms were found in the peroperative bile culture. The Escherichia coli, Klebsiella spp. and Enterococcus spp. were most frequently detected. In 11.3% of the positive cultures resistance for amoxycillin/clavulanic acid was found. Species resistant to amoxycillin/clavulanic acid were Hafnia alvei, Enterobacter cloacae and Escherichia coli (8/34). None of these resistant species caused a wound infection.

According to this study we concluded that a single dose amoxycillin/clavulanic acid is safe and effective in the prevention of infection in biliary surgery.

4.1 INTRODUCTION

Biliary tract surgery usually entails removal of noninflamed gallbladder and is associated with a low post-operative infection rate. However, the need to explore the common bile duct, the presence of biliary duct obstruction, acute cholecystitis, acute pancreatitis, cancer, and/or choledocholithiasis probably will increase the risk of post-operative wound infection[1].

The most prevalent bacteria responsible for postoperative infections are Escherichia coli, Klebsiella spp. and Staphylococcus aureus. Also Enterococcus spp. and anaerobic bacteria are often isolated, but they play a less important role.

The idea of a single dose of a prophylactic antibiotic in at-risk abdominal surgery was first examined over a decade ago[2-6] and there are now numerous studies in the literature. However, many trials have tested a single dose of one agent against multiple doses of one or more agents[7] and few series have achieved as many as hundred patients in each arm of a randomized trial[8-14]. Most studies have shown no significant difference between single and multiple dose regimes.

Amoxycillin/clavulanic acid has been shown to be at least equally effective to other single or multiple agents for infection prophylaxis in abdominal surgery[15-18]. The antibacterial spectrum of amoxycillin/clavulanic acid is especially suited to the organisms encountered in biliary tract surgery, since it covers beta-lactamase producing bacteria, aerobic Gram-negative organisms, Enterococcus spp. and anaerobes.

The aim of this prospective study is to determine the effect of a single dose amoxycillin/clavulanic acid on infection prophylaxis in open cholecystectomy. Endpoint is the percentage of complications, especially postoperative wound infections, in distinct risk groups.

4.2 PATIENTS AND METHODS

All patients aged 18 or over admitted for cholecystectomy to two surgical departments in two adjacent district general hospitals were included in this prospective trial.

4.2.1 Exclusions

All patients known to be allergic to penicillin were excluded. If patients had received antibiotics within the previous 48 hours, or if there was an intention to administer antibiotics other than the trial medication during the 72 hours after operation they were also excluded. Patients with (suspected) pregnancy were not entered into the trial. Patients with impaired renal function (creatinine-clearance < 30 ml/min) were also excluded. Patients with presence of an underlying disease or concomitant infection interfering with evaluation of response were excluded. Patients who declined consent were not entered into the trial although all received prophylactic antibiotics.

4.2.2 Trial design

Patients undergoing cholecystectomy received a single dose of Augmentin[R] at the induction of anaesthesia. Bile samples were collected from the unopened gallbladder and common bile duct for culture and identification.

Clinical chemistry and haematology examinations were performed in accordance with usual hospital routine. During postoperative hospital stay the patient was screened daily for infection, adverse events, and other postoperative complications.

Three weeks after leaving the hospital the patients were examined at the outpatient department, especially with respect to wound complications.

4.2.3 Preoperative assessment

Before operation medical history was taken and the patients underwent a physical examination. The following information was noted in the clinical record form:

- length

- weight
- preoperative diagnosis
- results of routine clinical chemistry and haematology
- general risk factors and
- specific risk factors.

Operation period (day 0)

The operation report must contain information concerning the following items:

- duration of operation
- operation technique
- exploration of the common bile duct
- drains
- perioperative complications and
- relative risk factors.

4.2.4 Prophylactic regimen

Augmentin[R] is a 1:10 combination of amoxycillin and clavulanic acid. Clavulanic acid is an inhibitor of many bacterial beta lactamases and greatly increases the active spectrum of amoxycillin included bacteroides spp. The trial drug was administered by slow intravenous bolus injection as 1.2g of powder dissolved in 10 ml water in a single dose.

Peri-operative sampling of bile for bacteriological examination

1. Perioperative bile samples

   0.5 ml to 1 ml of bile was collected from both the gallbladder and common bile duct by needle aspiration prior to manipulation and dissection.

   Bile samples were sent immediately for bacteriological examination.
2. T-tube samples

   On day 1, 6 and 11 a T-tube bile sample (0,5-1 ml) was collected for bacteriological examination in patients who underwent common bile duct exploration.

   On the seventh postoperative day routine cholangiography was performed and the T-tube was removed 5 days later.

4.2.5 Postoperative assessment

Patients were assessed daily during the hospital stay by measurement of temperature and physical examination, especially concerning symptoms of postoperative infections.

In case of suspected wound-, urinary tract- or other infections, specimens were taken from suspected sites of infection and send for bacteriological examination. This was done before the administration of any form of antimicrobial therapy.

The wound was scored for erythema, serous exudate, purulent exudate, wound edge necrosis and/or separation of deep tissue, daily during the first 7 post-operative days.

4.2.6 Definitions

Urinary tract infection was defined as the presence of more than 10^5 colony forming units of a single species of bacteria per millilitre of urine from a sample of catheter urine or midstream specimen.

The diagnosis of a respiratory tract infection was based on the results of physical examination and, if possible, confirmed by radiological examination of the chest and culture of a sputum sample.

Febrile morbidity was defined as two consecutive rectal temperatures of > 38°C.

4.2.7 Adverse events

Adverse events was recorded in the clinical record form noting the severity, duration and outcome of the event and the investigator judged whether the event was non drug-related, possibly drug-related or probably drug-related.

4.2.8 Bacteriology

Material obtained for bacteriological examination was cultured under aerobic and anaerobic conditions. The species of any organism isolated were identified. Sensitivity to amoxycillin and amoxycillin with clavulanic acid was determined.

In case of a urine sample the number of bacteria per millilitre was determined.

4.2.9 Statistical analysis

Statistical analysis was performed using either one-way analysis of variance for comparison, Chi square for assessing significance of observed versus expected values, or linear regression for correlation as appropriate. Significance was defined as $p < 0.05$.

4.3 RESULTS

There were 407 eligible patients available for the study between June 1989 and May 1991. Over the same period 110 otherwise eligible patients were excluded: 41 at the Haven Hospital and 69 at the Ikazia Hospital. Table 4.01 shows the reasons of exclusion per hospital.

Table 4.01: Reasons of exclusion per hospital.

N = 110	HAVEN	IKAZIA
Pat. < 18 years	0	2 (2.9%)
Hypersensitive to penicillin	4 (9.8%)	15 (21.7%)
Antibiotics < 48 hours preoperative	12 (29.3%)	19 (27.5%)
Antibiotics < 72 hours postoperative	8 (19.5%)	26 (37.7%)
Refused informed consent	5 (12.2%)	0
Partial cholecystectomy	5 (12.2%)	0
Protocol violation	7 (17.1%)	5 (7.2%)
Presence of other disease	0	1 (1.4%)
(Suspicion of) pregnancy	0	1 (1.4%)

3.4.1 Subgroup comparison for hospital

3.4.1.1 Demographic characteristics

The mean age was 53.9 with a range from 18.8 - 87.1. Females accounted for the majority of patients in both hospitals 80 at the Haven Hospital and 138 at the Ikazia Hospital. Age is not significant for both hospitals. Hospital stay showed a significant difference between the both hospitals (Table 4.02).

Table 4.02: Comparisons on demographic characteristics controlled for hospital.

	TOTAL	MALES	FEMALES
HAVEN	114 (38.4%)	34 (29.8%)	80 (70.2%)
IKAZIA	183 (61.6%)	45 (24.6%)	138 (75.4%)

(Chi square : X2=0.986; df=1; p=0.321: **N.S.**)

	TOTAL	HAVEN	IKAZIA
Age Mean	53.9	53.1	54.4
SD	15.8	16.0	15.6
Range	18.8-87.1	21.3-80.3	18.8-87.1
(Oneway : F=0.464: df=1: p=0.495: N.S.)			
Height (cm)			
Mean	168.6	169.6	168.0
SD	8.8	8.3	9.0
Range	146-196	146-186	146-196
(Oneway : F=2.12; df=1; p=0.15: N.S.)			
Weight (kg)			
Mean	75.2	74.6	75.6
SD	13.0	12.5	13.3
Range	47-131	47-131	49-129
(Oneway : F=0.439; df=1; p=0.508: N.S.)			
Days in hospital			
Mean	10.2	8.9	10.9
SD	4.7	4.6	4.6
Range	3-40	3-29	5-40
(Oneway : F=13.4; df=1; p<0.001: S.)			
Outpatient department			
Mean	16.3	17.2	15.8
SD	7.1	7.7	6.6
Range	2 - 47	3 - 37	2 - 47
Missing	18	14	4
(Oneway : F= 2.39; df=1: p=0.123: N.S.)			

4.3.1.2 Medical information on trial admission

The mean temperature at trial admission was 36.9 degrees Celsius, with a range from 35.3 to 38.6. There was no significant difference in temperature at trial admission between both hospitals.

Onehundred fourty-eight patients (50.2%) had no medical history; 112 (38%) had a single disease and 35 (11.9%) had multiple diseases. Significant differences between both hospitals were found in patients with multiple diseases (Table 4.03). The greatest incidence had hypertension 33 (11.1%), followed by other cardiovascular diseases 28 (9.4%), gastro-intestinal disease 23 (7.7%), diabetes mellitus 13 (4.4%) and cancer 13 (4.4%). Significantly more (p=0.007) gastro-intestinal diseases were seen at the Ikazia Hospital.

Table 4.03: Medical history, general risk factors.

	TOTAL 297 (100%)	HAVEN 114 (100%)	IKAZIA 183 (100%)	P-value
None	148 (50.2%)	61 (54.0%)	87 (47.8%)	N.S. (0.341)
Single disease	112 (38.0%)	44 (38.9%)	68 (37.4%)	N.S. (0.806)
Multiple diseases	35 (11.9%)	8 (7.0%)	27 (14.8%)	= **0.044**
Missing data	2	1	1	
Specified:				
Hypertension	33 (11.1%)	9 (7.9%)	24 (13.1%)	N.S. (0.187)
Cardiovasculair: other	28 (9.4%)	11 (9.6%)	17 (9.3%)	N.S. (1.000)
Gastrointestinal	23 (7.7%)	3 (2.6%)	20 (11.0%)	= **0.007**
Diabetes mellitus	13 (4.4%)	4 (3.5%)	9 (4.9%)	N.S. (0.772)
Cancer	13 (4.4%)	5 (4.4%)	8 (4.4%)	N.S. (1.000)
COPD	10 (3.4%)	3 (2.6%)	7 (3.8%)	N.S. (0.746)
Liver disease	8 (2.7%)	6 (5.3%)	2 (1.1%)	N.S. (0.058)
Drugs/alcohol abuse	4 (1.3%)	0	4 (2.2%)	N.S. (0.163)
Others	34 (11.4%)	16 (14.0%)	18 (9.9%)	N.S. (0.163)

From the total of 297 patients 129 (43.6%) had no specific risk factors for the development of wound infection or other septic complications; 110 (37.15) had a single and 57 (19.3%) had multiple specific risk factors as shown in Table 4.04. There was no significant difference in specific risk factors between both hospitals.

Table 04.07: Specific risk factors.

	TOTAL 297 (100%)	HAVEN 114 (100%)	IKAZIA 183 (100%)	P-value
None	129 (43.6%)	54 (47.8%)	75 (41.0%)	N.S. (0.335)
Single risk	110 (37.1%)	37 (32.7%)	73 (39.9%)	N.S. (0.217)
Multiple risk	57 (19.3%)	22 (19.5%)	35 (19.1%)	N.S. (0.999)
Missing data	1	1	0	
Specified:				
Age > 60 years	121 (40.7%)	48 (42.1%)	73 (39.9%)	N.S. (0.717)
History of abd.	80 (26.9%)	26 (22.8%)	54 (29.5%)	N.S. (0.227)
Both: >60 + abd	43 (14.5%)	17 (14.9%)	26 (14.2%)	N.S. (0.866)
Acute cholecystitis	10 (3.4%)	1 (0.9%)	9 (4.9%)	N.S. (0.095)
Obstructive jaundice	11 (3.7%)	4 (3.5%)	7 (3.8%)	N.S. (0.999)
Acute pancreatitis	1 (0.3%)	1 (0.9%)	0	N.S. (0.383)
Preoperative sepsis	1 (0.3%)	1 (0.9%)	0	N.S. (0.383)
Preoperative ERCP	5 (1.7%)	2 (1.8%)	3 (1.6%)	N.S. (1.000)
Reoperation	1 (0.3%)	1 (0.9%)	0	N.S. (0.383)

4.3.1.3. Preoperative investigation and diagnosis

The preoperative diagnosis was based on ultrasound examination in 234 patients, on oral cholecystography in 5 patients (1.7%), on i.v. cholecystography in one patient. Fifty-one patients (17.2%) underwent a combination of abovementioned tests (Table 4.05). An oral cholecystography was only used at the Haven Hospital. As a result of these radiological investigations bile stones were found in 244 patients (Table 4.06). From the 297 patients 246 (82.8%) patients had cholecystolithiasis as preoperative diagnosis, 12 (4.0%) in combination with choledocholithiasis, 20 patients (6.7%) had cholecystitis and 4 patients (1.3%) cholecystitis accompanied with choledocholithiasis (Table 4.07). Significantly more acute cholecystitis as preoperative diagnosis was seen at the Ikazia Hospital.

Table 4.05: Radiology.

	TOTAL 297 (100%)	HAVEN 114 (100%)	IKAZIA 183 (100%)	P-value
Ultrasonography	234 (78.8%)	82 (71.9%)	152 (83.1%)	= **0.028**
Oral cholecystography	5 (1.7%)	5 (4.4%)	0	= **0.007**
IV cholangiography	1 (0.3%)	0	1 (0.5%)	N.S. (0.999)
Others	1 (0.3%)	0	1 (0.5%)	N.S. (0.999)
Combinations	51 (17.2%)	25 (21.9%)	26 (14.2%)	N.S. (0.112)
Not done	3 (1.0%)	0	3 (1.6%)	N.S. (0.288)
Missing data	2	2	0	

Table 4.06: Results radiology.

	TOTAL 297 (100%)	HAVEN 114 (100%)	IKAZIA 183 (100%)	P-value
Gallstones	244 (82.2%)	92 (80.7%)	152 (83.1%)	N.S. (0.641)
Non-imaging gallbladder	3 (1.0%)	3 (2.6%)	1 (0.5%)	N.S. (0.301)
Thick gallbladder wall	1 (0.3%)	1 (0.9%)	0	N.S. (0.383)
Suspect gallstones	2 (0.7%)	1 (0.8%)	1 (0.5%)	N.S. (1.000)
Others	3 (1.0%)	1 (0.8%)	2 (1.1%)	N.S. (1.000)
Normal gallbladder	4 (1.3%)	2 (1.8%)	2 (1.1%)	N.S. (0.639)
Combinations	35 (11.8%)	13 (11.4%)	22 (12.0%)	N.S. (0.999)
Not done	3 (1.0%)	0	3 (1.6%)	N.S. (0.288)
Missing data	2	2	0	

Table 4.07: Preoperative diagnosis.

	TOTAL 297 (100%)	HAVEN 114 (100%)	IKAZIA 183 (100%)	P-value
Cholecystolithiasis	246 (82.8%)	95 (83.3%)	151 (82.5%)	N.S. (0.875)
+ choledocholithiasis	(12; 4.0%)	(5; 4.2%)	(7; 3.8%)	N.S. (0.999)
Cholecystitis	20 (6.7%)	3 (2.6%)	17 (9.3%)	= **0.03**
+ choledocholithiasis	(4; 1.3%)	(2; 1.7%)	(2; 1.1%)	N.S. (0.639)
Others	7 (2.3%)	4 (3.4%)	3 (1.6%)	N.S. (0.434)
Combinations	24 (8.1%)	12 (10.5%)	12 (6.6%)	N.S. (0.274)

4.3.1.4 Surgical findings

Twenty-seven patients (9.1%) were operated acutely and 270 (90.9%) electively. There was no significant difference between the moment of surgery in both hospitals. The mean time between the gift of amoxycillin/clavulanic acid and the incision was twelve minutes, with a range from 10 minutes to one hour. Mostly a form of subcostal incision was used (Table 4.09). The extension of the biliary explorations is given in Table 4.10. Common bile duct exploration was carried out for the usual indications such as history of jaundice, elevated liver functions tests, an elevated serum amylase level or a common bile duct greater than 10 mm. Remarkable was the fact that in the Ikazia Hospital significant more common bile duct explorations were performed, namely 23.5% against 9.6% in the Haven Hospital.

Of the 297 patients 72% had bile stones only, 5.3% had bile stones in combination with stones in the common bile duct and 3.4% in combination with an infiltrate (Table 4.11).

Table 4.08: Operation circumstances and duration of surgery.

	TOTAL 297 (100%)	HAVEN 114 (100%)	IKAZIA 183 (100%)	P-value
Acute	27 (9.1%)	10 (8.8%)	17 (9.3%)	N.S. (1.000)
Elective	270 (90.9%)	104 (91.2%)	166 (90.7%)	
Time surgery (hh:mm)				
Mean	0:57	0:58	0:57	
Median	0:58	0:60	0:50	
SD	0:23	0:18	0:26	
Range	0:20-3:30	0:30-1:45	0:20-3:30	

Table 4.09: Incision.

	TOTAL 297 (100%)	HAVEN 114 (100%)	IKAZIA 183 (100%)	P-value
Right subcostal	285 (96.0%)	106 (93.0%)	179 (97.8%)	N.S. (0.064)
Other subcostal	9 (3.0%)	8 (7.0%)	1 (0.5%)	= **0.002**
Median incision	3 (1.0%)	0	3 (1.6%)	N.S. (0.288)

Table 4.10: Surgical procedures.

	TOTAL 297 (100%)	HAVEN 114 (100%)	IKAZIA 183 (100%)	P-value
Subserosal cholecystectomy	228 (76.8%)	98 (86.0%)	130 (71.0%)	= **0.002**
+ CBD exploration	54 (18.2%)	11 (9.6%)	43 (23.5%)	= **0.003**
+ other intervention	14 (4.7%)	4 (3.5%)	10 (5.5%)	N.S. (0.577)
Non-subserosal cholecystec	1 (0.3%)	1 (0.9%)	0	N.S. (0.383)

Table 4.11: Surgical findings.

	TOTAL 297 (100%)	HAVEN 114 (100%)	IKAZIA 183 (100%)	P-value
Bilestones	213 (72.0%)	81 (71.1%)	132 (72.5%)	N.S. (0.894)
+ CBD stones	16 (5.3%)	6 (5.3%)	10 (5.5%)	N.S. (0.999)
+ infiltrate	10 (3.4%)	2 (1.8%)	8 (4.4%)	N.S. (0.328)
+ other's	40 (14.0%)	18 (14.0%)	25 (13.7%)	N.S. (0.615)
Infiltrate	1 (0.3%)	0	1 (0.5%)	N.S. (0.999)
No abnormalities	5 (1.7%)	1 (0.9%)	4 (2.2%)	N.S. (0.625)
Others	10 (3.4%)	8 (7.0%)	2 (1.1%)	= **0.015**
Missing data	1	0	1	

Twohundred eighty-three patients (95.6%) were operated without peroperative surgical complications. In five patients the operation was complicated by bleeding from the liver. There was one patient with an accidental lesion of the common bile duct and one with a lesion of the hepatic artery. In two patients there was a perforation of the gallbladder (Table 4.12). There was no significant difference in peroperative complications between both hospitals.

A risk factor of wound infection is peroperative bile leakage. In this prospective study 159 patients (53.5%) had no bile leakage. The mean bile leakage was 15.2 ml (Table 4.13). Statistical analysis showed significant more peroperative bile leakage at the Ikazia Hospital.

Table 4.12: Peroperative complications.

	TOTAL 297 (100%)	HAVEN 114 (100%)	IKAZIA 183 (100%)	P-value
None	283 (95.6%)	108 (95.6%)	175 (95.6%)	N.S. (0.781)
Bleeding liverbed	5 (1.7%)	3 (2.7%)	2 (1.1%)	N.S. (0.375)
Accidental CBD lesion	1 (0.3%)	1 (0.9%)	0	N.S. (0.383)
Unspecified bleeding	1 (0.3%)	0	1 (0.5%)	N.S. (0.999)
Hepatic artery lesion	1 (0.3%)	1 (0.9%)	0	N.S. (0.383)
Perforation gallbladder	2 (0.7%)	0	2 (0.9%)	N.S. (0.525)
Bleeding skin	1 (0.3%)	0	1 (0.5%)	N.S. (0.999)
Conversion	2 (0.7%)	0	2 (0.9%)	N.S. (0.525)
Missing data	1	1	0	

Table 4.13: Bile leakage.

	TOTAL 297	HAVEN 114	IKAZIA 183	P-value
Leakage no	159 (53.5%)	45 (39.5%)	114 (56.1%)	**< 0.0002**
yes	138 (46.5%)	69 (60.5%)	69 (37.7%)	
Mean (ml)	15.2	7.5	22.8	
SD	23.7	14.5	28.3	

Other factors concerning wound infection are abdominal washing, drains and wound washing. The results are shown in Table 4.14. There are some remarkable differences between the two hospitals. In 38.8 percent of the patients in the Ikazia Hospital abdominal washing was performed. The surgeons in the Ikazia Hospital used more wounddrains in contrary to the surgeons in the Haven Hospital. Wound washing was not done in the Haven Hospital.

Table 4.14: Factors concerning wound assessment.

	TOTAL 297 (100%)	HAVEN 114 (100%)	IKAZIA 183 (100%)	P-value
Abdominal washing				
No	199 (67.0%)	88 (77.2%)	111 (60.7%)	**= 0.003**
Saline	96 (32.3%)	25 (21.9%)	71 (38.8%)	
Missing data	2	1	1	
Drains				
None	99 (33.3%)	94 (82.5%)	5 (2.7%)	
T-tube only	1 (0.3%)	0	1 (0.5%)	
W-drain only	145 (48.8%)	9 (7.9%)	136 (74.3%)	**< 0.0001**
Both	52 (17.5%)	11 (9.6%)	41 (22.4%)	**= 0.004**
Wound washing				
No	239 (80.7%)	113 (99.1%)	126 (69.2%)	**< 0.0001**
Betadin solution	55 (18.6%)	1 (0.9%)	54 (29.7%)	
Other	2 (0.6%)	0	2 (1.0%)	
Missing data	1	0	1	

4.3.1.5 Postoperative information

There was a difference in postoperative wound treatment beween the Ikazia Hospital and the Haven Hospital. In the Haven Hospital most wounds were treated "open", while in the Ikazia Hospital all wounds were treated with a dry bandage. Only three wounds had to be treated extra because of a wound infection, two by means of evacuation of the purulence and one by a wet bandage (Table 4.15).

Table 4.15: Wound treatment.

	TOTAL 297 (100%)	HAVEN 114 (100%)	IKAZIA 183 (100%)	P-value
Open	107 (36.0%)	102 (89.5%)	5 (2.7%)	
Dry bandage	190 (64.0%)	12 (10.5%)	178 (97.3%)	
Extra wound treatment:				
No	294 (99.0%)	112 (98.2%)	182 (99.5%)	N.S. (0.560)
Drainage of pus	2 (0.7%)	2 (1.8%)	0	N.S. (0.146)
Wet bandage	1 (0.3%)	0	1 (0.5%)	N.S. (0.999)

There was no difference between the two hospitals in postoperative temperature elevations. Twohundred sixty-eight patients had no postoperative temperature elevation. In two patients the temperature elevation was caused by bile leakage and in one by a wound infection. In

7.1 percent of the patients the cause of the temperature elevation was uncertain (Table 4.16).

Table 4.16: Postoperative temperature elevation.

	TOTAL 297 (100%)	HAVEN 114 (100%)	IKAZIA 183 (100%)	P-value
No fever	268 (90.2%)	104 (91.2%)	164 (89.6%)	N.S. (0.693)
Wound infection	1 (0.3%)	1 (0.9%)	0	N.S. (0.383)
Pulmonary infection	1 (0.3%)	0	1 (0.5%)	N.S. (0.999)
Bile leakage	2 (0.7%)	1 (0.9%)	1 (0.5%)	N.S. (1.000)
Pancreatitis	1 (0.3%)	0	1 (0.5%)	N.S. (0.999)
Peritonitis	1 (0.3%)	0	1 (0.5%)	N.S. (0.999)
Haematoma	1 (0.3%)	0	1 (0.5%)	N.S. (0.999)
Gastritis	1 (0.3%)	0	1 (0.5%)	N.S. (0.999)
Uncertain	21 (7.1%)	8 (7.0%)	13 (7.1%)	N.S. (0.999)

Twohundred fifty-six patients (86.2%) were operated without postoperative complications. In the Ikazia Hospital 18 patients (9.8%) suffered from a wound haematoma, which needed surgical intervention, while in the Haven Hospital only 3 (2.6%). The postoperative complications are shown in Table 4.17. There was no postoperative mortality.

In 54 patients a T-tube cholangiography was performed, which showed in four patients retained stones.

Table 4.17: Postoperative complications.

	TOTAL 297 (100%)	HAVEN 114 (100%)	IKAZIA 183 (100%)	P-value
None	256 (86.2%)	105 (92.1%)	151 (82.5%)	**= 0.02**
Wound haematoma	21 (7.1%)	3 (2.6%)	18 (9.8%)	**= 0.019**
Haemorrhage	11 (3.7%)	1 (0.9%)	10 (5.5%)	N.S. (0.056)
Reoperation	1 (0.3%)	0	1 (0.5%)	N.S. (0.999)
Bile leakage	1 (0.3%)	1 (0.9%)	0	N.S. (0.383)
Other	7 (2.4%)	4 (3.5%)	3 (1.4%)	N.S. (0.434)

In 288 (97.0%) patients no post-operative infections were diagnosed. The in-hospital wound infection percentage was 5.1%. The incidence of wound infections was higher in the Ikazia than in the Haven Hospital namely 7.7% versus 0.9%. The other infections are shown in Table 4.18.

Table 4.18: Postoperative infections.

	TOTAL 297 (100%)	HAVEN 114 (100%)	IKAZIA 183 (100%)	P-value
None	288 (97.0%)	113 (99.1%)	175 (95.6%)	N.S. (0.160)
Urinary tract infection	4 (1.3%)	0	4 (2.2%)	N.S. (0.163)
Sepsis	2 (0.7%)	1 (0.9%)	1 (0.5%)	N.S. (1.000)
Pulmonary infection	2 (0.7%)	0	2 (1.1%)	N.S. (0.525)
Peritonitis	1 (0.3%)	0	1 (0.5%)	N.S. (1.000)

There were significant differences in histopathological diagnosis between the two hospitals. Chronic cholecystitis was diagnosed in 96.4% of the patients operated at the Haven Hospital. No sign of inflammation was found three times at the Ikazia Hospital (Table 4.24).

Table 4.19: Histopathological diagnosis.

	TOTAL 297 (100%)	HAVEN 114 (100%)	IKAZIA 183 (100%)	P-value
Chronic inflammation	250 (83.7%)	108 (96.4%)	142 (77.6%)	**< 0.0001**
Chronic active inflam	5 (1.7%)	2 (1.8%)	3 (1.6%)	N.S. (1.000)
Acute inflammation	10 (3.3%)	2 (1.7%)	8 (4.4%)	N.S. (0.326)
No sign of inflammation	7 (2.3%)	0	7 (3.8%)	**= 0.046**
Carcinoma	3 (1.0%)	0	3 (1.6%)	N.S. (0.288)
Others/combinations	20 (6.7%)	0	20 (10.9%)	**< 0.0001**
Missing data	2	2	0	

4.3.1.6 Follow-up information

Sixteen patients (5.4%) were lost from follow-up, 13 from the Haven and 3 from the Ikazia Hospital. Twohundred fourteen (76.4%) patients had no complaints; 21 patients (7.5%) complained about woundpain, and 11 (3.9%) had abdominal pain (Table 4.20).

Table 4.20: Outpatient department parameters.

	TOTAL 297 (100%)	HAVEN 114 (100%)	IKAZIA 183 (100%)	P-value
No complaints	214 (76.4)	76 (75.2%)	138 (77.1%)	N.S. (0.770)
Woundpain	21 (7.5%)	10 (9.9%)	11 (6.1%)	N.S. (0.344)
Abdominal pain	11 (3.9%)	4 (4.0%)	7 (3.9%)	N.S. (1.000)
Fever	1 (0.4%)	0	1 (0.6%)	N.S. (1.000)
Others	33 (11.8%)	11 (10.9%)	22 (12.3%)	N.S. (0.847)
Missing data	17	13	4	

4.3.2 Antimicrobial therapy

All patients received a single dose of Amoxycillin/clavulanic acid at the induction of anaesthesia. In fourteen patients, twelve women and two men, adverse events were reported. Three patients had severe adverse events, ten moderate and one mild. The symptoms were nausea in 7 cases, rash in three cases, vomiting in two and a combination of nausea and vomiting in one. One patient developed an anaphylactic shock. These patients were not excluded from this prospective study.

4.3.3 Survey of risk factors

Review of the literature shows many possible risk factors for developing postoperative wound infection[19]. Risk factors for developing different grade of complications in this study are shown in Table 4.21 subdivided in three categories: general, specific and relative risk factors.

Table 4.21: Risk factors for the development of wound infection.

Risk factor	No. of patients at risk
General	
Age > 60 years #	113 (38.0%)
Gender (Male / Female)	79 (26.6%) / 218 (73.4%)
Hospital (Haven / Ikazia)	114 (38.4%) / 183 (61.6%)
Quetelet index (>30)	45 (16.2%)
Diabetes mellitus	13 (4.4%)
Cardiovascular: hypertension	33 (11.2%)
Cardiovascular: other	28 (9.5%)
History of abdominal disease #	80 (26.9%)
(History of) cancer #	13 (4.4%)
Liver disease	8 (2.7%)
COPD	10 (3.4%)

Risk factor	No. of patients at risk
Specific	
Fever at admission	9 (3.1%)
Emergency (acute / elective)	27 (9.1%) / 270 (90.9%)
Acute cholecystitis *#	10 (3.4%)
Choledocholithiasis *#	14 (4.7%)
Obstructive jaundice *#	11 (3.7%)
Acute pancreatitis *#	1 (0.3%)
ERCP	5 (1.7%)
Preoperative sepsis	0
Relative	
Median incision	3 (1.0%)
Actual surgery + CBD exploration and/or other intervention	68 (22.9%)
Common bile duct stones	22 (7.4%)
Infiltrate/hydrops/gangreen/ perforation/other findings	63 (21.2%)
Peroperative complications	13 (4.4%)
Duration of operation (> 60 min.)	69 (23.4%)
Bile leakage	138 (47.3%)
Positive bile	37 (12.5%)
Closed woundtreatment / Open	190 (64.0%) / 107 (36.0%)
Postoperative complications	41 (13.8%)
Histopathological diagnosis (acute inflammation)	15 (5.1%)
Abdominal washing	96 (14.6%)
Wound washing	57 (19.2%)
Drains	200 (67.3%)

Note: * = confirmed after surgery
= risk factors listed in the protocol

4.3.4 Wound infections

4.3.4.1 Assessments of wound infection

Wound assessment was based on clinical observation and categorized into three groups namely: "no wound infection", "minor" (erythema, serous discharge) and "major wound infection" (purulence discharge, wounddehiscence and skin edge necrosis). According to the clinical observations there were 15 (5.1%) major wound infections and 32 (10.7%) minor wound infections. There was a significant difference between the incidence of wound infections in the Haven and the Ikazia Hospital. Significantly more major wound infections were seen at the Ikazia Hospital (Table 4.22).

Table 4.22: Clinical assessments of wound infections.

N = 297	Males	Females	P-value
No wound infection	68 (86.0%)	182 (83.5%)	N.S. (0.719)
Minor	7 (8.9%)	25 (11.5%)	N.S. (0.627)
Major	4 (5.1%)	11 (5.0%)	N.S. (0.999)
N = 297	**Haven**	**Ikazia**	
No wound infection	103 (90.4%)	147 (80.3%)	= **0.022**
Minor	10 (8.8%)	22 (12.0%)	N.S. (0.444)
Major	1 (0.9%)	14 (7.7%)	= **0.011**

4.3.4.2 Risk factors of wound infection

Estimated risk is calculated for each of the risk factors from Table 4.23. Risk is calculated by means of chi-square, Fisher's exact, Mantel-Haenszel and multivariate analysis. In Table 4.23 in the first column the number of patients at risk are given and the next column shows the number and percentage of wound infections. Significance is given by $p < 0.05$.

Table 4.23: Risk factor calculated for wound infection.

Risk factor		Number	Infection (%)
General			
Age	< 60 years	184	23 (12.5%)
	> 60 years	113	24 (21.2%)
(Fisher's exact; p=0.050: **S.**)			
Gender	Male	79	11 (13.9%)
	Female	218	36 (16.5%)
(Chi-square; p=0.718: **N.S.**)			
Hospital	Haven	114	11 (9.6%)
	Ikazia	183	36 (19.7%)
(Fisher's exact; p=0.022: **S.**)			
Quetelet index > 30		233	31 (13.3%)
(Chi-square; p=0.092: **N.S.**)			
Diabetes mellitus		13	2 (15.4%)
(Chi-square; p=1.00: **N.S.**)			
Cardiovascular: hypertension		33	5 (15.2%)
(Chi-square; p=1.00: **N.S.**)			
Cardiovascular: other		28	6 (21.4%)
(Chi-square; p=0.572: **N.S.**)			
History of abdominal disease		80	12 (15.0%)
(Chi-square; p=0.954: **N.S.**)			
(History of) cancer		13	4 (30.8%)
(Chi-square; p=0.268: **N.S.**)			
Liver disease		8	1 (12.5%)
(Chi-square; p=1.000: **N.S.**)			
COPD		10	4 (40.0%)
(Fisher's exact; p=0.060: **N.S.**)			

Specific			
Fever on admission		9	1 (11.1%)
(Chi-square; p=1.000: **N.S.**)			
Emergency	acute	27	9 (33.3%)
	elective	270	38 (14.1%)
(Fisher's exact; p=0.022: **S.**)			
Acute cholecystitis		10	4 (40.0%)
(Fisher's exact; p=0.060: **N.S.**)			
Choledocholithiasis		14	5 (35.7%)
(Fisher's exact; p=0.053: **N.S.**)			
Obstructive jaundice		11	3 (27.3%)
(Chi-square; p=0.0526: **N.S.**)			
Acute pancreatitis		1	0
ERCP		5	3 (60.0%)
(Fisher's exact; p=0.030: **S.**)			

Relative			
Median incision		3	2 (66.7%)
(Fisher's exact; p=0.070: N.S.)			
Cholecystectomy + CBD exploration and/or other interventions		68	22 (32.4%)
(Fisher's exact; p<0.001: S.)			
Common bile duct stones		22	8 (36.4%)
(Fisher's exact; p=0.012: S.)			
Infiltrate/hydrops/gangrene/ perforation/other findings		63	14 (22.2%)
(Chi-square; p=0.1698: N.S.)			
Peroperative complications		13	2 (15.4%)
(Chi-square; p=1.000: N.S.)			
Duration of operation	< 60 min.	226	29 (12.8%)
	> 60 min.	69	18 (26.1%)
(Fisher's exact; p=0.014: S.)			
Bile leakage		138	30 (21.7%)
(Chi-square; p=0.0125: S.)			
Bile	Negative	260	41 (15.8%)
	Positive	37	6 (16.2%)
(Chi-square; p=1.000: N.S.)			
Woundtreatment	closed	190	37 (19.5%)
	open	107	10 (9.4%)
(Fisher's exact; p=0.021: S.)			
Postoperative complications		41	7 (17.1%)
(Fisher's exact; p=0.281: N.S.)			
Histopathological diagnosis	acute	15	4 (26.7%)
	others	280	43 (15.4%)
(Chi-square; p=0.421: N.S.)			
Abdominal washing		96	14 (14.6%)
(Fisher's exact; p=0.618: N.S.)			
Wound washing		57	14 (24.6%)
(Fisher's exact; p=0.067: N.S.)			
Drains		200	40 (20.0%)
(Fisher's exact; p=0.004: S.)			

From this statistical analysis can be concluded that general risk factors for woundhealing are age > 60 years and the hospital were the patient was operated.

The specific risk factors for woundhealing were the emergency of the operation, also acute versus elective, and preoperative ERCP. There were no patients with acute pancreatitis in this study; so this risk factor could not be evaluated. Acute cholecystitis, obstructive jaundice and choledocholithiasis were no risk factors for postoperative wound infection.

Significant relative risk factors for wound infection were common bile duct exploration and/or other interventions added to the cholecystectomy, peroperative common bile duct stones, duration of the operation, closed versus the open woundtreatment, drains and bile leakage.

Multivariate analysis showed that the risk factor cholecystectomy with common bile duct exploration and/or other interventions was the only important risk factor.

4.3.5 Bacteriology

From 297 patients a total of 862 culture specimens were obtained, a mean of almost three cultures (2.90) per patient. The results are given in Table 4.24.

The predominant aerobic organisms were Escherichia coli (48 isolates), Klebsiella spp. (20 isolates), Enterococcus spp. (11 isolates) and Streptococcus spp. (7 isolates). The predominant anaerobic bacteria were Clostridium welchii (3 isolates). The sensitivity of micro-organism to amoxycillin and amoxycillin/clavulanic acid from operative bile cultures are shown in Table 4.25. Escherichia coli found in eight cultures out of four patients were resistant to amoxycillin/clavulanic acid; however, none of these patients developed a wound infection. Enterobacter cloacae and Hafnia alvei were resistant to amoxycillin/clavulanic acid.

Table 4.24: Survey of bacteriological cultures.

N = 862	NEGATIVE 624 (72.4%)	POSITIVE 238 (27.6%)
Time culture taken		
Pre-operative	3 (0.5%)	12 (5.0%)
Per-operative	426 (68.3%)	109 (45.8%)
Post-operative	195 (16.6%)	117 (49.2%)
Sources		
Peroperative bile gallbladder	246 (39.4%)	57 (23.9%)
Per-operative bile CBD	175 (28.0%)	49 (20.6%)
Bile T-tube	64 (10.3%)	31 (13.0%)
Tip T-tube	11 (1.8%)	16 (6.7%)
Tip W-drain	111 (17.8%)	33 (13.9%)
Urine (midstream)	1 (0.2%)	14 (5.9%)
Urine (catheter)	2 (0.3%)	20 (8.4%)
Blood	6 (1.0%)	1 (0.4%)
Sputum	0	10 (4.2%)
Wound smear	1 (0.2%)	1 (0.4%)
Others	7 (1.1%)	4 (1.7%)
Hospital		
Haven	169 (27.1%)	66 (27.7%)
Ikazia	455 (72.9%)	172 (72.3%)

Table 4.25: Micro-organisms and resistance for operative bile cultures (Amox = Amoxycillin, Amox/cl = Amoxycillin/clavulanic acid).

N=527	TOTAL	AMOX			AMOX/CL		
		nd	RES	SEN	nd	RES	SEN
No micro-organisms cultured	421						
Gram-negative							
Escherichia coli	48	1	13	34	9	8	31
Klebsiella spp.	20	1	19	0	1	0	19
Enterobacter spp.	2	0	2	0	0	2	0
Citrobacter freundii	2	0	1	1	0	0	2
Salmonella livingstone	2	0	0	2	2	0	0
Hafnia alvei	2	0	2	0	0	2	0
Aeromonas hydrophila	2	0	2	0	0	0	2
Gram-positive							
Enterococcus spp.	11	0	2	9	0	0	11
Streptococcus spp.	7	7	0	0	7	0	0
Diphteroids	2	0	0	2	2	0	0
Lactobacillus	1	1	0	0	1	0	0
Anaerobic							
Clostridium welchii	3	2	0	1	0	0	3
Fungi							
Candida spp.	1	1	0	0	1	0	0
Other micro-organisms	3	2	0	1	3	0	0

Note: nd = not done
RES = resistant
SEN = sensitive

4.4 DISCUSSION

In this prospective part of the study 407 patients were eligible for infection prophylaxis during biliary surgery. The inclusion criteria were met by 297 (73%) patients leaving 110 (27%) patients to be excluded. The included group were all treated prophylactically with a single dose of amoxycillin/clavulanic acid according to protocol. Subgroup stratification were done for hospital of admission.

Comparison of hospitals showed significant differences in medical history. More gastro-intestinal diseases were seen at the Ikazia Hospital. There were no differences in specific risk factors. Important differences were found in hospital policies: abdominal washing and washing of the wound with a betadin solution were done more often in the Ikazia Hospital. In the Ikazia Hospital a cholecystectomy was performed more often in combination with a common bile duct exploration. Drains were used in the Ikazia hospital as a standard, but not in the Haven Hospital. The most striking difference was the "open" wound treatment in the Haven Hospital against treatment with bandage in the Ikazia Hospital. There was a significant difference in hospital stay. Patients undergoing cholecystectomy in the Ikazia Hospital stayed on average two days longer probably due to the hospital policy and the fact that in the Ikazia Hospital more common bile duct explorations were performed.

According to clinical observations the incidence of major wound infection was 5.1% and of minor wound infection 10.1%. There was a significant difference in the number of major wound infections between both hospitals. In the Ikazia Hospital more wound infections were observed probably due to the high incidence of wound hematoma and the fact that in the Ikazia Hospital more extended biliary surgery was performed.

Other infections reported were urinary tract infections (1.3%), pulmonary infections (0.7%), sepsis (0.7%) and peritonitis (0.3%). In this prospective study there was no mortality.

The influence of risk factors after prophylactic treatment was determined posthoc. The group of patients (n=47) with minor and major wound infections versus patients with no wound infections were compared in a relative risk analysis. From this study can be concluded that risk factors for the development of wound infection are age > 60 years, emergency procedure, peroperative common bile duct stones and common bile duct exploration and/or other interventions added to the cholecystectomy. These risk factors were already described in 1976 by Keighley et al[19]. Other risk factors for wound infection in this study were preoperative ERCP, duration of the operation, closed versus the open woundtreatment, drains and bile leakage. The risk factors acute cholecystitis and current or recent history of jaundice were not significant for the development of wound infection, this is in contrary with the results described in the literature[19].

The bacteriological efficacy was determined by taking a bile culture peroperatively. In 79.9% of the cultures from gallbladder and common bile duct no micro-organisms were found. The Escherichia coli, Klebsiella spp. and Enterococcus spp. were most frequently detected; these results are comparable with the results described by other authors[20]. In 11.3% of the positive cultures resistance for amoxycillin/clavulanic acid was found. Species resistant to amoxycillin/clavulanic acid were Hafnia alvei, Enterobacter cloacae and Escherichia coli (8/34). None of these resistant species caused a wound infection.

This prospective study cannot be compared with the retrospective study described in chapter 3. One of the problems was the fact that no standard treatment existed in the retrospective group. Antibiotics were given in the primary group in 40% of all cases, and in 9% prophylactically. The most important problem leading to a difference between the groups was caused by the exclusion of patients. Although intentionally, more than a quarter of the patients in the prospective group had to be excluded. From the retrospective group virtually nobody was excluded. A major problem was that the evaluation of wound infections was done much more thoroughly in the prospective group than in the retrospective group. These problems made the two groups incomparable[21].

Because of the fact that both groups were incomparable, we compared the results of amoxycillin/clavulanic acid prophylaxis of the prospective group with results reported by other authors. Major wound infections occurred in the prospective group with an incidence of 5.1%. This incidence is in concordance with the infection rate found after application of antibiotics in general[22,23] and with the infection rate found after prophylaxis with amoxycillin/clavulanic acid in particular[24].

The postoperative wound infection rate of 3.1% in the retrospective study seems very low considering the fact that 60% of the patients received no prophylactic antibiotic treatment. This may be caused by a degree of uncertainty about retrospective determination of wound infections and by a insufficient description of the postoperative follow-up in the clinical records.

Adverse events to antibiotic prophylaxis were found in 14 patients in the prospective group. The most frequently occurring complaints were nausea and vomiting. These events did not differ from the events reported in other clinical trials with amoxycillin/clavulanic acid. The value of these data is very limited since 10 out of 14 patients were recorded to have gastro-intestinal complaints, events which are quite common in patients undergoing general anaesthesia.

Interpretation of the results of peroperative bile cultures showed more bacteria in the retrospective group in which most patients did not receive antibiotics. Bacteria were found in this group in 42.1% of the cases against 20.1% in the prospective group. The species and incidences of the bacteria isolated from the bile in both groups were comparable. Escherichia coli, Klebsiella spp. and Streptococcus spp. were found very frequently. Concerning the anaerobes, Clostridium welchii was isolated frequently and bacteroides less.

According to these results and the incidence of 5.1% major wound infections in the prospective study we concluded that a single dose amoxycillin/clavulanic acid is safe and effective in the prevention of infection in biliary surgery.

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CHAPTER 5

MANAGEMENT OF GALLSTONE DISEASE AFTER INTRODUCTION OF LAPAROSCOPIC CHOLECYSTECTOMY IN A GENERAL HOSPITAL

ABSTRACT

Laparoscopic cholecystectomy is a successfull treatment modality for the management of gallstone disease. The aims of this study were to determine the mortality and morbidity in biliairy surgery after introduction of the laparoscopic cholecystectomy and an analysis of the differences in risk factors, per- and postoperative complications and histopathological diagnosis. All patients aged 18 or older admitted for gallstone disease to the surgical department of our training hospital between June 1991 and April 1993 were included in a prospective trial.

From 340 patients 125 (36.8%) underwent open cholecystectomy with or without common bile duct exploration and from 215 cholecystectomies (63.2%), which started laparoscopically, 26 were converted to open cholecystectomy.

Comparison of the risk factors between the open and the laparoscopic group showed significant differences in: age > 60 years ($p<0.0001$), history of abdominal disease or surgery ($p<0.02$), emergency procedures ($p<0.0001$), acute cholecystitis ($p<0.0001$), obstructive jaundice ($p<0.0001$) and acute pancreatitis ($p<0.0001$). Patients who underwent open cholecystectomy were at higher risk for the development of postoperative wound infections or other septic complications. The postoperative complication rate in the whole series was 7.1%. The incidence of postoperative infections was 7.6%. Comparison of the open and the laparoscopic group showed a significant difference ($p<0.002$) in infection rate in favour of the laparoscopic group. The mortality rate was 0.3%.

Patients with complicated gallbladder disease will still need open cholecystectomy.

5.1 INTRODUCTION

Cholecystectomy is the treatment of choice for symptomatic gallstone disease. For decades nearly all these procedures have been performed through a right Kocher oblique paracostal incision or a vertical median supra-umbilical incision, and this has proved to be an exceedingly safe and effective means of managing cholelithiasis. The hospital mortality rate is less than 1%, morbidity rates are low, and long-term results are excellent, with most patients rendered asymptomatic after cholecystectomy[1]. Despite the outstanding results obtained with standard cholecystectomy, during the past decade a variety of alternative treatment options have been introduced, for example extracorporeal shock wave lithotripsy[2-7] and mini-cholecystectomy[8].

The most successfull treatment modality used for the management of gallstone disease became laparoscopic cholecystectomy. The benefits of laparoscopic cholecystectomy compared with open cholecystectomy are well described in literature[9,10]. The mortality rate of laparoscopic cholecystectomy is low, varying from 0-0.8%[11-16].

Complication rates for laparoscopic cholecystectomy of 2.1-6.4%[11-13,15-17] compare well with those after open cholecystectomy.

In literature "high-risk" categories for biliary tract surgery are described. One set of criteria for this high-risk category was established by Keighley et al[18] and is widely used: age greater than 60 years, recent cholangitis, recent acute cholecystitis, previous biliary surgery, current or recent history of jaundice, choledocholithiasis and emergency surgery. These categories define patients with bacteria in the bile, who are most at risk from postoperative woundinfection and other septic complications. Most can be categorized preoperatively, although the presence of choledocholithiasis may not be detected until surgery.

The aims of this study were, firstly, to determine the morbidity and mortality of biliary surgery after introduction of the laparoscopic cholecystectomy in a general district training hospital. The second aim was an analysis of risk factors, per- and postoperative complications and histopathological diagnosis between the laparoscopic and conversion group compared with the open group.

5.2 PATIENTS AND METHODS

All patients aged 18 or older admitted for gallstone disease to the surgical department of the Ikazia hospital between June 1991 and April 1993 were included in a prospective trial. The exclusion criteria were hypersensitive to penicillin, usage of other antibiotics than used in this trial and pregnancy.

All operations were performed in the Ikazia Hospital, a district general hospital with an educational program affiliated with the University Hospital Rotterdam. Laparoscopic cholecystectomies were done by three of four surgeons and five residents (postgraduate years 1 to 3). At first the laparoscopic cholecystectomies were performed by the surgeons who were all trained in laparoscopic surgery abroad. This training included lectures, laboratory training and active participation in the OR.

Before the residents started operating laparoscopically, each resident assisted at least 15 laparoscopic cholecystectomies. Residents performing laparoscopic cholecystectomies as operating surgeon were always assisted by a surgeon.

Open cholecystectomy was done through a 8-15 cm right Kocher oblique paracostal incision. Common bile duct exploration was carried out when indicated.

Laparoscopic cholecystectomy was performed by the Anglo-American method[17,19]. The gallbladder was dissected free with electrocautery. No routinely intraoperative cholangiography was performed. Absolute contraindications for laparoscopic cholecystectomy were performance of concomitant upper abdominal surgery and choledocholithiasis. Initially patients with acute cholecystitis and upper or mid-abdominal scarring were not considered suitable for laparoscopic cholecystectomy. With increasing experience, these exclusions were abolished.

Patients undergoing cholecystectomy received a single dose of the combination of amoxycillin and clavulanic acid, as a single slow intravenous bolus injection of 1.2 g, at the induction of anaesthesia.

Patient data compiled included the following: whether the case was started laparoscopically or open, and of those started laparoscopically, whether a conversion to an open procedure had taken place, risk factors, per- and postoperative complications, the pathologic diagnosis of the gallbladder and postoperative morbidity.

5.2.1 Statistical analysis

A two-sided Mann-Whitney U test was used to detect differences between groups. A Mantel-Haenszel chi-square statistic was used to test independence between two categoric sets of data. If an expected value of one of the categories was less than 5, we used Fisher's exact test.

$P < 0.05$ was considered statistically significant, and all p-values were calculated two sided.

5.3 RESULTS

There were 357 eligible patients available for the study between June 1991 and April 1993. Seventeen patients were excluded. Reasons for exclusion were age < 18 years (n=2), hypersensitive to penicillin (n=6), usage of other antibiotics than used in this trial (n=7) and pregnancy (n=2).

From the remaining 340 patients, 125 (36.8%) underwent open cholecystectomy. In 50.4% of these patients, there was also an indication for exploring the common bile duct. In 20 (31.7%) patients common bile duct stones were found peroperatively.

From the 215 cholecystectomies (63.2%), which started laparoscopically, 26 (12.1%) were converted to open cholecystectomy. The main reasons for conversion were either technical problems caused by adhesions (n=16) or cholecystitis. Other reasons for conversion were instrumental defects (n=5) and uncontrolable bleeding (n=3) or unclear anatomy (n=1). In one patient conversion was performed because of recognized clipping of the common bile duct. There were no conversions due to the presence of common bile duct stones. Significantly ($p<0.001$) more women were operated laparoscopically than men.

The demographic characteristics of the patients controlled for operation are listed in Table 5.01.

Table 5.01: Characteristics controlled for operation (OC = Open Cholecystectomy, LC = Laparoscopic Cholecystectomy).

	TOTAL 340	OC 125	LC 189	Conversion 26
Demographic characteristics				
Men	91 (26.8%)	47 (37.6%)	37 (19.6%)	7 (26.9%)
Women	249 (73.2%)	78 (62.4%)	152 (80.4%)	19 (73.1%)
Mean age	51.9	59.1	47.4	51.6

Risk factors

The greatest incidence of risk factors had age > 60 years (34.4%), followed by history of abdominal disease (27.9%), emergency procedure (17.1%), acute cholecystitis (10.9%), obstructive jaundice (3.2%) and acute pancreatitis (2.6%). Eight patients preoperatively underwent an ERCP (Table 5.02).

In the open group the patients had significantly more risk factors than in the laparoscopic group. The most important differences were age > 60 years ($p<0.0001$), history of abdominal disease or surgery ($p<0.02$), emergency procedures ($p<0.0001$), acute cholecystitis ($p<0.0001$), obstructive jaundice ($p<0.0001$) and acute pancreatitis ($p<0.0001$).

Comparison of the conversion group with the open group showed significant differences in emergency procedure ($p=0.01$) and history of abdominal disease ($p=0.04$).

Table 5.02: Comparison of risk factors for biliary surgery between Laparoscopic Cholecystectomy (LC), conversion and Open Cholecystectomy (OC).

	TOTAL 340 (100%)	OC 125 (100%)	LC 189 (100%)	Conversion 26 (100%)
Age > 60 years	117 (34.4%)	63 (50.4%)	44 (23.3%) **($p<0.0001$)***	10 (38.5%) (N.S.)#
History of abd.	95 (27.9%)	46 (36.8%)	45 (23.8%) **($p=0.02$)**	4 (15.4%) **($p=0.04$)**
Emergency procedure	58 (17.1%)	48 (38.4%)	7 (3.7%) **($p<0.0001$)**	3 (11.5%) **($p=0.01$)**
Acute cholecystitis	37 (10.9%)	30 (24.0%)	4 (2.1%) **($p<0.0001$)**	3 (11.5%) (N.S.)
Obstructive jaundice	11 (3.2%)	11 (8.8%)	0 **($p<0.0001$)**	0 (N.S.)
Acute pancreatitis	9 (2.6%)	9 (7.2%)	0 **($p<0.0001$)**	0 (N.S.)
Preoperative ERCP	8 (2.4%)	6 (4.8%)	2 (1.1%) (N.S.)	0 (N.S.)

Note: * = Open vs. Laparoscopic
= Open vs. Conversion

Peroperative complications

Twohundred fourty-nine patients were operated without peroperative surgical problems. In the open and the conversion group no major peroperative complications occurred. The two major complications in the laparoscopic group consisted of a duodenal perforation during dissection of the peritoneum and an accidental clipping of the common bile duct. The minor peroperative complications are listed in Table 5.03.

Comparison of the laparoscopic and the open group showed significantly more perforations of the gallbladder ($p<0.0001$) and intra-abdominal stone loss ($p<0.01$) in the laparoscopic group.

Table 5.03: Comparison in peroperative complications between Laparoscopic Cholecystectomy (LC), conversion and Open Cholecystectomy (OC).

	TOTAL 340 (100%)	OC 125 (100%)	LC 189 (100%)	Conversion 26 (100%)
None	249 (73.2%)	119 (95.2%)	102 (54.0%)	23 (88.5%)
Major				
Perforation duodenum	1 (0.3%)	0	1 (0.5%) (N.S.)*	0 (N.S.)#
Bile duct lesion	1 (0.3%)	0	1 (0.5%) (N.S.)	0 (N.S.)
Minor				
Damage liverbed	2 (0.6%)	1 (0.8%)	1 (0.5%) (N.S.)	0 (N.S.)
Bleeding liverbed	1 (0.3%)	0	0 (N.S.)	1 (3.8%) (N.S.)
Perforation GB	75 (22.1%)	5 (4.0%)	67 (35.4%) **($p<0.0001$)**	3 (11.5%) (N.S.)
A. cystica bleeding	2 (0.6%)	0	2 (1.1%) (N.S.)	0 (N.S.)
Intra-abdominal stone loss	10 (2.9%)	0	10 (5.3%) **($p<0.01$)**	0 (N.S.)
Bleeding trocar site	2 (0.6%)	0	2 (1.1%) (N.S.)	0 (N.S.)
Broken instruments	6 (1.8%)	0	6 (3.2%) (N.S.)	0 (N.S.)

Note: * = Open vs. Laparoscopic
= Open vs. Conversion

Postoperative complications

Threehundred sixteen patients (92.9%) were operated without postoperative complications. The major postoperative complications in the open group were fascial dehiscention and reoperation because of retained common bile duct stones. Major postoperative complications in the laparoscopic group were seen in five patients. One patient died because of an unrecognized intra-abdominal bleeding from the umbilical trocar site. In two cases a reoperation was performed because of a subfrenic abscess. Other major problems were an incarcerated hernia at the trocar site and a pulmonary embolism. The minor postoperative complications are listed in Table 5.04.

Postoperative infections were seen in 26 patients. Twenty patients (5.9%) developed a wound infection, three (0.9%) an urinary tract infection, two (0.6%) a pulmonary infection and one an urosepsis. Three patients, which were all conventionally operated, had retained common bile duct stones. One was re-operated, in the other two cases the common bile duct stones were cleared by ERCP.

Table 5.04: Comparison in postoperative complications and infections between Laparoscopic Cholecystectomy (LC), conversion and Open Cholecystectomy (OC).

	TOTAL 340 (100%)	OC 125 (100%)	LC 189 (100%)	Conversion 26 (100%)
Postoperative complications				
None	316 (92.9%)	119 (95.2%)	173 (91.5%)	24 (92.3%)
Major				
Haemorrhage	1 (0.3%)	0	1 (0.5%) (N.S.)*	0 (N.S.)#
Fascial dehiscention	1 (0.3%)	1 (0.8%)	0 (N.S.)	0 (N.S.)
Reoperation	3 (0.9%)	1 (0.8%)	2 (1.1%) (N.S.)	0 (N.S.)
Hernia trocar site	1 (0.3%)	0	1 (0.5%) (N.S.)	0 (N.S.)
Pulmonary embolism	1 (0.3%)	0	1 (0.5%) (N.S.)	0 (N.S.)
Minor				
Paralytic ileus	2 (0.6%)	1 (0.8%)	0 (N.S.)	1 (3.8%) (N.S.)
Severe vomitus	12 (3.5%)	1 (0.8%)	11 (5.8%) **(p=0.03)**	0 (N.S.)
Urine retention	2 (0.6%)	2 (1.6%)	0 (N.S.)	0 (N.S.)
Atrial flutter	1 (0.3%)	0	0 (N.S.)	1 (3.8%) (N.S.)

Postoperative infections				
None	314 (92.4%)	109 (87.2%)	178 (94.7%)	26 (100%)
Wound infection	20 (5.9%)	10 (8.0%)	10 (5.3%) (N.S.)	0 (N.S.)
Urinary tract infection	3 (0.9%)	3 (2.4%)	0 (N.S.)	0 (N.S.)
Sepsis	1 (0.3%)	1 (0.8%)	0 (N.S.)	0 (N.S.)
Pulmonary infection	2 (0.6%)	2 (1.6%)	0 (N.S.)	0 (N.S.)

Note: * = Open vs. Laparoscopic, # = Open vs. Conversion

Pathologic diagnosis of the gallbladder

In analyzing the histopathological diagnosis significantly more acute inflammation ($p<0.0001$) was seen in the open group (Table 5.05).

Table 5.05: Comparison of histopathological diagnosis between Laparoscopic Cholecystectomy (LC), conversion and Open Cholecystectomy (OC).

	TOTAL 340 (100%)	OC 125 (100%)	LC 189 (100%)	Conversion 26 (100%)
Chronic inflammation	292 (85.9%)	95 (76.0%)	177 (93.7%) **($p<0.0001$)***	20 (76.9%) (N.S.)#
Chronic inflammation with acute component	16 (4.7%)	9 (7.2%)	5 (2.6%) (N.S.)	2 (7.7%) (N.S.)
Acute inflammation	25 (7.4%)	19 (15.2%)	2 (1.1%) **($p<0.0001$)**	4 (15.4%) (N.S.)
No inflammation	4 (1.2%)	0	4 (2.1%) (N.S.)	0 (N.S.)
Carcinoma	2 (0.6%)	2 (1.6%)	0 (N.S.)	0 (N.S.)
Polyps	1 (0.3%)	0	1 (0.5%) (N.S.)	0 (N.S.)

Note: * = Open vs. Laparoscopic, # = Open vs. Conversion

Operating time and hospital stay

The mean operating time was 63 min in the open group, 65 min in the laparoscopic group and 81 min in the conversion group. Hospital stay averaged 3 days in the laparoscopic group , 7 days in the conversion group and 10 days in the open group.

5.4 DISCUSSION

This study evaluates results of laparoscopic and open cholecystectomy after introduction of laparoscopic cholecystectomy. Risk factors, mortality and complications were specificially considered.

After initiation of laparoscopic cholecystectomy 63.2% of the patients with gallstone disease were operated laparoscopically. The conversion rate from laparoscopic to open cholecystectomy was 12.1%, this is comparable with the results reported by other authors. The conversion rate is varying from 3.6% in patients treated for symptomatic cholecystolithiasis to 18% in complicated cholelithiasis[20-24]. In the study by Zucker et al. of 83 patients with acute cholecystitis, 22 (27%) required conversion[25]. In another study by Ratner et al. of 20 patients with acute cholecystitis, the observation was made that the incidence of conversion was directly related to the time interval between admission and operation. The overall conversion rate in his series was 35%[26]. No special effort was made in our study to shorten the interval between diagnosis and operative intervention.

In the whole series 18.2% underwent primairy open cholecystectomy because of relative or absolute contraindications for laparoscopy.

The reports about the rate of common bile duct exploration vary from 15% to 30%, with stones being found about half the time[27-29]. This corresponds to the 18.3% frequency in this series with stones recovered in 32% of these cases. The incidence of recurrent or residual common bile duct stones was 0.9%, which is comparable with the rates described in literature[29].

Demographic characteristics showed that significantly more women were operated laparoscopically. In analyzing the open, the laparoscopic and the conversion group differences in risk factors have been observed. In the open group the patients had significantly more risk factors than in the laparoscopic group. The most important significant differences were age > 60 years, history of abdominal disease or surgery, emergency procedures, acute cholecystitis, obstructive jaundice and acute pancreatitis. The patients in the open group were at higher risk, which was also seen in analyzing the histopathologic diagnosis of the gallbladder. Significantly more acute inflammation was observed in the open group compared with the laparoscopic group.

A comparison between the complication rates of open cholecystectomy and laparoscopic cholecystectomy cannot be objectively defined in this study due to the selection bias. It is likely that in our institution's early experience with laparoscopic cholecystectomy, high-risk patients, along with those requiring common bile duct intervention, were assigned to be done conventionally.

Peroperative complications occurred in 26.8% of all patients. Most peroperative complications occurred in the laparoscopic group. Significantly more perforations of the gallbladder and intra-abdominal stone loss were seen in the laparoscopic group. In series of laparoscopic cholecystectomy complications directly related to the operation are more common[12,22]. Willingness to convert the laparoscopic operation to an open procedure is essential to reduce the incidence of operation related complications[12,15,22,30].

The postoperative complication rate in the whole series was 7.1 %. This may seem high, it should be noted that most of these complications were transient and of a less severe nature. No postoperative bile duct injuries occurred.

In the whole series the incidence of postoperative infections was 7.6%. Comparison of the open and the laparoscopic group showed a significant difference ($p<0.002$) in favour of the laparoscopic group.

The mortality rate in this study was 0.3%, which is comparable to the literature[11-16,31]. One patient died because of an unrecognized bleeding from the trocar site after laparoscopic cholecystectomy.

In the literature, little is known about the morbidity in the conversion group of patients. Our study showed only minor morbidity and no mortality in the conversion group.

From this study can be concluded that after the introduction of laparoscopic cholecystectomy in our clinic complicated gallbladder disease will still be operated conventionally. In view of the present and other recent studies[32,33] it is clear that cholecystectomy, either conventionally or laparoscopically, is a safe procedure with low mortality rate. Minor complications do occur, but complications with severe degrees of morbidity or residual disability are rare, in particular local injury to the biliary tract.

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CHAPTER 6

LAPAROSCOPIC AND OPEN CHOLECYSTECTOMY: A COMPARISON BETWEEN TWO CONSECUTIVE PROSPECTIVE TRIALS

ABSTRACT

Since its introduction, laparoscopic cholecystectomy has been performed with increasing frequency.

The aim of this study was to determine the changes in complications of patients treated for symptomatic cholecystolithiasis before and directly after initiation of laparoscopic cholecystectomy by means of a comparison of two consecutive prospective trials.

Between August 1989 and May 1991, 130 patients were operated by cholecystectomy only (Open group). Between June 1991 and April 1993, after introduction of laparoscopic cholecystectomy, a second prospective trial (Laparoscopic group) was performed with the same trial design in order to compare the laparoscopic cholecystectomy with the open cholecystectomy. In this period 189 patients underwent laparoscopic cholecystectomy.

Mortality in the open group was zero versus 0.5% in the laparoscopic group. Comparison of morbidity in both groups, revealed more serious morbidity in the laparoscopic group. Three patients had to be reoperated, where as in the open group no reoperation was performed. The conversion group showed no mortality and very low morbidity.

With the evolution of laparoscopic cholecystectomy as the standard procedure for the treatment of symptomatic cholecystolithisis, it is not appropriate to expand indications for surgery.

6.1 INTRODUCTION

Open cholecystectomy, performed for more than 100 years[1], has been an effective method of treating gallstone disease and has demonstrated an acceptable low morbidity and a minimal mortality, between 0 to 0.8 percent[2-6]. Thus open cholecystectomy represents an acceptable risk-benefit ratio for patients and until recently has been regarded as "the gold standard"[7] for comparison with new therapies.

Laparoscopic cholecystectomy varies in many respects from open cholecystectomy. The goal for both techniques is identical: a safe removal of the gallbladder with no mortality, low morbidity and early recovery. Comparison between open and laparoscopic cholecystectomy can be made in many ways including indication, contraindication, complications, equipment, technique, outcome, results, costs, benefits to the patient and surgeon and credentialing.

It has been suggested that unbiased randomized trials comparing laparoscopic and open cholecystectomy are impossible, because nowadays a patient would not accept an open cholecystectomy when the minimal access technique is available[8]. Data from recent series of elective open cholecystectomy (i.e., just before the era of laparoscopic cholecystectomy) are critical for comparison when evaluating alternatives to open cholecystectomy. Comparisons between laparoscopic and open cholecystectomy should not be made with outdated historic series of open cholecystectomy, but with the results that were attainable in the latest period before it became superseded by laparoscopic cholecystectomy[9, 10].

The aim of this study was to determine the mortality and the changes in complications of patients treated for cholecystolithiasis directly before and after introduction of the laparoscopic cholecystectomy.

6.2 PATIENTS AND METHODS

All patients aged 18 or older admitted for cholecystectomy to the surgical department of our training hospital between August 1989 and May 1991 were included in a prospective trial (Open group). From June 1991 to April 1993, a second prospective study (Laparoscopic group) was performed with the same trial design in order to compare the laparoscopic procedure with the open cholecystectomy. The exclusion criteria are shown in Table 6.01.

Open cholecystectomy was done through a 8-15 cm right subcostal incision, with transsection of the rectus abdominis muscle. Laparoscopic cholecystectomy was performed by the Anglo-American method[11-13]. The gallbladder was dissected free with by electrocautery. No routinely intraoperative cholangiography was performed. Absolute contraindications for laparoscopic cholecystectomy were performance of concomitant upper abdominal surgery and choledocholithiasis. Initially patients with acute cholecystitis and upper or mid-abdominal scarring were not considered suitable for laparoscopic cholecystectomy. With increasing experience, these conditions did not exclude patients for laparoscopic cholecystectomy.

Laparoscopic cholecystectomies were done by three of the four surgeons and five residents (postgraduate years 1 to 3). At first the laparoscopic cholecystectomies were performed by the surgeons who were all trained in laparoscopic surgery abroad. Residents performing laparoscopic cholecystectomies as operating surgeon were always assisted by a surgeon.

Patients undergoing cholecystectomy received a single dose of the combination of amoxycillin and clavulanic acid, as a single slow intravenous bolus injection of 1.2 g, at the induction of anaesthesia.

Risk factors for complications, duration of the operation, incidence of complications, and length of hospital stay were recorded. Patients were seen once at the outpatient department after discharge from the hospital.

Percentages or two-way tables were analysed with the chi-square test. For two by two tables with small expected freqencies Fisher's exact test was used. Values for $p<0.05$ were considered to be significant.

Table 6.01: Reasons of exclusion.

	Open group	Laparoscopic group
Pat. < 18 years	2	2
Hypersensitive to penicillin	15	6
Antibiotic others than used in this trial <48 hours preoperative, or <72 hours postoperative	45	7
Protocol violation	1	0
Presence of other disease	1	0
Pregnancy	1	2
Total	69	17

6.3 RESULTS

Between August 1989 and May 1991, a period of 22 months, there were 252 eligible patients available for the study. Ninety-six patients were excluded for reasons given in Table 1. All the remaining 183 patients were operated by subserosal cholecystectomy, in 43 cases (23.5%) an additional exploration of the common bile duct was performed and in 10 cases (5.5%) another intervention was added. Thus, the study group consisted of 130 patients who underwent conventional cholecystectomy only.

For the second trial, where the indications for cholecystectomy had not been altered, between June 1991 and April 1993, there were 357 eligible patients available in a period of 21 months. Seventeen patients were excluded for reasons listed in Table 6.01. From the remaining 340 patients 125 (36.8%) underwent open cholecystectomy, because there were contraindications for laparoscopic surgery. From the 215 cholecystectomies (63.2%), which started laparoscopically, 26 were converted from laparoscopic to open cholecystectomy. Thus, the study group consisted of 189 patients who underwent laparoscopic cholecystectomy.

After introduction of laparoscopic cholecystectomy there was an significant increase in patients admitted for cholecystectomy, despite the fact that the indications for this procedure had not been altered.

Conversion group

The characteristics of the conversion group are listed in Table 6.02. The conversion rate from laparoscopic to open cholecystectomy was 12.1%. The main reasons for conversion were either technical problems caused by adhesions (n=16) of previous laparotomy or cholecystitis. Other reasons for conversion were instrumental defect (n=5) and uncontrolable bleeding (n=3) or unclear anatomy (n=1). In one patient the common bile duct was clipped as recognized during the procedure. There were no conversions for common bile duct exploration.

Minor peroperative complications in the conversion group were perforation of the gallbladder in 3 patients and bleeding of the gallbladder bed in one patient. Postoperatively one patient developed a paralytic ileus. There were no postoperative infections.

Table 6.02: Characteristics and risk factors of the conversion group (n=26).

Demographic characteristics	
Male/female	7(27%)/19(73%)
Mean age	51.6
General medical history	
Diabetes mellitus	0
Hypertension	0
Cardiovascular disease	2 (7.7%)
Cancer	1 (3.8%)
COPD	0
Specific medical history	
Obstructive Jaundice	0
ERCP	0
Operation characteristics	
Emergency procedure	3 (11.5%)
Operative diagnosis:	
- Acute cholecystitis with cholecystolithiasis	3 (11.5%)
- Symptomatic cholecystolithiasis	23 (88.5%)
Duration of surgery	81 min.

Comparison of stratification

The characteristics and risk factors for developing complications of the two patient groups are listed in Table 6.03. Comparison of demographic characteristics showed a significant difference in age. Females accounted for the majority of the patients who underwent cholecystectomy. Comparison of general medical history showed a significant difference in hypertension. Duration of surgery was significantly longer in the laparoscopic group. The median hospital stay was 9 days in the open group versus 3 in the laparoscopic group.

Table 6.03: Characteristics and risk factors of two groups of patients operated by either open or laparoscopic cholecystectomy.

	Open group (n=130)	Laparoscopic group (n=189)	P-value
Demographic characteristics			
Male/female	31(24%)/99(76%)	37(20%)/152(80%)	NS
Mean age	52.7	47.3	**< 0.002**
Quetelet index	26.8	26.3	NS
General medical history			
Diabetes mellitus	8 (6.2%)	6 (3.2%)	NS
Hypertension	19 (14.6%)	2 (1.1%)	**< 0.001**
Cardiovascular disease	9 (6.9%)	23 (12.2%)	NS
Cancer	4 (3.1%)	2 (1.1%)	NS
COPD	6 (4.6%)	8 (4.2%)	NS
Specific medical history			
Obstructive Jaundice	1 (0.8%)	0	NS
ERCP	0	2 (1.1%)	NS
Operation characteristics			
Emergency procedure	7 (5.4%)	7 (3.7%)	NS
Operative diagnosis:			
- Acute cholecystitis with cholecystolithiasis	4 (3.1%)	4 (2.1%)	NS
- Symptomatic cholecystolithiasis	126 (96.9%)	184 (97.9%)	NS
Duration of surgery	49 min.	65 min.	**< 0.0001**

Comparison of complications

Open group: Ninety-four patients were operated without peroperative surgical problems. No common bile duct lesions occurred. Thirty-six patients (27.7%) had minor peroperative complications as listed in Table 6.04. The most occurring peroperative complication was bile spillage (24.6%).

Postoperative complications were seen in 25 patients (19.2%). These complications are listed in Table 6.05. Wound haematoma were observed most frequently.

In 111 patients (85.4%) no postoperative infections were diagnosed. The incidence of wound infections was 12.3%. Two patients (1.5%) suffered from a urinary tract infection and one (0.8%) had a pulmonary infection. There was no mortality in this group.

Laparoscopic group: Onehundred and two patients (54%) were operated without peroperative surgical problems. Major peroperative complications consisted of a duodenal perforation during dissection of the peritoneum and an accidental clipping of the common bile duct. Minor peroperative complications in laparoscopic cholecystectomy were bile spillage in 80 patients (42.3%), perforation of the gallbladder in 67 patients (35.4%), loss of intra-abdominal stones in 10 patients (5.3%) and in two patients (1.1%) a persistend bleeding on the trocar site. Six times (3.2%) we had technical problems with the laparoscopic instruments.

Onehundred seventy-three patients (91.5%) had no postoperative complications. Major postoperative complications were seen in five patients. In two cases a reoperation was performed because of a subfrenic abscess. Another major problem was a incarcerated hernia at the trocar site twenty-four hours postoperatively, which lead to a small bowel resection. In one patient a pulmonary embolism was diagnosed. One patient died because of an unrecognized intra-abdominal bleeding from the umbilical trocar site. Also the mortality rate in the laparoscopic group was 0.5%. A minor postoperative complication consisted of vomiting in 11 patients (5.8%). However this should not be considered a surgical complication. It is probably related at least in large part to anaesthesia technique.

Ten patients (5.3%) developed a wound infection. No other postoperative infections occurred in the laparoscopic group.

Table 6.04: Peroperative complications in open and laparoscopic cholecystectomy.

	Open group (n=130)	Laparoscopic group (n=189)	P-value
None	94 (72.3%)	102 (54.0%)	**= 0.001**
Major			
Perforation duodenum	0	1 (0.5%)	N.S.
Common bile duct lesion	0	1 (0.5%)	N.S.
Minor			
Bleeding gallbladder bed	2 (1.5%)	1 (0.5%)	N.S.
Cystic artery bleeding	0	2 (1.1%)	N.S.
Unspecified bleeding	1 (0.8%)	0	N.S.
Perforation gallbladder	0	67 (35.4%)	**< 0.001**
Intra-abdominal stone loss	0	10 (5.3%)	**< 0.01**
Bile spillage	32 (24.6%)	80 (42.3%)	**= 0.001**
Bleeding skin	1 (0.8%)	0	N.S.
Bleeding trocar site	0	2 (1.1%)	N.S.
Broken Instruments	0	6 (3.2%)	**< 0.05**

Table 6.05: Postoperative complications and infections in open and laparoscopic cholecystectomy.

Postoperative complications	Open group (n=130)	Laparoscopic group (n=189)	P-value
None	105 (80.8%)	173 (91.5%)	< **0.01**
Major			
Haemorrhage	9 (6.9%)	1 (0.5%)	< **0.002**
Reoperation	0	2 (1.1%)	N.S.
Incisional hernia	0	1 (0.5%)	N.S.
Pulmonary embolism	0	1 (0.5%)	N.S.
Minor			
Wound haematoma	14 (10.8%)	0	< **0.001**
Abdominal pain	2 (1.5%)	0	N.S.
Severe vomitus	0	11 (5.8%)	< **0.004**
Postoperative infections			
None	111 (85.4%)	178 (94.2%)	= **0.01**
Wound infection	16 (12.3%)	10 (5.3%)	< **0.04**
Urinary tract infection	2 (1.5%)	0	N.S.
Pulmonary infection	1 (0.8%)	0	N.S.

Follow-up (Table 6.06)

Open group: All patients were seen 12-14 days after discharge from the hospital. Ninety-seven of them (74.6%) had no complaints. Six (4.6%) complained of wound pain. Another six patients (4.6%) reported abdominal pain. Twenty-one patients (16.2%) reported minor complaints including weakness or minor gastrointestinal complaints.

Laparoscopic group: Onehundred seventy-nine patients (95.2%) had no complaints. Seven (3.7%) complained of abdominal pain. One patient reported pain at the sites of introduction of the trocars. In one patient a pulmonary embolism was diagnosed.

Table 6.06: Outpatient department parameters in open and laparoscopic cholecystectomy.

	Open group (n=130)	Laparoscopic group (n=188)	P-value
No complaints	97 (74.6%)	179 (95.2%)	**< 0.001**
Woundpain	6 (4.6%)	1 (0.5%)	**= 0.02**
Abdominal pain	6 (4.6%)	7 (3.7%)	N.S.
Pulmonary embolism	0	1 (0.5%)	N.S.
Others	21 (16.2%)	0	**< 0.0001**

6.4 DISCUSSION

Randomised clinical trials comparing laparoscopic with open cholecystectomy have become almost impossible, or consisted of limited number of patients[14], due to the rapid acceptance of laparoscopic cholecystectomy. However, objective analysis of the results and especially complications remains warranted. Therefore we decided to compare our laparoscopically cholecystemized patients with conventionally treated patients operated directly before the introduction of laparoscopic cholecystectomy.

Comparing the number of operations for symptomatic cholecystolithiasis showed remarkable more operations after introduction of laparoscopic cholecystectomy. Possible reasons for this increase include the performance of laparoscopy on patients previously assessed as too risky to undergo the conventional procedure, laparoscopy on mildly symptomatic patients who had previously put off a perceived higher risk open procedure and a possible broadening of indications for gallbladder surgery.

Conversion of laparoscopic to open cholecystectomy occurred in 12% of the patients. Others have reported conversion rates that are lower[15-19]. The conversion group showed no mortality and very low morbidity.

Comparison of the demographic characteristics and risk factors for complications between the open and the laparoscopic group showed a significant difference in age and hypertension (Table 6.03). We have no explanation for this differences. The higher age in the open group may have been associated with a increased incidence of previous laparotomies compared with the laparoscopic group.

Comparison of operation characteristics showed, as expected, a significant difference in duration of surgery. However there is a slight decrease in operation time for laparoscopic cholecystectomy with increasing experience.

Mortality in the open group was zero. One patient died during this series of laparoscopic cholecystectomy. The cause of death was an unregonized intra-abdominal bleeding from the trocar site. Reported mortality in other series varied from 0-0.8%[11, 16, 20-22]. Morbidity of open cholecystectomy was comparable with the results reported by other authors[5, 7]. When comparing both groups, morbidity was more serious in the laparoscopic group. Three patients had to be reoperated, whereas in the open group no reoperation were performed. Two patients were operated because of an intra-abdominal abscess and one because of a incisional hernia at the trocar site. This occurrence is more likely when the site is enlarged to remove the gallbladder. Suture closure of the fascial defect is therefore required.

In series of laparoscopic cholecystectomy complications directly related to the operation are more common[15, 20]. This series showed significantly more directly related surgical complications in the laparoscopic group compared with the open group. In the laparoscopic group, one accidental common bile duct lesion had to be repaired. In the open group common bile duct lesions did not occur. The expected rate of damaging of the common bile duct during open cholecystectomy is 0.1-0.2%[23]. The incidence during our laparoscopic operations was 0.5%, which is comparable with the results reported by others[16, 20-22, 24]. Spill of gallbladder contents during laparoscopic cholecystectomy is not rare. In our laparoscopic group the incidence of bile spillage is 42.3% and of intra-abdominal stone loss 5.3% (Table 4), which is higher compared with other series[25]. Bile spillage occurred not only by perforating the gallbladder during dissection, but also when the gallbladder was removed from the trocar site. Many surgeons concluded that the intraoperative loss of gallstones is a relatively innocuous event in the performance of laparoscopic cholecystectomy. Soper[25] observed no difference in complication rates when the gallbladder was perforated in comparison to cases where this event did not occur. Conversely, others had suggested delayed infectious complications[26, 27]. Jones et al[28] concluded that intraoperative gallbladder perforation does not cause adverse long-term complications, when accompanied by operative lavage and stone removal.

Infectious complications of laparoscopic cholecystectomy seem to be rare[21]. Comparison of the postoperative infections in both groups (Table 6.05) showed significantly more wound infections in the open group ($p<0.04$). Wound infection rate in this series was high, caused by the wide definition of wound infection. Not only the appearance of purulence was defined as a wound infection but also the appearance of serous discharge and erythema.

The follow-up of both patient groups showed significant more complaints in the open group. There was no significant difference in abdominal pain.

In two patients pulmonary emboli were diagnosed. Review of the literature showed a growing number of reports of deaths secondary to venous thromboembolism occurring after laparoscopic cholecystectomy[24, 29-31]. Caprini et al[32] concluded that laparoscopic cholecystectomy, despite being a "minimally invasive procedure", may be associated with a definite risk of developing postoperative venous thromboembolism that could extend beyond hospital discharge.

Laparoscopic cholecystectomy can safely be performed by appropriately trained surgeons in more than 90% of patients suffering from gallbladder disease[33]. For selective surgery, laparoscopic cholecystectomy is even superior to open cholecystectomy and must be seen as a new "gold standard" for cholecystectomies[34]. Our study showed a slightly higher morbidity in laparoscopically operated patients compared with conventionally operated patients.

With the evolution of laparoscopic cholecystectomy as the standard procedure for the treatment of symptomatic cholecystolithiasis, broadening of the indications for surgery is not warranted.

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CHAPTER 7

WOUND INFECTION AFTER LAPAROSCOPIC CHOLECYSTECTOMY: AN ANALYSIS OF RISK FACTORS

ABSTRACT

Postoperative wound infection and the need for antibiotic prophylaxis are well documented in open biliary surgery. However, these data cannot be extrapolated to laparoscopic procedures.

The aim of this study was to determine the incidence of postoperative wound infection after laparoscopic cholecystectomy and to identify which patients were at risk for developing a postoperative wound infection.

Between June 1991 and June 1993 a prospective trial was performed. All patients aged 18 years or older admitted for laparoscopic cholecystectomy were entered into the study.

There were 232 eligible patients available for the study. Seventeen patients were excluded. From the remaining 215 patients 189 patients (87.9%) were operated laparoscopically. In 26 patients (12.1%) the operation was converted from laparoscopic to open cholecystectomy.

The incidence of wound infections was 5.3%. General risk factors did not influence the woundhealing. Significant specific risk factors for developing a wound infection were emergency of the operation ($p=0.046$) and acute cholecystitis ($p=0.014$). Significant relative risk factor for wound infection was acute inflammation of the gallbladder as histopathologically determined ($p=0.046$). Multivariate analysis showed that the risk factor "acute cholecystitis" was the most important risk factor for developing a postoperative wound infection.

Antibiotic prophylaxis as recommended for biliary operations in general may no longer be justifiable. This would be advantageous in terms of expense and the avoidance of antibiotic resistance, but a double blind randomised trial is needed to confirm this hypothesis.

7.1 INTRODUCTION

Since the first successful laparoscopic cholecystectomy, the operation has been accepted in general surgical practice more rapidly than any other new surgical procedure. Laparoscopic cholecystectomy has become an accepted alternative to open cholecystectomy. Numerous studies have demonstrated its efficacy. Morbidity and mortality are comparable[1-13]. Major complications of laparoscopic cholecystectomy, such as bowel perforation, bile duct injury and retained stones, have been reviewed in the literature[7, 14-16].

Postoperative wound infection is a major cause of postoperative morbidity. It will delay the discharge of a patient and will result in additional cost of care, both in the hospital and in the community.

A number of risk factors are frequently quoted as being associated with an increased risk of postoperative wound infection. These include age, diabetes, concurrent disease or immunosuppression, emergency procedure, duration of operation and obesity. The relative importance of these risk factors in laparoscopy is unclear. Each may render the patient more susceptible to a wound infection, but their influence is still dependent upon the degree of endogenous contamination during surgery. It has been suggested that elderly patients have a higher wound infection rate because they undergo a higher proportion of contaminated operations, and that at the time of surgery the degree of contamination is greater[17], though this has not been confirmed when the type of operation has been accounted for[15]. Postoperative wound infection and the need for antibiotic prophylaxis are well documented in open biliary surgery[19]. The use of antibiotic prophylaxis, however, for laparoscopic procedures is not yet founded, as there are no studies that outline the indications.

The current investigation was initiated to determine the incidence of postoperative wound infection after laparoscopic cholecystectomy and to identify which groups were at risk for developing a postoperative wound infection.

7.2 PATIENTS AND METHODS

Between June 1991 and June 1993 a prospective trial was performed. All patients aged 18 or older admitted for laparoscopic cholecystectomy were entered into the study. Absolute contraindications for laparoscopic cholecystectomy were inability to tolerate general anaesthesia, history of upper abdominal operations and the presence of choledocholithiasis. Initially patients with upper or mid-abdominal scarring were considered not suitable for laparoscopic cholecystectomy. However, with increasing experience, these conditions did not exclude patients from laparoscopic cholecystectomy.

All patients allergic to penicillin were excluded. If patients had received antibiotics within the previous 48 hours, or if they received antibiotics other than the standard antibiotics used in this trial during 72 hours after operation they were also excluded. Patients with pregnancy were not entered into the trial as were patients with impaired renal function (creatinine-clearance < 30 ml/min). Patients with presence of an underlying disease or concomitant infection interfering with evaluation of response were excluded.

Laparoscopic cholecystectomy was performed by the Anglo-American method[20,21]. The gallbladder was dissected free with by electrocautery. All operations were performed with reusable instruments. No routinely intraoperative cholangiography was performed.

Patients undergoing laparoscopic cholecystectomy received a single dose of Augmentin[R] at the induction of anaesthesia. It was administered as a single slow intravenous bolus injection of 1.2g of powder dissolved in 10 ml water. Augmentin[R] is a combination of amoxycillin and clavulanic acid. Clavulanic acid is an inhibitor of many bacterial beta lactamases and greatly increases the active spectrum of amoxycillin included Bacteriodes spp. Bile samples were collected from the unopened gallbladder for culture and identification.

Patients were assessed daily during their hospital stay. Clinical assessment included physical examination, especially concerning symptoms of postoperative infections and measurement of temperature. All patients were seen at the outpatient department one week after discharge of the hospital.

Wound infections were scored using the scoring method "no/minor/major" infection, based on the presence or absence of apparent signs of infection[22]. Wound infections were graded as follows: ("no") no sign of infection; "minor" infection: erythema or serous discharge, "major" infection: skin edge necrosis and/or purulent discharge and/or superficial or deep wound dehiscence.

The variables considered as a risk factor of wound infection were divided into general, specific and relative risk factors and are listed in Table 7.01.

Statistical analysis was performed by the Department of Biostatistics/Epidemiology of the Erasmus University Rotterdam. Percentages or two-way tables were analysed with the chi-square test. For two by two tables with small expected frequencies Fisher's exact test was used. Multi-variate analysis were performed according to Mantel-Haenszel. Values for $p<0.05$ were considered to be significant.

Table 7.01: List of risk factors.

General risk factors
Age
Gender
Quetelet index
Diabetes mellitus
History of abdominal disease
(History of) Cancer
Liver disease
Cardiovascular disease
Chronic obstructive pulmonary disease
Specific risk factors
Fever on admission
Emergency procedure
Acute cholecystitis
ERCP
Relative risk factors
Peroperative surgical finding (infiltrate, hydrops, gangrenae)
Per- / post-operative complications
Histopathological diagnosis
Bile spillage
Bile culture
Abdominal washing

7.3 RESULTS

There were 232 eligible patients available for the study between June 1991 and June 1993. Seventeen patients were excluded for reasons listed in Table 7.02. From the remaining 215 patients 189 patients (87.9%) were operated laparoscopically. In 26 cases (12.1%) there was a conversion from laparoscopic to open cholecystectomy, these patients were also excluded. The reasons for conversion were either problems caused by adhesions (n=16) of previous laparotomy or cholecystitis. Other reasons for conversion were instrumental defect (n=5), uncontrolable bleeding of the cystic artery (n=2) or the liver (n=1) and unclear anatomy (n=1). In one patient the common bile duct was clipped. No wound infections occurred in the conversion group.

Table 7.02: Reasons of exclusion.

Patients < 18 years	2 (0.6%)
Allergic to penicillin	6 (1.7%)
Antibiotics < 48 hours preoperative	4 (1.1%)
Antibiotics < 72 hours postoperative	3 (0.8%)
Pregnancy	2 (0.6%)
Total	17 (4.8%)

Females accounted for the majority of the laparoscopically operated patients namely 152 (80.4%) and 37 men (19.6%). The mean age was 47 years with a range from 18 to 85 years. The mean hospital stay was 5 days with a median of 3 days. The patients were seen at the outpatient department after an average of 7 days.

Concerning the general risk factors there were 153 (81.0%) without a history of (previous) disease. Most occurring general risk factors were cardiovascular diseases (12.2%), followed by chronic obstructive pulmonary diseases (4.2%), diabetes mellitus (3.2%) and cancer (1.1%). Other preoperative risk factors studied in the 189 laparoscopically operated patients were history of abdominal disease (23.8%), acute cholecystitis (2.1%), preoperative ERCP (1.1%) and fever on admission > 38.5 °C (0.5%).

All operations were performed under general anaesthesia regardless of the condition of the patients. Seven patients were operated acutely (3.7%). The mean time of surgery was 65 minutes.

Onehundred fifteen patients were operated without peroperative surgical problems. Major peroperative complications consisted of a duodenal perforation and an accidental clipping of the common bile duct. Minor peroperative complications in laparoscopic cholecystectomy were perforation of the gallbladder in 67 patients (35.4%), loss of intra-abdominal stones in 10 patients (5.3%) and in two patients persistent bleeding of the trocar site. In five patients there were technical problems with the laparoscopic instruments.

Postoperative complications were seen in five patients. In two cases a reoperation was performed because of a subfrenic abscess. Another major problem was a hernia accretta at the trocar site twenty-four hours postoperatively, which lead to a resection of the small bowel. One patient suffered from a pulmonary embolism. One patient died because of a postoperative intra-abdominal bleeding. Also the mortality rate in the laparoscopic group was 0.5%.

Wound infection

Wound assessment was based on clinical observation. According to these observations there were no major wound infections, while there were four minor wound infections (2.1%). These were characterised by erythema and needed no further treatment. There were no patients with serous discharge.

During follow-up at the outpatient department six patients (3.2%) showed minor wound infections. No major wound infections occurred. Crosstabulation between the in-hospital wound infections and the wound infections at the outpatient department showed no relationship. In total, the incidence of wound infection after laparoscopic cholecystectomy was 5.3% with a 95%-confidence interval between 2.1% and 8.5%.

No wound infections have been observed in the conversion group.

Univariate analysis

Estimated risk of wound infections, both in hospital and at the outpatient department, was calculated for each of the risk factors.

Statistical analysis showed that there were no general risk factors involved in the development of a wound infection (Table 7.03). There were only two patients with hypertension, two with a history of cancer, one with a liver disease and eight with COPD; none of these patients developed a wound infection.

A specific risk factor for wound healing was the emergency of the operation. Patients who were operated acutely had a significant risk of developing a postoperative wound infection. Acute cholecystitis was also a significant risk factor for developing a postoperative wound infection. The temperature on admission tended to be significant (p=0.053). Two patients underwent an ERCP preoperatively, but had no disturbed woundhealing (Table 7.04).

A significant relative risk factor for wound infection was acute inflammation (in combination with chronic inflammation) of the gallbladder as histopathologically determined (Table 7.05). Remarkably, bile spillage occurring in 79 patients did not influence the woundhealing. In only 5 patients (2.8%) a positive bile culture was found and only one developed a wound infection.

Multivariate analysis

Multivariate analysis with the abovementioned significant risk factors showed that the risk factor "acute cholecystitis" was the most important risk factor for developing a postoperative wound infection.

Bacteriology

From 189 peroperative bile cultures 184 were negative. The organism isolated were Escherichia coli (n=2), Streptococcus spp. (n=2) and Candida albicans (n=1). Both Escherichia coli and streptococcus spp. were sensitive for Augmentin^{R}.

Table 7.03: General risk factor calculated for wound infection.

General risk factor	Number	Infection (%)
Gender Male	37	1 (2.7%)
Female	151	9 (6.0%)
(Chi square; p=0.702: **N.S.**)		
Age		
(Mann-Whitney - Wilcoxon Rank test; p=0.1577: **N.S.**)		
Quetelet index		
(Mann-Whitney - Wilcoxon Rank test; p=0.1178: **N.S.**)		
Diabetes mellitus	6	1 (16.7%)
(Fisher's exact; p=0.280: **N.S.**)		
Cardiovascular diseases	23	1 (4.3%)
(Chi-square; p=1.000: **N.S.**)		
History of abdominal disease	45	2 (4.4%)
(Chi-square; p=1.000: **N.S.**)		
(History of) Cancer	2	0
Liver disease	1	0
COPD	8	0

In the first column the number of patients at risk are given. Next column shows the number of wound infections, both in-hospital and at the outpatient department, in percent. Significance is given by $p < 0.05$.

Table 7.04: Specific risk factor calculated for wound infection.

Specific risk factor	Number	Infection (%)
Fever on admission (Fisher's exact; p=0.053: **N.S.**)	1	1 (100%)
Emergency procedure (Fisher's exact; p=0.046: **S.**)	7	2 (28.6%)
Duration of operation (Mann-Whitney - Wilcoxon Rank test; p=0.1094: **N.S.**)		
Acute cholecystitis (Fisher's exact; p=0.014: **S.**)	4	2 (50.0%)
ERCP	2	0

In the first column the number of patients at risk are given. Next column shows the number of wound infections, both in-hospital and at the outpatient department, in percent. Significance is given by $p < 0.05$.

Table 7.05: Relative risk factor calculated for wound infection.

Relative risk factor	Number	Infection (%)
Infiltrate/hydrops/gangrenae/perforation (Fisher's exact; p=0.100: **N.S.**)	2	1 (50.0%)
Peroperative complications (Chi-square; p=1.000: **N.S.**)	73	4 (5.5%)
Postoperative complications	3	0
Histopathological diagnosis (acute) (Fisher's exact; p=0.046: **S.**)	7	2 (28.6%)
Bile spillage (Chi-square; p=1.000: **N.S.**)	79	4 (5.1%)
Positive bile culture (Chi-square; p=0.608: **N.S.**)	5	1 (20.0%)
Abdominal washing (Chi-square; p=0.601: **N.S.**)	70	5 (7.1%)

In the first column the number of patients at risk are given. Next column shows the number of wound infections, both in-hospital and at the outpatient department, in percent. Significance is given by $p < 0.05$.

7.4 DISCUSSION

Wound infection after cholecystectomy happens with an incidence of 15-25%[23-26]. While not all these infections are serious, they uniformly add to the patient's discomfort. With the use of antibiotics a decrease of postoperative wound infections to 3-5% is reached[27]. These data, however, cannot be extrapolated to laparoscopic procedures.

Laparoscopy has been the most significant advance in minimal invasive surgery in the past decade. It has proven to minimize surgical trauma, shorten the hospital stay, minimize analgetic use and decrease reconvalescense[5, 28, 29]. In less than four years, laparoscopic cholecystectomy has become the gold standard for the treatment of cholecystolithiasis. Therefore, assessment of antibiotic prophylaxis and its indication in minimal invasive procedures is warranted.

Several authors believe that they can distinguish high-risk from low-risk surgical patients and advocated prophylactic antibiotics only in high-risk patients[23, 30]. The high-risk category as established by Keighley et al. is widely used: age over 60 years, emergency surgery and acute cholecystitis. These categories delineate patients with infected bile, and are especially at risk for postoperative wound infections.

Other authors believe in antibiotic prophylaxis for all patients[31]. The use of a single dose of antibiotic would appear to have little adverse effect on the ecology or economy. Side effect reactions to antibiotics are infrequent and generally mild.

In our study all laparoscopically operated patients received antibiotic prophylaxis as a result of our antibiotic prophylactic regimen before the introduction of the laparoscopic cholecystectomy. The incidence of wound infections after laparoscopic cholecystectomy was 5.3%. With shortening of hospital stay more wound infections were diagnosed at the outpatient department. The clinical significance of this minor wound infections was nil. None of the wound infections categorized as "minor" needed treatment.

In literature, age above 60 years is described as a significant risk factor for developing postoperative wound infection after open cholecystectomy[30]. According to this study, age is not significant risk factor for developing a wound infection and/or disturbance after laparoscopic cholecystectomy. Bile spillage was a frequently occurring relative risk factor with no influence on wound healing. Most important significant risk factor for developing a postoperative wound infection after laparoscopic cholecystectomy was acute cholecystitis.

It is obvious that wound infection can be almost completely avoided by giving all patients antibiotic prophylaxis. This is however probably "overkilling" in most instances. The logical question to be asked is which patients need antibiotic prophylaxis. Antibiotic prophylaxis as recommended for biliary operations in general may no longer be justifiable. This would be advantageous in terms of expense and the avoidance of antibiotic resistance, but a double blind randomised trial is needed to confirm this hypothesis.

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CHAPTER 8

INFECTIONS AND BACTERIOLOGICAL DATA AFTER LAPAROSCOPIC AND OPEN GALLBLADDER SURGERY

ABSTRACT

In two hospitals 637 patients undergoing a cholecystectomy between June 1989 and June 1993 were entered into a prospective trial.

The aim of this study was to determine the incidence of postoperative infections, especially wound infections, after open and laparoscopic biliary surgery and to assess the bacteriological data on these patients.

The incidence of minor wound infection was 10.4% (66/637) and of major wound infection 3.6% (23/637), the overall incidence 14% (89/637). Cross-tabulation between in-hospital wound infection and delayed wound infections showed no correlation. There was a significant difference in in-hospital wound infections between the laparoscopic and the open group. The overall incidence of wound infection after laparoscopic cholecystectomy was 5.3%. The incidence of non-surgical related infections was low. There was no significant difference in non-surgical related infections between the open, laparoscopic and conversion group. The mortality rate was 0.2%.

Overall, bile cultures were positive in 22% (220/999). There were 85 patients (13.3%) with positive bile from the gallbladder. From the laparoscopically operated patients 2.8% had a positive bile culture. The predominant micro-organism from gallbladder bile were E. coli (56 isolates), Klebsiella spp. (20 isolates) and streptococcus spp. (16 isolates). There was no relationship between gallbladder cultures and wound infection. The consequences of wound infections can be serious. Especially in large wounds as in open gallbladder surgery it can lead to early dehiscence and late incisional hernia. Antibiotic prophylaxis in open gallbladder surgery has been generally accepted and this study showed a morbidity rate comparable with the literature.

The incisions used in laparoscopic gallbladder surgery are less susceptible to major problems because they are small. This combined with the significantly lower incidence of wound infections after laparoscopic cholecystectomy suggests that routine antibiotic prophylaxis as recommended for biliary surgery in general is now disputable.

8.1 INTRODUCTION

Cholecystectomy is one of the most frequent types of abdominal surgery performed. Usually it entails removal of a noninflamed gallbladder and is associated with a low postoperative infection rate. Postoperative infection rates are higher in patients with certain risk factors of which there are many described in literature[1,2].

Wound infection may have serious consequences for a patient, as it can lengthen the hospital stay, and promote the chance to develop a wound rupture or incisional hernia and cause a cosmetically unacceptable scar. Attempts to reduce postoperative wound infections are therefore very important.

Postoperative wound infections in biliary tract surgery are largely due to endogeneous contamination produced by opening the biliary tract in patients with bacteria in the bile, which is present in 15% to 50% of high-risk patients[3,4].

Presently laparoscopic operations are performed with increasing frequency. The benefits of laparoscopic cholecystectomy over the open procedure are numerous and well documented in the general surgery literature.

The aim of this study was to determine the incidence of postoperative infections, especially wound infections, after laparoscopic and open biliary surgery and to assess the bacteriological data on these patients.

8.2 PATIENTS AND METHODS

In two participating hospitals, a teaching and a non-teaching, both in Rotterdam, patients undergoing a cholecystectomy between June 1989 and June 1993 were entered in a prospective trial. The patients all had symptomatic gallstones and all underwent abdominal ultrasound and liver function tests before operation. Open cholecystectomy was performed by right subcostal incision or median laparotomy. Laparoscopic cholecystectomy was introduced in June 1991 and has been the preferred method of treatment of cholecystolithiasis since.

8.2.1 Patient population

All patients undergoing a cholecystectomy, elective as well as non-elective, were eligible. Excluded were patients with the following conditions: age below 18 years, hypersensitivity to penicillins/cephalosporins, pregnany, impaired renal function (creatinine clearance below 30 ml/min.), the presence of an underlying disease or concomitant infection which would interfere with the evaluation of response, any antibiotic within 48 hours prior to surgery and a pre- or peroperative intention to administer antibiotics other than the trial antibiotics during the 72 hours after operation.

8.2.2. Treatment regimen

A combination of amoxicillin 1 g and clavulanic acid 200 mg, was chosen as a suitable antimicrobial drug for prophylaxis in surgery involving the upper gastrointestinal tract[5-8]. The drug was administered, at the induction of anaesthesia, by slow intravenous bolus injection as 1.2 g of powder dissolved in 10 ml water.

8.2.3 Definitions

Wound infections were scored using the scoring method "no/minor/major" infection, based on the presence or absence of apparent signs of infection. Wound infections were graded as follows: ("no") no sign of infection; "minor" infection: erythema or serous discharge, "major" infection: skin edge necrosis, purulent discharge and superficial or deep wound dehiscence[9].

The clinical signs of wound infection may be detected within a few days after the operation (in hospital wound infection) or it may appear after discharge (delayed wound infection).

The diagnosis of respiratory tract infection was based on physical examination and if possible, confirmed by radiological examination of the chest and culture of a sputum sample.

Urinary tract infection was defined as otherwise unexplained fever with local symptoms of urinary tract infection and/or positive urine culture ($> 10^5$ micro-organism/mL).

Sepsis was defined as positive blood cultures and/or chills with rectale temperatures higher than 39^0 C or axillary higher than 38^5 C.

8.2.4. Surveillance of postoperative wound infection

Every day in hospital the wounds were scored to the aspects of disturbed healing: serous exudate, erythema, purulent discharge and separation of deep tissue. On follow-up at the outpatient department, these aspects were judged again. In case of unexplained fever radiological and bacteriological assessment of respiratory or urinary infections was made in the postoperative period.

8.2.5 Clinical assessment

Preoperatively a complete medical history was obtained in all cases, consisting of quetelet index, temperature at admission, age, risk factors for infection, diagnosis, results of routine clinical and haematology, results of radiological examination.

Peroperatively the following items were recorded: participating hospital, duration of the operation, interval between administration of the antibiotics and the incision, type of operation, macroscopical appearance of the gallbladder and the common bile duct, the presence of bilestones, placement of drains, leakage of bile and complications.

Postoperatively the patients were assessed in hospital every day for wound infection and three times a week for non-infective postoperative complications, other infections and adverse events.

8.2.6. Bacteriological assessment

Peroperatively bile samples were taken from the gallbladder and common bile duct by needle aspiration for bacteriological examination. From patients with a T-tube, drain samples were collected. Microbiologic evaluation was performed according to standard methods[10,11].

8.2.7. Statistics

All data were analyzed using SPSS software (Chicago,Ill.). Fisher's exact test was used for comparing categorical variables[12]. Mean values were compared by Student's t test. All P values were two sided. Values for $p<0.05$ were considered to be significant.

8.3 RESULTS

In the period of enrollment 764 patients were scheduled for elegible procedures. The number of patients included was 637. Also 127 patients were withdrawn from analysis. The reasons for not including these patients were age < 18 years (n=4), penicillin allergy (n=25), use of other antibiotics pre- or postoperatively (n=72), refused informed consent (n=5), protocol violation (n=12), partial cholecystectomy (n=5), presence of other disease (n=1) and pregnancy (n=3).

Elective cholecystectomy was done for symptomatic gallstones in 552 patients (86.7%). Emergency operation were performed in 85 patients. There were 467 women and 170 men. The mean age was 52.8 years. The risk factors for gallbladder surgery are listed in Table 8.01.

The indications for operation were symptomatic cholecystolithiasis (n=515), cholecystolithiasis with common bile duct stones (n=33), cholecystitis (n=57), cholecystitis with common bile duct stones (n=5), non-calculous cholecystitis (n=9), polyps (n=3) and others (n=15).

In 291 patients an open cholecystectomy was performed, 117 patients underwent an additional common bile duct exploration. In 14 patients an open cholecystectomy was performed with another non-biliary intervention. Laparoscopic cholecystectomy was done in 189 patients. In twenty-six patients a conversion from laparoscopic to open cholecystectomy was necessary.

Table 8.01: Patient characteristics in 637 patients operated for gallbladder surgery (LC = laparoscopic cholecystectomy).

	TOTAL 637 (100%)	Open 422 (100%)	LC 189 (100%)	Conversion 26 (100%)
Risk factors:				
Age > 60 years	238 (37.4%)	184 (43.6%)	44 (23.3%)	10 (38.5%)
History of abdominal disease	175 (27.5%)	126 (29.9%)	45 (23.8%)	4 (15.4%)
Acute cholecystitis	47 (7.4%)	40 (9.5%)	4 (2.1%)	3 (11.5%)
Obstructive jaundice	22 (3.5%)	22 (5.2%)	-	-
Acute pancreatitis	10 (1.6%)	10 (2.4%)	-	-
Preoperative ERCP	13 (2.0%)	11 (2.6%)	2 (1.1%)	-
Operation:				
Acute	85 (13.3%)	75 (17.8%)	7 (3.7%)	3 (11.5%)
Elective	552 (86.7%)	347 (82.2%)	182 (96.3%)	23 (88.5%)
Time surgery (min.)	62	59	65	81

Mortality

One patient died from haemorrhage within twenty-four hours after laparoscopic cholecystectomy. The mortality rate was 0.2%.

Infective complications

The incidence of wound infections after open and laparoscopic biliary surgery are listed in Table 8.02. Fivehundred forty-eight patients showed a satisfactory healing of the wound. The incidence of minor wound infection was 10.4% (66/637) and of major wound infection 3.6% (23/637). The overall incidence of wound infection was 14% (89/637). Cross-tabulation between the in-hospital wound infection and the outpatient or delayed wound infections showed no correlation. There was a significant difference in in-hospital wound infections between the open and the laparoscopic group (Table 8.02).

The incidence of minor wound infection after laparoscopic cholecystectomy was 5.3%. No major wound infections occurred in the laparoscopic group. All major wound infections were diagnosed in the open group. In the conversion group from laparoscopic to open cholecystectomy five minor postoperative wound infections were observed, and no major wound infections. The major wound infections were categorized as skin edge necrosis (n=6), skin edge necrosis with superficial wound dehiscence (n=8) and skin edge necrosis with superficial wound dehiscence and with purulent discharge (n=9).

Of the 23 major wound infections nine needed additional treatment. In four patients there was a drainage of purulent exudate; in another four the stitches were removed and, once the wound was covered with a wet bandage. The wound infections caused no prolonged hospital stay.

In the laparoscopic group two patients (0.3%) developed a subhepatic abscess. No other postoperative infections occurred in the laparoscopic group. In the open group there were seven urinary tract infections (1.1%), four respiratory tract infections (0.6%) and three patients with a sepsis (0.5%). There were no significant differences between these infections in the open and laparoscopic group. In the conversion group from laparoscopic to open cholecystectomy no other postoperative infections were observed.

Table 8.02: Infections after laparoscopic and open gallbladder surgery (LC = laparoscopic cholecystectomy).

	TOTAL 637 (100%)	Open 422 (100%)	LC 189 (100%)	Conversion 26 (100%)	P-value
In hospital wound infection:					
No	576 (90.4%)	365 (86.5%)	185 (97.9%)	26 (100%)	**< 0.001**
Minor	39 (6.1%)	35 (8.3%)	4 (2.1%)	0	**< 0.01**
Major	22 (3.5%)	22 (5.2%)	0	0	**< 0.001**
Delayed wound infection:					
No	608 (95.6%)	405 (96.0%)	182 (96.8%)	21 (80.8%)	**< 0.01**
Minor	27 (4.2%)	16 (3.8%)	6 (3.2%)	5 (19.2%)	**< 0.01**
Major	1 (0.2%)	1 (0.2%)	0	0	N.S.
Other infections:					
Urinary tract	7 (1.1%)	7 (1.7%)	0	0	N.S.
Pulmonary	4 (0.6%)	4 (0.9%)	0	0	N.S.
Sepsis	3 (0.5%)	3 (0.7%)	0	0	N.S.
Subhepatic abscess	2 (0.3%)	0	2 (1.1%)	0	N.S.

Bacteriological assessment

From 637 patients 662 bile cultures were peroperatively obtained from the gallbladder and 237 from the common bile duct. Postoperatively 100 bile cultures were obtained from the T-tube. Overall, bile cultures were positive in 22% (220/999).

The organisms isolated from positive cultures in bile from gallbladder, common bile duct and T-tube are listed in Table 8.03.

There were 85 patients (13.3%) with positive bile from the gallbladder. From the laparoscopically operated patients 2.8% had a positive bile culture. The predominant micro-organisms from gallbladder bile were E. coli (56 isolates), Klebsiella spp. (20 isolates) and Streptococcus spp. (16 isolates).

Fifty-two patients showed a single micro-organism per culture, 23 patients showed two micro-organism, 7 patients three micro-organism and three patients showed four micro-organism per culture. In 19 of the positive cultures resistance to amoxycillin\clavulanic acid was found. Three of these resistant species caused a wound infection. Sensitivity and resistance to amoxycillin\clavulanic acid in operative bile cultures related to wound infections are shown in Table 8.04.

In the nine major wound infections with purulent discharge the drainage was cultured, six were positive. Organisms isolated were Staphylococcus aureus (n=2), E. coli (n=1), Enterobacter spp. (n=1) and skin flora (n=2). In three cultures no micro-organisms were found. There was no correlation between positive gallbladder cultures and the wound infection cultures. Two patients developed a subhepatic abscess. The organism isolated from the culture of the first subhepatic abscess was S. aureus. From the second subhepatic abscess no culture was available.

The urinary tract infections were caused by E. coli (4 isolates), Morganella morganii (1 isolate) and mixed flora (2 isolates). The respiratory tract infections were caused by Streptococcus pneumoniae (2 isolates), P. aeruginosa (1 isolate), H. influenzae (1 isolate), Moraxella catarrhalis (1 isolate) and mouth flora (1 isolate). Two patients showed 2 micro-organisms in the sputum culture. From the three patients with urosepsis two blood cultures were negative and in one S. aureus was isolated.

Table 8.03: Organisms isolated from positive cultures (GB = Gallbladder, CBD = Common bile duct).

Organisms	Number of isolates			
	LAPARO-SCOPIC	**OPEN**		
Bile from	GB	GB	CBD	T-tube
Gram-negative				
E. coli	2 (40%)	56 (42.7%)	23 (42.6%)	13 (37.1%)
Klebsiella spp.	0	20 (15.2%)	9 (16.7%)	6 (17.1%)
Enterobacter spp.	0	5 (3.8%)	1 (1.9%)	4 (11.4)
Proteus vulgaris	0	2 (1.5%)	0	0
Salmonella spp.	0	2 (1.5%)	1 (1.9%)	0
Aeromonas hydrophila	0	2 (1.5%)	1 (1.9%)	0
Gram-positive				
Streptococcus spp.	2 (40%)	16 (12.2%)	6 (11.1%)	1 (2.9%)
Enterococcus spp.	0	9 (6.8%)	5 (9.3%)	3 (8.6%)
Staphylococcus aureus	0	2 (1.5%)	0	5 (14.3%)
Anaerobic				
Clostridium spp.	0	9 (6.8%)	1 (1.9%)	0
Others	1 (20%)	8 (6.1%)	7 (13.0%)	3 (8.6%)
Total	5	126	54	35

Table 8.04: Sensitivity and resistance for amoxycillin\clavulanic acid in operative bile cultures related to wound infections. (RES = resistant, SEN = sensitive, ND = not determined, **WI** = wound infection)

Organisms	Total	RES **WI**	SEN **WI**	ND **WI**
Gram-negative				
E. coli	92	9	60 **14**	23
Klebsiella spp.	35	0	34 **4**	1
Enterobacter spp.	10	8 **2**	**1**	1
Proteus vulgaris	2	0	2	0
Salmonella spp.	3	0	0	3
Aeromonas hydrophila	3	0	3 **1**	0
Gram-positive				
Streptococcus spp.	23	0	1 **1**	22 **2**
Enterococcus spp.	17	0	15 **2**	2
Staphylococcus epidermidis	7	2 **1**	1 **1**	4
Anaerobic				
Clostridium spp.	10	0	10 **1**	0

8.4 DISCUSSION

Postoperative wound infection is a major cause of postoperative morbidity, with an incidence after biliary surgery varing from 4.2 - 21%[13-16]. Review of published wound infection rates after laparoscopic cholecystectomy shows a variation from 0.3 - 1.8%[17-21]. Our overall incidence of wound infection after biliary surgery was 14% in conventional and 5.3% after laparoscopic cholecystectomy, which shows a highly significant difference. The rates are higher than described in literature; mainly caused by the variation in the definition of wound infection. The definition of a wound infection varies and makes comparison of wound infection rates, treatment and prophylaxis difficult. The National Research Council[22] defined wound infection as "a break in the skin, due to surgery, burns or trauma, which is discharging pus". However, the requirement to see purulent discharge may result in an artificially low infection rate. According to that definition the incidence in our study was 1.3%. Others have taken the presence of a positive culture, together with discharge, as an evidence of an infection[23], while some believe that any discharge is an infection[24].

The spectrum of bacteria found in the bile in this study is comparable with the results reported in literature[25]. The most common bacteria were E. coli, Klebsiella spp. and Streptococcus spp., which together constituted 70.1% of all isolates from the gallbladder and 70.4% of all isolates from the common bile duct. Other organisms were relatively infrequent and anaerobic organisms constituted a very small percentage of the total. In this study 39% had more than one micro-organism per culture.

Remarkable is the significant difference in positive bile cultures between open and laparoscopically operated patients. We have no explanation for this difference. The significant higher incidence of wound infections in the open group may have been associated with the significant difference in positive bile cultures compared with the laparoscopic group.

Introduction of foreign bodies, such as T-tubes, into the biliary tract led to a change of bacterial spectrum (Table 8.03). Staphylococcus epidermidis were uncommon in bile (1.5%), rather frequent in bile from the T-tube (14.3%) and in major wound infections (22%). This findings have also been reported by others[26,27].

Correlation between positive gallbladder cultures and wound infections with the same micro-organisms has been confirmed by several investigators[1,28], but this study showed no relationship between gallbladder cultures and wound infection. This suggest that peroperative routine gallbladder culture as recommended for biliary surgery can be abolished.

The consequences of wound infections can be serious. Especially in large wounds as in open gallbladder surgery it can led to early dehiscence and late incisional hernia. Antibiotic prophylaxis in open gallbladder surgery has been generally accepted and also this study showed a morbidity rate comparable with the literature[13-16].

The incisions used in laparoscopic gallbladder surgery are less susceptible to problems as wound dehiscence or incisional hernia because they are small. This combined with the significantly low incidence of wound infections after laparoscopic cholecystectomy suggests that routine antibiotic prophylaxis as recommended for biliary surgery in general may no longer be justifiable.

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CHAPTER 9

LAPAROSCOPIC CHOLECYSTECTOMY: AN ANALYSIS OF RISK FACTORS FOR CONVERSION TO OPEN CHOLECYSTECTOMY

ABSTRACT

Review of the literature showed a great difference in conversion rate from laparoscopic to open cholecystectomy.

The aim of this prospective study was to determine the conversion rate from laparoscopic to open cholecystectomy and to identify which patients were at risk for conversion.

From the 215 cholecystectomies which started laparoscopically between June 1991 and June 1993, 189 (87.9%) were completed successfully, whereas 26 (12.1%) had to be converted to open cholecystectomy. The cause of conversion was electively in 22 patients (84.6%) and enforced in 4 patients (15.4%). Significant risk factors for conversion from laparoscopic to open cholecystectomy were acute cholecystitis ($p=0.04$), intraoperatively infiltrate ($p=0.002$), acute inflammation as histopathological diagnosis ($p=0.001$) and positive bile culture ($p=0.01$).

In conclusion, intraoperative infiltrate, acute inflammation as histopathological diagnosis and positive bile culture all contributed to the possibility of conversion. The clinical diagnosis of an acute cholecystitis was the best factor predicting conversion from laparoscopic to open cholecystectomy. This predictive finding allow the surgeon to discuss the higher risk of conversion preoperatively and allow for an earlier judgment decision to convert if intraoperative difficulty is encountered.

9.1 INTRODUCTION

Laparoscopic cholecystectomy has become the gold standard procedure for symptomatic cholecystolithiasis. This technique was first carried out for uncomplicated cholelithiasis. After a training period in which the technique was used exclusively in selected patients, most surgeons extended this technique to complicated gallstone disease. However, there still remains cases which are too difficult to be performed laparoscopically and where the procedure has to be converted from laparoscopic to open cholecystectomy.

Review of the literature showed a great difference in conversion rate from laparoscopic to open cholecystectomy (Table 9.01). Conversion is required in 1.8-11.2% of the patients treated for cholecystolithiasis and in most patients is not predictable prior to surgery.

The aim of this study was to determine the conversion rate from laparoscopic to open cholecystectomy and to identify which patients were at risk for conversion.

Table 9.01: Review of the literature concerning conversion rate from laparoscopic to open cholecystectomy.

Study	Patients	Conversion rate (%)
The Southern Surgeons club[9]	1518	4.7
Cushieri et al[19]	1236	3.6
Marti et al[20]	806	11.2
Soper et al[21]	618	2.9
Spaw et al[22]	500	1.8
Go et al[23]	413	6.8
Wolfe et al[24]	381	3.0
Bailey et al[25]	375	5.0
Graves et al[26]	304	6.9
Peters et al[14]	283	2.8
Schirmer et al[16]	152	8.5

9.2 PATIENTS AND METHODS

Between June 1991 and June 1993 a prospective trial was performed. All patients aged 18 or older admitted for laparoscopic cholecystectomy were entered into the study. Absolute contraindications for laparoscopic cholecystectomy were inability to tolerate general anaesthesia and the presence of choledocholithiasis. Initially patients with upper or mid-abdominal scarring were considered not suitable for laparoscopic cholecystectomy. However, with increasing experience, these conditions did not exclude patients from laparoscopic cholecystectomy.

Laparoscopic cholecystectomies were done by three of the four surgeons and five residents (postgraduate years 1 to 3). Residents performing laparoscopic cholecystectomies as operating surgeon were always assisted by a experienced surgeon.

Laparoscopic cholecystectomy was performed by the Anglo-American method[1,2]. The gallbladder was dissected free with electrocautery. No routinely intraoperative cholangiography was performed. The laparoscopic cholecystectomy was converted to open cholecystectomy either due to complications (=enforced) or due to individual judgment of the surgeon (=elective).

Patients undergoing laparoscopic cholecystectomy received a single dose of Augmentin[R] at the induction of anaesthesia. Bile samples were collected from the unopened gallbladder for culture and identification.

The variables considered as a risk factor for conversion were divided into general, specific and relative risk factors and are listed in Table 9.02. Acute cholecystitis was defined as patients experiencing right upper quadrant pain, temperature > 38°C, leucocyte count greater than 11,000 and an ultrasound with a thick gallbladder wall .

Statistical analysis was performed by the Department of Biostatistics/Epidemiology of the Erasmus University Rotterdam. Percentages or two-way tables were analysed with the chi-square test. For two by two tables with small expected frequencies Fisher's exact test was used. Values for $p<0.05$ were considered to be significant.

9.3 RESULTS

From the 215 cholecystectomies which started laparoscopically between June 1991 and June 1993, 189 (87.9%) were completed successfully, whereas 26 (12.1%) had to be converted to open cholecystectomy. The cause of conversion was electively in 22 patients (84.6%) and enforced in 4 patients (15.4%). Sixteen of 26 patients intraoperatively showed dense adhesions to the gallbladder due to previous laparotomy or acute inflammation. Other reasons for an electively performed conversion were instrumental defect (n=5) and unclear anatomy (n=1). Enforced conversion was necessary in three patients with an uncontrolable bleeding. In one patient the common bile duct was clipped as recognized during the procedure. There were no conversions for common bile duct exploration.

Females accounted for the majority of the patients namely 19 versus 7 men. The mean age was 52 years. Three patients were operated acutely. The mean hospital stay was 9 days with a range from 5 to 18 days. The patients were seen at the outpatient department after an average of 10 days.

There was no mortality. Minor peroperative complications were perforation of the gallbladder in three patients and bleeding of the gallbladder bed in one patient. Postoperatively one patient developed a paralytic ileus. There were no postoperative infections.

9.3.1 Analysis of risk factors for conversion

Estimated risk for conversion to open cholecystectomy was calculated for each of the risk factors. Statistical analysis showed that there were no general risk factors for conversion (Table 9.02).

A significant specific risk factor for conversion was acute cholecystitis (p=0.04). Fever on admission, an emergency procedure and preoperative ERCP were no significant specific risk factors.

Significant relative risk factors for conversion to open cholecystectomy were intraoperatively infiltrate (p=0.002) and acute inflammation of the gallbladder as histopathologically determined (p=0.001). Bile spillage was no significant risk factor. However, a positive bile culture proved to be a significant relative risk factor for conversion from laparoscopic to open cholecystectomy (p=0.01).

Table 9.02: Analysis of risk factors for conversion.

General risk factors	P-value
Age	NS
Gender	NS
Quetelet index	NS
Diabetes mellitus	NS
History of abdominal disease	NS
(History of) Cancer	NS
Liver disease	NS
Cardiovascular disease	NS
Hypertension	NS
Chronic obstructive pulmonary disease	NS
Specific risk factors	
Fever on admission (> 38°)	NS
Emergency procedure	NS
Acute cholecystitis	**0.04**
Preoperative ERCP	NS
Relative risk factors	
Intraoperatively infiltrate	**0.002**
Peroperative complications	NS
Acute inflammation as histopathological diagnosis	**0.001**
Bile spillage	NS
Positive bile culture	**0.01**
Abdominal washing	NS
Wound washing	NS

9.4 DISCUSSION

Conversion to open cholecystectomy should never be viewed as a complication of laparoscopic cholecystectomy. On the contrary, conversion to an open cholecystectomy should occur whenever the surgeon is unable to definitively identify the important landmarks. These landmarks include the infundibulum of the gallbladder, the junction of the gallbladder neck with the cystic duct, and the junction of the cystic duct with the common bile duct.

The conversion rate from laparoscopic to open cholecystectomy varies from 1.8-11.2% in patients treated for cholecystolithiasis and 6-35% for acute cholecystitis[3-11]. Our conversion rate from laparoscopic to open cholecystectomy is higher compared with the conversion rates described in literature. This probably will be caused by the great number of electively converted cholecystectomies. The enforced conversion rate was only 1.9%. The main cause for conversion was adhesions precluding identification of the biliary anatomy. In these patients the procedure was electively converted in order to avoid ductal or vessel injury. Diffuse bleeding in three cases hampered proper view and necessitated conversion to avoid complications.

In literature many factors have been identified as leading to the need for conversion to open cholecystectomy[9,12-16]. The statistics reported from different authors, however, are conflicting, at best. A prospective analysis of potential causes of conversion from laparoscopic to open cholecystectomy revealed only that three preoperative parameters were associated with a high risk of conversion: a contracted gallbladder, as demonstrated on ultrasound, gallstone pancreatitis and a previous history of upper abdominal surgery[17]. Surprisingly, acute cholecystitis did not increase the likelihood of the need to convert to an open cholecystectomy in this study. In contrary to our and other studies[13,18] in which acute cholecystitis was correlated with a higher conversion rate. As already described in literature[9] no statistical significance was found between conversion and age, gender and history of abdominal disease or surgery.

In conclusion, intraoperative infiltrate, acute inflammation as histopathological diagnosis and positive bile culture all contributed to the possibility of conversion. The clinical diagnosis of an acute cholecystitis was the best factor predicting conversion from laparoscopic to open cholecystectomy. This predictive finding allow the surgeon to discuss the higher risk of conversion preoperatively and allow for an earlier judgment decision to convert if intraoperative difficulty is encountered.

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CHAPTER 10

COMMON BILE DUCT STONES: IS THERE STILL A PLACE FOR OPEN SURGICAL EXPLORATION?

ABSTRACT

Data on 244 consecutive patients who underwent open surgical exploration of the common bile duct between 1986 and 1993 were retrospectively analysed, 237 (97.1%) underwent common bile duct exploration with choledochoscopy, in 5 cases (2.0%) a choledochoduodenostomy was performed and in 2 cases (0.8%) a transduodenal sphincterotomy.

The aims of this study were to determine, retrospectively, the results, complications and mortality in patients who underwent surgical common bile duct exploration.

From all 244 patients 48 (19.7%) had no risk factors, 100 (41.0%) had a single and 96 (39.3%) had multiple risk factors for postoperative complications after biliary surgery.

Peroperative complications were 3 injuries of the common bile duct (1.2%) and one duodenal perforation (0.4%).

The overall incidence of wound infections was 10.2%. Other surgical related postoperative infections were bile peritonitis (0.8%), subhepatic abscess (0.8%) and cholangitis (0.4%). Mortality in this series was 0.8% (2 not surgical related deaths).

Fourteen patients (5.7%) had retained stones. In seven patients the retained common bile duct stones were cleared by ERCP, one patient was re-operated. Six patients with suspected retained common bile duct stones have been treated expectatively to date.

According to these results an open common bile duct exploration seems to be justified as long as the results of laparoscopic choledochotomy have not been proven to be superior.

10.1 INTRODUCTION

It is generally agreed that only patients with symptomatic cholecystolithiasis require therapy[1-3]. From the symptomatic patients 10-15% develop biliary colics[4]. Stones in the common bile duct are sometimes the reason for these colics. About 9-16% of the patients with symptomatic cholecystolithiasis have accompanied choledocholithiasis[5,6].

In 1882 Langenbuch in Germany initiated surgery of the biliary tree by removing the gallbladder completely. He thought that gallstones were formed in the gallbladder and that only it's removal would prevent reformation of stones. Following Langenbuch's operation progress was rapid, and soon thereafter with Courvoisier as one of the first surgeons, the common bile duct was opened surgically and its stones retrieved.

Presently the management of patients with both cholecystolithiasis and choledocholithiasis has been discussed extensively in the literature. Next to the surgical techniques, common bile duct calculi may be removed by endoscopic retrograde cholangiography pancreaticography (ERCP) combined with endoscopic sphincterotomy (ES). In case of impacted common bile duct stones, ES can be combined with ESWL as a non-invasive, effective treatment modality. ESWL treatment can clear the common bile duct of difficult stones in up to 88% of cases[7]. It may be that by careful selection of patients for these procedures, the approach to the management of gallstones can be modified with a consequent reduction in mortality and morbidity.

As techniques for laparoscopic exploration of the common bile duct have improved, another alternative became available for the treatment of common bile duct stones. Intraoperative cholangiography can be followed by laparoscopic exploration of the common bile duct. However before introducing this technique, the results of open common bile duct exploration had to be studied as recent historical controls in further trials.

The aims of this study were to determine retrospectively the results, mortality and complication rate in patients who underwent open surgical common bile duct exploration in the last decade.

10.2 PATIENTS AND METHODS

Data on 244 consecutive patients, 175 women and 69 men, who underwent primary open surgical exploration of the common bile duct between 1986 and 1993 were retrospectively analysed. All records were available for review. The mean age was 60 years with a range from 19 to 89 years.

Risk factors for the development of wound infection or other septic complications in biliary surgery were categorized according to Keighley et al[8]. From the total of 244 patients, 48 (19.7%) had no risk factors, 100 (41.0%) had a single and 96 (39.3%) had multiple risk factors. The majority had age > 60 years (58.6%) as risk factor. This was followed by risk factors as history of abdominal disease (27.9%), obstructive jaundice (20.1%), acute cholecystitis (12.3%), preoperative ERCP (6.1%), acute pancreatitis (4.1%) and reoperation (0.8%). Acute pancreatitis did not occur as a single risk factor but always in combination with other risk factors.

Ultrasonography was performed in almost all patients; namely 233 (95.5%). In 42 patients (17.2%) intravenous cholangiography was done, in 10 (4.1%) an oral cholecystography, 6 (2.5%) an ERCP and in 4 (1.6%) a CT-scan was performed.

From the 244 patients 111 patients (45.5%) had gallbladder stones as preoperative diagnosis and 80 patients (32.8%) in combination with common bile duct stones, 33 patients (13.5%) had cholecystitis, 12 patients (4.9%) in combination with common bile duct stones. Two patients (0.8%) had a non-calculous cholecystitis. One patient (0.4%) underwent a common bile duct exploration for a jaundice due to a carcinoma of the gallbladder.

All operations were performed under general anaesthesia. Routine antibiotic prophylaxis was given for all procedures. Sixty-nine patients (28.2%) were operated acutely and 175 (71.7%) electively.

Common bile duct exploration with choledochoscopy was performed in 97.1%, in 5 cases (2.0%) a choledochoduodenostomy was performed and in 2 cases (0.8%) a transduodenal sphincterotomy. The mean operation time was 78 minutes with a range from 25 to 200 minutes.

In the management of retained common bile duct stones all patients having common bile duct exploration had a post-operative T-tube cholangiography. Retained stones were defined as filling defects on the postoperative X-ray (with or without later stone retrieval).

The mean hospital stay was 14 days with a range from 8 - 79 days.

10.3 RESULTS

Peroperatively 119 patients (48.8%) had gallbladder stones, in 105 patients (43.0%) accompanied with common bile duct stones. In 16 patients an infiltrate of the gallbladder was found. Two times (0.8%) no abnormalities were found. In one patient (0.4%) a carcinoma of the gallbladder was diagnosed.

Two hundred thirty-three patients (95.5%) were operated without peroperative surgical problems. Major peroperative complications occurred in four patients. In three patients (1.2%) an injury of the common bile duct was seen and in one (0.4%) a duodenal perforation.

Postoperatively 222 patients (91%) had no complications. Ten patients (4.1%) had to be reoperated. The reasons for reoperation were postoperative bleeding (n=3), ileus (n=3), fascial dehiscence (n=2) and wound hematoma (n=2). In one patient a percutaneous drainage was performed, because of bile leakage (Table 10.1).

The surgical related postoperative infections were bile peritonitis (0.8%), subhepatic abscess (0.8%) and cholangitis (0.4%). No postoperative pancreatitis was observed. There were 12 (4.9%) minor and 13 (5.3%) major wound infections. The not related surgical infections were urosepsis (4.1%), urinary tract infection (2.5%) and pulmonary infection (1.2%).

Mortality in this series was 0.8% (Table 10.2). There was no surgery related death. One patient died because of respiratory failure and another of ischemic heart disease. Post mortem data were not available on these two patients.

In fourteen patients (5.7%) retained stones were diagnosed, in seven they were cleared by ERCP. One patient was successfully re-operated. Six patients with retained common bile duct stones on cholangiography were left untreated and have not yet required further surgery. The total common duct clearance rate was 96.7%.

Table 10.1: Complications of biliary surgery in 244 patients.

Peroperative complications:		
Common bile duct injury	3	1.2%
Duodenal perforation	1	0.4%
Postoperative complications:		
Bile leakage	1	0.4%
Reoperation:		
- postoperative bleeding	3	1.2%
- ileus	3	1.2%
- fascial dehiscention	2	0.8%
- wound hematoma	2	0.8%

Table 10.2: Results of biliary surgery in 244 patients.

	Number	Mortality
Positive exploration	105 (43%)	1 (1%)
Negative exploration	139 (57%)	1 (0.7%)
Re-exploration	1	0
Total	245	2 (0.8 %)

10.4 DISCUSSION

The mortality of common bile duct exploration by laparotomy averaged about 2% in studies reported from 1980 onwards[9] and is rising to 8% in elderly (> 60 years) or high risk patients[10-12]. Mortality is even higher in emergency procedures regardless of age[13]. The mortality rate in our series was 0.8%, without mortality in elective surgery.

In 1974 endoscopic retrograde cholangiography combined with endoscopic sphincterotomy was introduced[14,15]. Common bile duct stones can be extracted endoscopically in several groups of patients: the elderly frail patients, often with the gallbladder in situ[16], those in whom surgery may present technical problems, patients having calculus obstructive jaundice, septic cholangitis or retained common bile duct stones in these higher risk patients. Mortality from endoscopic sphincterotomy is about 1-2% and does not increase with age or the presence of medical risk factors[17-19].

Three randomized trials[20-22] have demonstrated that preoperative endoscopic retrograde cholangiography and sphincterotomy for stone removal followed by open cholecystectomy is not superior to open cholecystectomy, cholangiography and, when required, common bile duct exploration in patients fit for surgery. In multivariate analysis, preoperative endoscopic retrograde cholangiography was an independent risk factor in patients with choledocholithiasis fit for surgery[20]. Those unfit for surgery could be treated exclusively by endoscopic sphincterotomy without further operation[16].

During the last 4 years there has been a dramatic transformation in biliary surgery, with the rapid adoption of laparoscopic cholecystectomy. This has rekindled the debate concerning the management of common bile duct stones. If these stones are known to be present before laparoscopic cholecystectomy, then most surgeons agree that they should be removed endoscopically before performing laparoscopic cholecystectomy. However there is disagreement concerning the need to identify these patients and how to identify them. Indications for preoperative ERCP included elevated liver functions tests (especially bilirubin, alkaline phosphatase, or gamma-glutamyl-transpherase), obstructive jaundice, cholangitis, gallstone pancreatitis, or a high index of suspicion for choledocholithiasis based on preoperative ultrasonography. Between 1986 and 1993 we used these criteria for surgical common bile duct exploration, which lead to a positive exploration percentage of 43%. According to this results we should reconsider our indications for open common bile duct exploration. In patients with a low risk of stones in the common bile duct, alkaline phosphatase 126-180 IU/L and/or serum bilirubin 33-50 umol/l[23], intraoperative cholangiography should be performed before exploration of the common bile duct.

If common bile duct stones are detected at laparoscopic cholecystectomy there is debate concerning how to proceed. Laparoscopic techniques for removal of common bile duct stones are practised at very few centres where clearance rates may be greater than 60%[24-26]. Most surgeons will opt for either endoscopic removal soon after operation, or conversion to open exploration of the common bile duct.

The role of laparoscopic common bile duct exploration remains to be established. After intraoperative cholangiography, stones are extracted either through the cystic duct or by choledochotomy. This limits the treatment to one therapeutic intervention while maintaining the advantages of the laparoscopic approach. Laparoscopic choledochotomy should be the preferred technique above extraction through the cystic duct. The size and tortuosity of the cystic duct, its site of insertion, and its angulation on the common bile duct may all act as limiting factors for extraction through the cystic duct that is technically even more difficult if stones are located proximal to the cystic duct. As further experience is gained in laparoscopy, laparoscopic common bile duct exploration could become the preferred treatment for choledocholithiasis.

Before introducing laparoscopic common bile duct exploration in our hospital, first the results of open common bile duct exploration were analysed retrospectively. The morbidity in our study was low and comparable with other series described in the literature[10]. The residual stone rate after duct exploration (3.3%) was comparable with the rates reported in literature[27,28].

According to these results an open common bile duct exploration seems to be justified as long as the non-invasive results of laparoscopic choledochotomy have not been proven to be superior.

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CHAPTER 11

PROSPECTS FOR GALLSTONE DISEASE

11.1 INTRAOPERATIVE CHOLANGIOGRAPHY

Choledocholithiasis is found in approximately 10-15% of patients presenting for cholecystectomy[1,2]. Most common duct stones originate in the gallbladder and migrate into the common bile duct. While small stones may spontaneously pass into the duodenum, the narrowed lower end of the choledochus frequently obstructs their passage, resulting in obstructive jaundice or biliary pancreatitis.

With the advent of endoscopic and laparoscopic therapeutic alternatives, the management decisions for treating choledocholithiasis have become more complex. Given the low risk (1-6%) of unsuspected stones[3] as well as the inherent risks associated with perioperative endoscopic intervention[4] the issue being debated now is whether or not all patients should routinely have intraoperative cholangiography or whether it should be confined to select cases with a high index of suspicion of common duct stones, or in those cases where there is a need to delineate the biliary anatomy.

Surgeons are still divided into selective and routine users of intraoperative cholangiography. Those advocating routine use point to the improved anatomical information the procedure provides and argue that fewer duct injuries occur[5-7]. In addition, the routine use of intraoperative cholangiography has an impact on the training of surgeons that is generally accepted as beneficial.

The disadvantage of routine intraoperative cholangiography is the time and cost involved. The time includes that required for cannulating the cystic duct, manupulating the radiographic equipment and then waiting for the film to be processed.

Several published studies support the view that selective cholangiography in at-risk patients (history of recent jaundice or pancreatitis, abnormal liver function test results, dilated common bile duct on preoperative ultrasonography, large cystic duct) is an acceptable alternative to routine cholangiography[8-9]. Although this selective approach will avoid unnecessary cholangiography, there are two disadvantages. First, in the absence of the above criteria, unsuspected common bile duct stones still occur in 3%[10,11]. However the presence of undetected asymptomatic common bile duct stones does not necessarily lead to significant morbidity[12]. Secondly, cholangiography detects abnormalities of clinical relevance, missed if intraoperative cholangiography is not performed routinely[13].

If the biliary anatomy during laparoscopic cholecystectomy can be defined with the same ease and efficiency as during open cholecystectomy, then the choice should be made on the same criteria as for open cholecystectomy. In open cholecystectomy, the majority of evidence fails to support the use of routine intraoperative cholangiography. Once the experience and the level of skill for laparoscopic cholecystectomy is similar to open cholecystectomy, a strong argument for selective cholangiography can be made.

The controversy of routine versus selective intraoperative cholangiography will certainly continue for several more years and the fact that this issue has never been conclusively settled for open cholecystectomy is illustrative[11,12].

11.2 "RENDEZ VOUZ" BETWEEN SURGEON AND GASTROENTEROLOGIST

When open cholecystectomy was the surgical treatment for symptomatic cholecystolithiasis, common bile stones were usually treated by choledochotomy. Now that laparoscopic cholecystectomy has become the standard treatment for symptomatic cholecystolithiasis, debate has arisen regarding the appropriate treatment of common bile duct stones. Many surgeons currently advocate integration of ERCP and endoscopic sphincterotomy for patients suspected of harboring common bile duct stones. In fact, the National Institute of Health Consensus Conference on gallstones and laparoscopic cholecystectomy recently made the following recommendation: "percutaneous transhepatic cholangiography or ERCP should be considered prior to laparoscopic cholecystectomy to optimize all therapeutic options[14].

Endoscopic removal of stones from the common bile duct was introduced into clinical practice in 1974 by Classen et al[15]. and Kawai[16]. Initially, this modality found favor among two specific groups of patients; the elderly, who were felt to be at prohibitive risk for any type of surgical procedure, and those found to have retained stones after cholecystectomy. Later there was the unanimous agreement for the utility of ERCP in the postoperative period for the successful management of various problems, i.e. retained stones, bile leaks, etc[17-19]. Presently, with the laparoscopic cholecystectomy as the standard procedure for the treatment of cholecystolithiasis, a major role is established for the nonoperative management of common bile duct stones by the combination of ERCP with endoscopic sphincterotomy and stone extraction prior to surgery[19]. Several controversies regarding the utility and timing of ERCP for choledocholithiasis have been expounded upon in the literature[20]. The topics include the role of ERCP in younger patients, and more importantly, whether preoperative ERCP offers any advantage to operation alone for the removal of common bile duct stones.

The complication rate of ERCP is generally listed around 10%[21]. Complications include cholangitis, pancreatitis, common bile duct perforation and hemorrhage, which account for approximately 50% of all complications[22]. Successful stone clearance is seen in approximately 90% of the patients undergoing the procedure[23]. Because endoscopic papillotomy results in a permanent anatomic destruction of the ampullary sphincteric mechanism, concern has been raised over biliary tract infection following these procedures.

Since the introduction of laparoscopic cholecystectomy significant more ERCPs are now being performed[24]. The liberal use of preoperative ERCP for suspected common bile duct stones means that many more patients than necessary will be subjected to the inherent morbidity and mortality of this procedure. In the literature reporting on laparoscopic cholecystectomy, the liberal use of preoperative ERCP was not efficient as most patients who underwent diagnostic ERCP did not have stones in the common bile duct[25-29]. The yield of diagnostic ERCP can be increased by refining the criteria for selection[30,31]. Intraoperative cholangiography should be done for patients with low risk of associated common bile duct stones. Kum et al[31] defined low risk patients as having mildly raised serum alkaline phosphatase activity (126-180 IU/l) or bilirubin concentration (33-50 micromol/l). Patients at high risk of associated common bile duct stones, such as jaundice, pancreatitis, dilated common bile duct, cholangitis or stones seen on ultrasonography, should continue to have preoperative ERCP.

Several options are available for the management of common bile duct stones diagnosed on intraoperative cholangiography. Small stones in the common bile duct, particularly < 0.5 cm with a normal size of the common bile duct, are associated with an uncertain natural history and may pass spontaneously without harm[32]. This suggests a policy of wait-and-see or ERCP if symptoms occur after operation. Patients with stones 0.5-1 cm and with a dilated common bile duct have to undergo ERCP after the laparoscopic cholecystectomy. For larger impacted stones common bile duct exploration will remain the treatment of choice.

In this rapidly changing era of laparoscopic surgery, surgeons have become experienced with laparoscopic common bile duct exploration. Not only does laparoscopic surgery nearly eliminate the complications noted in earlier studies[22]; namely, wound infection and incisional hernia but it also lessens mean hospital stay and allows for a more expedient return to work. Many authors have demonstrated that laparoscopic common bile duct exploration can be performed with a low complication rate[33-37]. Although minimal morbidity has been reported, operation and hospitalization time, as well as conversion rates to open common bile duct exploration, are clearly beyond the accepted norms for routine laparoscopic cholecystectomy[38,39].

Laparoscopic common bile duct exploration is an approach for common bile duct stones which permits a definitive procedure in one stage, without pre- or postoperative endoscopic sphincterotomy. Further improvement in instrumentation and technique should make the laparoscopic approach not only comparable but preferable to the standard choledochotomy.

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CHAPTER 12

GENERAL DISCUSSION AND CONCLUSIONS

12.1 GENERAL DISCUSSION AND CONCLUSIONS

This thesis described a period of 8 years of biliary surgery in a teaching district general hospital, a period which brought the excitement of minimal invasive surgical procedures. Surgeons were forced to face new concepts, not only involving the technique and surgical approach, but also related to the judgement and recognition of indications. With the introduction of minimal invasive surgery, the term conversion was introduced. This referred to the critical decision point during which the surgeon realizes that further operative progression utilizing laparoscopy may not be appropriate because of temporal or physiological considerations or because of anatomical limitations which make further endoscopic dissection more hazardous. Laparoscopic cholecystectomy has become the standard procedure for removal of the diseased gallbladder, however in this rapidly changing era discussion has arised about the handling of common bile duct stones.

When surgeons practicing in three different hospitals in three countries on three continents are brought together to address aspects of a topic, such as biliary disease, a divergence of opinion and, may be differing practice guidelines would normally be expected. This is also the case in this thesis. Differences were seen in the hospital policies. However, there were no significant differences in the results or the complication rates between the hospitals. It is my view that this occurrence reflects the current problems in a rapidly changing field.

Gallstones are common. In most instances they originated in the gallbladder and migrated to the common bile duct. Rarely, pigment stones orginate in the common bile duct. Common bile duct stones present clinically with biliary pain. However, stones also may present with jaundice, cholangitis and/or pancreatitis. In patients with an intact biliary tree, the pain of common bile duct stones cannot be differentiated from that of gallbladder stones. Ultrasonography is a useful noninvasive investigation of the biliary tract in patients suspected of symptomatic gallstones. Its efficacy is high for the diagnosis of stones in the gallbladder, but has a low diagnostic yield for common bile duct stones. The most sensitive and specific investigation of stones in the common bile duct is by ERCP. Although an invasive investigation, it allows not only an accurate diagnosis, but also an ability to treat stones by endoscopic sphincterotomy.

Antibiotic prophylaxis in primarly open biliary tract surgery has been generally accepted in prevention of postoperative infections. In the literature on antibiotic prophylaxis for open biliary surgery many antimicrobial agents have been described[1-3]. From this study it can be concluded that the combination of amoxycillin and clavulanic acid is safe and efficient for the prevention of infections following biliary surgery. Risk factors for the development of wound infection after open biliary surgery were age > 60 years, an emergency procedure, peroperative common bile duct stones and common bile duct exploration and/or other interventions added to the cholecystectomy. These risk factors were already described in 1976 by Keighley et al[4]. Other risk factors for wound infection were preoperative ERCP, duration of the operation, closed versus the open wound treatment, drains and bile leakage. The risk factors acute cholecystitis and current or recent history of jaundice were not significant for the development of wound infection after open surgery, this is in contrast with the results described in the literature[4].

Information on the details and extent of patient selection for laparoscopic cholecystectomy is rarely reported[5-7]. In this study 63.2% of the patients with gallstone disease were operated laparoscopically, which is lower than the results reported in the literature[8]. Varying selection criteria are undoubtedly influencing the results reported. Selection criteria for patients who were not eligble for laparoscopic cholecystectomy were initially acute cholecystitis, previous upper abdominal surgery and suspicion of common bile duct stones. In these patients a higher frequency of complications may be anticipated[9]. Also, complicated gallbladder disease will still be operated open.

Conversion to the open procedure by a qualified laparoscopic surgeon should not be considered as a complication or as an operative failure. Rather it should be seen as representing good surgical judgement. We advise conversion to an open procedure: If the cystic duct and the triangle of Calot cannot be clearly defined; if bleeding is uncontrollable; and if there is a suspicion of common bile duct injury.

Experienced surgeons will use laparoscopic cholecystectomy to treat patients presenting with acute cholecystitis. Cholecystectomy under these circumstances is more difficult and challenging. The potential for postoperative complications is also greater. However, with patience and careful dissection, proper identification of the vital structures may be accomplished and the cholecystectomy may be completed. Distortion of the essential anatomy by the inflammatory process frequently presents technical problems of considerable magnitude. It is certainly acceptable to convert when such circumstances are encountered. It requires only 10-15 minutes to realize that inflammation or anatomical considerations should dictate conversion to an open approach.

The introduction of laparoscopic cholecystectomy has enabled to minimize the problems of major wound infection in biliary surgery. In a prospective study with 189 patients, who underwent laparoscopic cholecystectomy no major wound infections were seen. The incidence of minor wound infection was 5.3%. Risk factors for these wound infections after laparoscopic cholecystectomy were acute cholecystitis, emergency procedure and acute inflammation of the gallbladder as histopathological diagnosis. Antibiotic prophylaxis as recommended for biliary surgery in general may no longer be justifiable. Antibiotic prophylaxis in laparoscopic cholecystectomy should be used only in those patients exhibiting risk factors, such as acute cholecystitis.

In series of laparoscopic cholecystectomy complications directly related to the operation are more common[5,10]. Spill of gallbladder contents during laparoscopic cholecystectomy is not rare. Many surgeons conclude that the intraoperative loss of gallstones is a relatively - innocuous event in the performance of laparoscopic cholecystectomy. Soper[11] observed no difference in complication rates when the gallbladder was perforated in comparison to cases where this event did not occur. Conversely, others had suggested delayed infectious complications[12,13]. It is a basic surgical principle to remove debris and leave the operative area clean; we should not deviate from this just because the case is performed laparoscopically. The surgeon should remove as many spilled stones as possible and irrigate the area well.

In elderly patients with stones in both the gallbladder and the bile duct who are undergoing ERCP and endoscopic sphincterotomy for the treatment of common bile duct stones, laparoscopic cholecystectomy is not justified unless symptoms from the gallbladder stones occur. It is more likely that symptoms will develop in patients with a obstructed cystic duct or in patients whose initial presentation was accompanied with cholangitis. However, in other patients there is only a 10% to 15% chance of further symptoms.

Many small stones found in the bile duct at the time of laparoscopic cholecystectomy can be treated during the same operation. A number will flush through the sphincter of Oddi after its relaxation, and others can be removed by balloon catheter or Dormia-type basket introduced into the common bile duct via the cystic duct. If these simple techniques do not achieve a clear common bile duct, then a number of options for treatment have been presented by the different authors. Small stones in a normal common bile duct are associated with an uncertain natural history and may pass spontaneously without harm. For patients with larger stones and for large diameter common bile ducts, subsequent treatment of common bile duct stones that cannot be removed through the cystic duct requires specialized treatment. Such treatment may consist of: laparoscopic choledochotomy or postoperative ERCP and endoscopic sphincterotomy. If these techniques are not successfull, then open choledochotomy may be conducted.

12.2 REFERENCES

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SUMMARY

Chapter 1 is a general introduction and describes the epidemiology of gallbladder disease, the microbiology of bile and the role of antibiotics in biliary tract surgery. At the end of chapter 1 the aims of the study are presented. In 1989 this study was initiated to determine the effect of a single dose amoxycillin/clavulanic acid as infection prophylaxis in open cholecystectomy. However with the introduction of laparoscopic cholecystectomy the aims were extended and the particular role of laparoscopic cholecystectomy in the whole spectrum of treatment modalities for symptomatic cholelithiasis was evaluated.

Chapter 2 gives a review of the literature on the currently available treatment modalities for symptomatic cholelithiasis. Open cholecystectomy, ESWL and mini-cholecystectomy are discussed in detail and compared with the laparoscopic cholecystectomy. Indications, contraindications, risk factors and complications of laparoscopic cholecystectomy are described.

Chapter 3 shows the results of a retrospective study of a 3 year period (1986-1989) of 659 patients treated for gallstone disease in a teaching and a non-teaching hospital. Fourhundred sixty-five patients (70.6%) were operated at the Ikazia Hospital and 194 (29.4%) at the Haven Hospital. Patients operated at the Ikazia Hospital were significantly older. As to patient differences the patients in the Ikazia Hospital were more at risk. Differences in surgical procedures were observed. Differences in hospital policies were standard use versus non standard use of drains, bandage versus open treatment of surgical wounds and the use of antibiotics. Despite this differences, there were no significant differences in complications and infection rate between both hospitals.

Analyzing the whole group showed a mortality rate of 0.9%. The incidence of major wound infections was 3.1%. According to the great number of patients at risk for the development of postoperative wound infection and the high incidence of positive bile cultures the use of antibiotic prophylaxis in open biliary surgery seems to be justified.

Chapter 4 evaluates in a prospective study of 297 patients the effect of a single dose amoxycillin/clavulanic acid as infection prophylaxis in open cholecystectomy.
The incidence of major wound infections was 5.1% and of minor wound infection 10.1%. Risk factors for the development of wound infection were age > 60 years, emergency procedure, preoperative ERCP, common bile duct stones, common bile duct exploration, duration of the operation, closed versus the open wound treatment, drains and bile leakage. The incidence of non surgical related infections was low. There was no mortality.
In 79.9% of the cultures no pathogenic micro-organism were found in the peroperative bile culture. Species resistant to amoxycillin/clavulanic acid were Hafnia alvi, Enterobacter cloacae and Escherichia coli (8/34).

Based on these findings, it can be concluded that a single dose amoxycillin/clavulanic acid is safe and efficient in the prevention of infection in biliary surgery.

Chapter 5 shows a prospective study on the results of biliary surgery after introduction of laparoscopic cholecystectomy. In a period of 3 years (1991-1993) 340 patients with gallstone disease were operated, 215 (63.2%) were eligble for laparoscopic cholecystectomy, 62 (18.2%) underwent open cholecystectomy and 63 (18.3%) open cholecystectomy with exploration of the common bile duct. Analyzing the risk factors for biliary surgery showed that patients who underwent an open procedure had a higher risk for the development of a postoperative woundinfection and/or other septic complications.
The postoperative complication rate in the whole series was 7.1%. The incidence of postoperative infections was 7.6%. Most infections were seen in the conventionally operated patients. The mortality rate was 0.3%.
In conclusion, patient selection is an important factor for laparoscopic cholecystectomy. Complicated gallbladder disease will still be operated conventionally.

Chapter 6 describes a comparative study between two consecutive prospective trials. A comparison is made between 189 laparoscopically operated patients and 130 historical controls who recently underwent open cholecystectomy. Comparison of morbidity in both groups, revealed more serious morbidity in the laparoscopic group. More directly surgical related complications categorized as minor were seen in the laparoscopic group. Mortality in the open group was zero versus 0.5% in the laparoscopic group.

Chapter 7 describes the incidence of postoperative wound infection after laparoscopic cholecystectomy and gives an analysis of patients at risk for developing a postoperative wound infection. No major wound infections were diagnosed. The incidence of minor wound infections was 5.3%. Specific risk factors for developing a wound infection were emergency of the operation and acute cholecystitis. Significant relative risk factor was acute inflammation of the gallbladder as histopathological determined. Multivariate analysis showed that the risk factor acute cholecystitis was the most important risk factor for developing a postoperative wound infection.
Antibiotic prophylaxis in laparoscopic cholecystectomy should be used only in those patients exhibiting risk factors, such as acute cholecystitis.

Chapter 8 evaluates the bacteriological data of 637 patients who underwent open or laparoscopic cholecystectomy in a five years period (1989-1993). Overall, bile cultures were positive in 22% (220/999). From the laparoscopically operated patients only 2.8% had a positive bile culture. The predominant micro-organism were Escherichia coli, Klebsiella spp. and streptococcus species. Introduction of foreign bodies, such as T-tubes, into the biliary tract led to a change of the bacterial spectrum.
The incidence of minor wound infections was 10.4% and of major wound infections 3.6%. No relationship between gallbladder cultures and wound infections were observed. According to these results intraoperative routine gallbladder culture as recommended for biliary surgery can be abolished.

Chapter 9 gives an analysis of risk factors for conversion from laparoscopic to open cholecystectomy. The conversion rate was 12.1%, 26 conversions out of 215 cholecystectomies, which started laparoscopically. The cause of conversion was elective in 22 patients and enforced in 4 patients.
Intraoperative infiltrate, acute inflammation as histopathological diagnosis and positive bile culture all contributed to the possibility of conversion. The clinical diagnosis of an acute cholecystitis was the most common factor for conversion from laparoscopic to open cholecystectomy.

Chapter 10 shows the results of a retrospective study of an 8 years period (1986-1993), analyzing 244 patients who underwent open surgical exploration of the common bile duct. In 105 patients (43%) common bile duct stones were found intraoperatively. The complication rate was low. The mortality in this study was 0.8%. Duct clearance was achieved in 94.3%.
From this results it can be concluded that an open common bile duct exploration seems to be justified as long as the non-invasive results of laparoscopic choledochotomy have not been proven to be superior.

Chapter 11 gives an overview of the literature concerning selective or routine intraoperative cholangiography and the management of common bile duct stones.

SAMENVATTING

Hoofdstuk 1 is de algemene inleiding van dit proefschrift en geeft een overzicht van de literatuur over de epidemiologie van cholelithiasis, de microbiologie van gal en de rol van antibiotica in de biliaire chirurgie. De doelstellingen van het onderzoek worden aan het einde van dit hoofdstuk geformuleerd. In 1989 werd dit onderzoek gestart om het effect te bepalen van de combinatie amoxycilline en clavulaanzuur als infectie profylaxe bij de open cholecystectomie. Na de introductie van de laparoscopische cholecystectomie werden de doelstellingen uitgebreid en werd met name de rol van de laparoscopische cholecystectomie in het gehele arsenaal van therapievormen voor symptomatische cholecystolithiasis geevalueerd.

Hoofdstuk 2 geeft een overzicht van de thans beschikbare therapievormen voor symptomatische cholecystolithiasis. De open cholecystectomie, schokgolfvergruizing en mini-cholecystectomie worden besproken en vergeleken met de laparoscopische cholecystectomie.
De indicaties, contraindicaties, risicofactoren en complicaties van laparoscopische cholecystectomie worden beschreven.

Hoofdstuk 3 beschrijft de resultaten van een retrospectief onderzoek over een period van 3 jaar waarin 659 patienten werden geopereerd in verband met galsteenlijden. Vierhonderd vijfenzestig patienten (70,6%) werden geopereerd in het Ikazia Ziekenhuis, een opleidingskliniek en 194 patienten (29,4%) werden geopereerd in het Haven Ziekenhuis. Patienten in het Ikazia Ziekenhuis hadden meer risicofactoren voor het ontwikkelen van een postoperatieve wondinfectie en/of andere infectieuze complicaties. De verschillen tussen beide ziekenhuizen waren meer choledochus exploraties in het Ikazia Ziekenhuis, het standaard inbrengen van drains en het gebruik van antibiotica. Ondanks deze verschillen, waren er geen verschillen in infecties en andere complicaties tussen beide ziekenhuizen.
In de gehele groep was de mortaliteit 0,9%. De incidentie van ernstige wondinfecties was 3,1%. Door het grote aantal patienten at risk voor het krijgen van een wondinfectie en de hoge incidentie van positieve galkweken lijkt het gebruik van antibiotica als profylaxe in de

open biliaire chirurgie te rechtvaardigen.

Hoofdstuk 4 beschrijft een prospectief onderzoek naar het effect van een eenmalige dosis amoxycilline/clavulaanzuur als infectie profylaxe voor een open cholecystectomie bij 297 patienten. De incidentie van ernstige wondinfecties was 5,1% en van lichte wondinfecties 10,1%. Risicofactoren voor het krijgen van een wondinfectie zijn: leeftijd boven de 60 jaar, acute operatie, preoperatieve ERCP, choledocholithiasis, choledochotomie, duur van de operatie, behandeling van de wond, gebruik van drains en gallekkage. De incidentie van niet chirurgisch gerelateerde infecties was laag. Er was geen mortaliteit.

In 79,9% van de peroperatieve galkweken was er geen groei van micro-organismen. Micro-organismen resistent voor amoxycilline/clavulaanzuur waren Hafnia alvi, Enterobacter cloacae en Escherichia coli (8/34).

Gebaseerd op deze bevindingen kunnen we concluderen dat een eenmalige dosis amoxycilline/clavulaanzuur veilig en effectief is voor het voorkomen van infecties na biliaire chirurgie.

Hoofdstuk 5 geeft middels een prospectief onderzoek de resultaten weer van de biliaire chirurgie na de introductie van de laparoscopische cholecystectomie. In een periode van 3 jaar (1991-1993) werden 340 patienten met galsteenlijden geopereerd, 215 patienten (63,2%) kwamen in aanmerking voor laparoscopische cholecystectomie, 62 patienten (18,2%) ondergingen een open cholecystectomie en 63 (18,3%) een open cholecystectomie gecombineerd met een choledochotomie. Analyse van de risicofactoren voor biliaire chirurgie toonde dat de open geopereerde patienten een hoger risico liepen op postoperatieve wondinfecties en/of andere infectieuze complicaties.

De incidentie van postoperatieve complicaties was in de gehele groep 7,1%. De incidentie van postoperatieve infecties was 7,6%. De meeste infecties werden gezien in de open groep. De mortaliteit was 0,3%.

Concluderend kunnen we stellen dat patienten selectie een belangrijke rol speelt in de laparoscopische cholecystectomie. Galsteenlijden gepaard gaand met infectieuze complicaties wordt nog steeds open geopereerd.

Hoofdstuk 6 beschrijft een vergelijkend onderzoek tussen twee opeenvolgende prospectieve studies. Er wordt een vergelijking gemaakt tussen 189 laparoscopisch geopereerde patienten en 130 historische controles die kort daarvoor een open cholecystectomie hebben ondergaan. Een vergelijking van de morbiditeit tussen de twee groepen laat ernstiger complicaties zien in de laparoscopische groep. Tevens werden er meer kleine, direct aan de operatie gerelateerde complicaties gezien in de laparoscopische groep. De mortaliteit in de open groep was nihil versus 0,5% in de laparoscopische groep.

Hoofdstuk 7 beschrijft de incidentie van postoperatieve wondinfecties na laparoscopische cholecystectomie en geeft een analyse van de kans voor het krijgen van een wondinfectie. Er werden geen ernstige wondinfecties gediagnostiseerd. De incidentie van lichte wondinfecties was 5,3%. Specifieke risicofactoren voor het krijgen van een wondinfectie zijn acute cholecystitis en de acute operatie. Een significante relatieve risicofactor was acute onsteking van de galblaas als histologische diagnose. Multivariant analyse toonde dat de risicofactor acute cholecystitis de belangrijkste risicofactor was voor het krijgen van een wondinfectie.
Antibiotische profylaxe zou alleen gebruikt moeten worden in die patienten die blootstaan aan risicofactoren, zoals bijvoorbeeld acute cholecystitis.

Hoofdstuk 8 evalueert de bacteriologische gegevens van 637 patienten die een open of laparoscopische cholecystectomie ondergingen over een periode van 5 jaar (1989-1993). In de gehele groep was 22% (220/999) van de galkweken positief. In de laparoscopische groep had slechts 2,8% een positieve galkweek. De meest voorkomende micro-organismen waren Escherichia coli, Klebsiella en Streptococcen species. Introductie van een vreemd lichaam, zoals bijvoorbeeld een choledochusdrain, leidde tot een verandering van de bacteriele flora. De incidentie van lichte wondinfecties was 10,4% en ernstige wondinfecties 3,6%. Er bestond geen relatie tussen de galkweken en de wondinfecties. Naar aanleiding van deze resultaten kan de routine peroperatieve galkweek, welke wordt aanbevolen tijdens biliaire chirugie, worden afgeschaft.

Hoofdstuk 9 geeft een analyse van risicofactoren voor conversie van laparoscopische naar open cholecystectomie. De conversie ratio was 12,1%; van de 215 patienten die in aanmerkingen kwamen voor een laparoscopische cholecystectomie werden er 26 geconverteerd.
In 22 gevallen was er sprake van een electieve conversie en in 4 gevallen was conversie noodzakelijk. Het intraoperatief aanwezig zijn van infiltraat, acute ontsteking van de galblaas als histologische diagnose en een positieve galkweek dragen allen bij tot de mogelijkheid van conversie. De klinische diagnose acute cholecystitis was de belangrijkste factor in het voorspellen van conversie.

Hoofdstuk 10 geeft een retrospectief analyse van de bevindingen in 244 patienten, die een open choledochotomie ondergingen, over een periode van 8 jaar (1986-1993). Bij 105 patienten (43%) werden er peroperatief stenen in de ductus choledochus aangetroffen. Het aantal complicaties was laag. De mortaliteit in deze studie was 0,8%. Er werd een steen klaring verkregen van 94,3%.
De resultaten zijn zodanig dat open choledochotomie te rechtvaardigen lijkt zolang de resultaten van de laparoscopische choledochusexploratie niet beter zijn.

Hoofdstuk 11 geeft een overzicht van de literatuur over het selectief danwel routinematig verrichten van een peroperatief cholangiogram en achtereenvolgens wordt het beleid bij stenen in de ductus choledochus behandeld.

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LIST OF ABBREVIATIONS

CBD	Common Bile Duct
ERCP	Endoscopic Retrograde CholangioPancreaticography
ES	Endoscopic Sphincterotomy
ESWL	Extracorporeal Shock Wave Lithotripsy
GB	Gallbladder
IOC	Intraoperative Cholangiography
LC	Laparoscopic Cholecystectomy
MC	Mini Cholecystectomy
OC	Open Cholecystectomy

CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 17 november 1965 te Rotterdam. De middelbare school-opleiding (VWO) werd gevolgd aan de Christelijke scholengemeenschap Melanchthon te Rotterdam. In september 1984 werd de medische studie begonnen aan de Erasmus Universiteit Rotterdam. Het doctoraal examen werd behaald in november 1988. Na het behalen van het artsexamen in februari 1991 werd de militaire dienstplicht vervuld. Van maart 1991 tot mei 1992 was de auteur gedetacheerd in het Perifere Team Roosendaal van de Krijgsmacht Hospitaal Organisatie. Gedurende deze periode werd gewerkt op de afdeling Algemene Heelkunde van het Franciscus Ziekenhuis te Roosendaal onder supervisie van kolonel-chirurg A. van der Linde.

Na de militaire dienstplicht werd van mei 1992 tot en met december 1992 gewerkt als arts-assistent (AGNIO) op de afdeling Algemene Heelkunde van het Ikazia Ziekenhuis. Op dezelfde afdeling werd per 1 januari 1993 de opleiding tot algemeen chirurg aangevangen (opleider: Dr H.F. Veen).

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