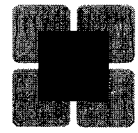

What are the indications for cholecystectomy?

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■ Cholecystectomy is indicated in the presence of gallbladder trauma, gallbladder cancer, acute cholecystitis, and other complications of gallstones. More controversial are the indications for elective cholecystectomy. To properly determine the indications for elective cholecystectomy, the risk of the operation (taking into account the age and comorbid factors of the individual patient) must be weighed against the risk of complications and death without operation (taking into account the symptomatic status of the individual and the functional status of the gallbladder). Cholecystectomy (or some other form of gallstone therapy) is indicated in most patients with symptomatic cholelithiasis—especially those with nonfunctioning gallbladders. Cholecystectomy is not indicated in most patients with asymptomatic stones.

□ INDEX TERM: CHOLELITHIASIS □ CLEVE CLIN J MED 1990; 57:40–47

IT HAS BEEN estimated that as many as 20 million Americans harbor gallstones, and that the total annual cost of gallstone disease in the United States exceeds $1 billion. At one time it was estimated that as many as 600,000 cholecystectomies were performed annually in this country,[1] but this number appears to be declining and may now be fewer than 475,000.[2] This decrease has occurred in spite of an increasing population and an increasingly older population with a presumably greater incidence of cholelithiasis.[3] Nonoperative techniques for gallstone eradication are now available. These include gallstone dissolution, either medically using oral bile acids[4–9] or invasively using methyl tert-butyl ether infused directly into the gallbladder via a percutaneous transhepatic catheter,[10] and gallstone lithotripsy.[11–15] Results with each of these techniques are promising in terms of gallstone eradication in selected cases, but they have in common several limitations. First, without removal of the source of gallstones (the diseased gallbladder), a recurrence rate of 50% five years following treatment is predicted for each.[14,16] Also, their use is limited to patients with cholesterol stones of relatively small size, to patients with functioning gallbladders as evidenced by oral cholecystography, and to elective circumstances. A more complete discussion of these techniques is beyond the scope of this communication and is the subject of reviews cited, but clearly their very limited use to date has not significantly impacted upon the incidence of cholecystectomy.

What appears to have changed most is the pattern of referral for cholecystectomy.[17,18] The mere presence of gallstones was, for many years, considered adequate indication for operation. More recently, however, there appears to be an increasing reluctance to refer patients for elective cholecystectomy. This is evidenced by the numerous pleas in the medical literature for "conservative" (medical) management of gallstones[19,20] as well as trends in the status of patients undergoing cholecystectomy. One study comparing the cholecystectomy populations of 1980 and 1986 in a referral hospital noted a highly significant decrease in the incidence of elective cholecystectomy.[17] Data collected by individuals in

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other institutions verify that trend, as do data collected by the American College of Surgeons.[17]

Although the effort to decrease the incidence of unnecessary operations is laudable, a disturbing corollary to the reduction in the number of elective cholecystectomies is becoming apparent. At the same time that the total number of cholecystectomies is decreasing, the absolute number and certainly the percentage of cholecystectomies that are performed urgently for complications of cholelithiasis are both increasing.[17] In the study previously cited, the increase in incidence of both acute cholecystitis ($P<.0001$) and complicated acute cholecystitis ($P<.000001$) were both highly significant.[17] Although not statistically analyzed in this fashion, other studies corroborate this finding.[17]

Cholecystectomy is also performed increasingly commonly in older age groups,[17,21] and the prevalence of complicated cholelithiasis necessitating urgent or emergent operation in that segment of the population is dramatic.[21–24] In one recent study, 53% of patients aged 65 years and older presented with complicated cholelithiasis.[25] In another, 70% of patients were operated upon either urgently or emergently.[21] In the latter, 89% of patients were previously known to have gallstones, indicating that lack of elective cholecystectomy played a major role in their coming to operation both late in life and under suboptimal conditions.

If it is true that at some point cholecystectomy was performed too freely, it seems equally true that the pendulum has now swung back beyond a neutral position. A careful review of the indications for cholecystectomy is therefore necessary.

In order to delineate the indications for any therapeutic intervention:

1. It is necessary to know the natural history of the disease to be treated, which is to say the risk that the disease itself poses to the patient,
2. It is necessary to know the risk associated with the intervention itself, and
3. It is necessary to know the extent to which the intervention interrupts the natural history of the disease.

With respect to cholecystectomy, it is clear that the intervention completely halts the natural progression of the disease. Although biliary lithiasis can occur subsequent to cholecystectomy in the form of primary common duct stones, such cases are distinctly uncommon and are generally associated with anatomic or physiologic abnormalities that are lithogenic. The indications for cholecystectomy, then, must be determined on the basis of comparing the risk associated with the operation to the risk inherent in the natural history of the disease.

RISK OF CHOLECYSTECTOMY

Although it was published nearly 20 years ago, the National Halothane Study provides what are probably still the best available prospectively gathered data regarding the risk of mortality in elective cholecystectomy. The study population included some 17,000 cholecystectomy patients who were prospectively studied in a large number of institutions. An overall mortality rate of less than one percent was found.[26] Numerous more recent but smaller and retrospective series indicate that mortality rates for elective cholecystectomy now approach nil,[27–31] but the National Halothane Study remains of value because of its prospective nature and because of its large population, which allows determination of relative risk for age and sex. These and other studies have identified three factors which influence the risk of cholecystectomy: patient age, operative status, and comorbid disease.

The risk of death from cholecystectomy increases with age.[26,28,32–34] In the National Halothane Study, the risk for a male under the age of 50 years was 0.054%, whereas for a man greater than 70 years the risk multiplied some 25 times to 1.31%.[26] The same increase was noted in the female population. Mortality is also dramatically affected by the status of the cholecystectomy, ie, elective or emergent.[28,35,36] For an individual less than 60 years of age, the mortality of emergent cholecystectomy is approximately 1%[36] or approximately 20 times the risk of elective cholecystectomy in a similar age group. The risk of emergent cholecystectomy in individuals older than 70 years is 18%–20%,[36] again approximately a twenty-fold increase over elective mortality rates. While there is little question that specific comorbid disease processes increase the risk of cholecystectomy, documentation of this in the form of large, prospective series is surprisingly lacking. Still, studies that are relatively small, retrospective, or both have documented increased mortality from cholecystectomy in the face of renal failure,[32] atherosclerotic coronary artery disease,[34] hypertension,[34] and impaired liver function.[32,33] The effect of diabetes mellitus on mortality from cholecystectomy in elective and emergent cases is controversial.[37,38]

Complications other than death should be considered as well in assessing the risk of cholecystectomy. The two significant complications which can occur intraoperatively are bleeding and common duct injury. Bleeding is usually significant only in patients with portal hypertension, but in that group it is the principal factor cited in exceedingly high reported mortality rates.[39,40] Common

duct injury at cholecystectomy occurs in less than 0.5% of cases and is becoming even less common as board-certified surgeons perform a greater proportion of the operations.[41] In the early postoperative period, wound infection is the most common significant complication. It occurs in approximately 2% of elective cholecystectomies,[42] a number which is increased by common duct exploration, acute cholecystitis, and other factors at operation.[42] Late postoperative complications occur in 5% of patients or less[43] and include such problems as retained common duct stones, biliary stricture, and sphincter stenosis.

NATURAL HISTORY OF GALLSTONES

Cholesterol gallstones form through a process of precipitation and agglomeration in the presence of supersaturated bile. It has been estimated that they grow at a rate of approximately 2.6 mm per year.[44] Less is known of the natural history of calcium-bilirubinate stones. Ultrasound is a highly sensitive tool for the detection of gallstones.[45–47] It is convenient and inexpensive and can also provide other valuable information such as the thickness of the gallbladder wall, the presence of pericystic fluid, and the diameter of intrahepatic and extrahepatic bile ducts. Oral cholecystography is similar to ultrasound in sensitivity for the detection of gallstones.[45–47] Because it is less convenient and carries a slight risk of reaction to the oral agent, oral cholecystography has yielded to ultrasound as the method of choice for diagnosing the presence of gallstones.[48,49] Still, oral cholecystography is of value because it can be used to assess the presence of gallbladder function. Gallbladder function is a requirement for both lithotripsy and gallstone dissolution by orally administered bile acids. Gallbladder function is also of value in predicting the risk of developing complications in the presence of cholelithiasis.[50]

In order of increasing frequency, complications associated with the presence of gallstones include fistula formation, gallbladder cancer, choledocholithiasis, and acute cholecystitis.

GALLSTONE ILEUS

In the presence of gallstones, fistulas can form from the gallbladder to any intra-abdominal portion of the alimentary tract, the common bile duct, the genitourinary tract, and even the skin of the abdominal wall. All are rare. The prototypical gallbladder fistula results in gallstone ileus, of which there are only slightly more than 1,000 cases reported in the English literature since 1950.[51]

GALLBLADDER CANCER

The incidence of gallbladder cancer is 2.5 per 100,000 population, and about 6,500 persons die each year in the United States of this disease.[52] The case for gallstones as an etiological factor in carcinoma of the gallbladder is circumstantial. Gallbladder cancer occurs in approximately the same female-to-male ratio as do gallstones,[53] and gallstones are found in the presence of 80%–90% of all gallbladder carcinomas. The risk of gallbladder cancer appears to increase with the size of the stones present,[54] but remains quite low. Fitzpatrick et al[55] calculated the risk of gallbladder cancer developing in the presence of gallstones to be 0.43% in 20 years. Special mention should be made of calcification of the wall of the gallbladder or "porcelain gallbladder." This uncommon condition is associated with an increased risk of gallbladder cancer[56] and is viewed by some as a premalignant condition, thus an indication for cholecystectomy.

CHOLEDOCHOLITHIASIS

A more frequent complication of cholelithiasis is choledocholithiasis. Common duct stones are found in 10%–15% of patients undergoing cholecystectomy. A much smaller number of common duct stones are found on the basis of complications other than at the time of cholecystectomy. In some patients, common duct stones may spontaneously pass. It can also be assumed that some patients harbor asymptomatic and undiscovered common duct stones until death. Thus, the incidence of choledocholithiasis may never be known with accuracy. Two rare complications of choledocholithiasis are stricture and *fistula* formation. More common are biliary pancreatitis and obstruction.

BILIARY PANCREATITIS

Approximately 5% of patients with cholelithiasis develop acute pancreatitis.[57,58] The stones that are recovered from the stool of patients with biliary pancreatitis are usually quite small and are generally associated with multiple, small, irregular, and mulberry stones in the gallbladder.[59] Still, it must be remembered that small fragments can also be found in the presence of and presumably originating from large stones. Biliary pancreatitis recurs within the first six months in approximately 50% of patients who have not undergone

cholecystectomy.[60,61] Still, the most frightening feature of this complication is that death occurs in 2%–8% of cases and is almost always associated with the primary attack.[62]

BILIARY OBSTRUCTION

Choledocholithiasis can result in partial or complete obstruction of the biliary tree. Complete obstruction usually presents with biliary colic, followed 24–48 hours later by the onset of jaundice. The presentation of partial obstruction is often more insidious. It may be detected incidentally in the form of an elevated alkaline phosphatase; it may present with pruritus, anorexia, or vague discomfort, or it may initially present in the form of biliary cirrhosis. Partial or complete bile duct obstruction may also present as ascending or suppurative cholangitis, which has a mortality rate of 30%–50%.[63]

ACUTE CHOLECYSTITIS

The most common complication of cholelithiasis and the one associated with the greatest morbidity and mortality (in absolute terms) is acute cholecystitis. Acute cholecystitis is a disease of mature adulthood, with the preponderance of cases occurring in the fourth through the eighth decades of life. Some 95% of acute cholecystitis is associated with gallstones, and it is very important in the context of the present discussion to note that the majority of cases of acute cholecystitis occur against a background of known, previously symptomatic cholelithiasis. Certainly, a stone lodged in the neck of the gallbladder or the cystic duct can give rise to acute cholecystitis. Ascending luminal infection,[64,65] increased intraluminal concentrations of lysolecithin (a product of the hydrolysis of lecithin which is catalyzed by phospholipase A),[66] alterations of the bile acid pool,[67,68] and prostaglandins[69] have also been proposed as mechanisms of onset of acute cholecystitis. Unusual forms of acute cholecystitis include *hydrops* of the gallbladder and *emphysematous* cholecystitis. A special form of acute cholecystitis is the *acalculous* type, which makes up some 5% of all cases of acute cholecystitis. Acute cholecystitis generally occurs in the setting of the critically ill patient, and prolonged fasting has been implicated in its etiology.[70,71] It is worthy of mention in the present discussion only as a very nearly absolute indication for cholecystectomy.

Unrelenting pain is the force that moves most patients with acute cholecystitis to operation, but the real threat of this disease is in the development of the complications of empyema of the gallbladder and spontaneous perforation of the gallbladder. *Empyema,* also called suppurative cholecystitis, is manifested by high fever, chills, and marked leukocytosis, and untreated may rapidly progress to septic shock and death.[23] *Perforation* occurs in about 10% of cases of acute cholecystitis.[72] Perforation may be contained in the form of a localized abscess, or it may be free and give rise to generalized peritonitis. Perforation in the face of acute cholecystitis can also give rise to the same variety of fistulas previously mentioned.[73]

INDICATIONS FOR CHOLECYSTECTOMY

Having reviewed many of the potential complications of cholelithiasis, the critical issue in determining the indications for cholecystectomy is how frequently such complications arise. No prospectively studied and properly stratified series is available to answer this crucial question. The best available data come from three retrospective analyses of patients with gallstones who have been followed for a number of years. Each study has other flaws in addition to its retrospective limitation, and some of these will be described in the following discussion. Each study segregated symptomatic from asymptomatic patients. While such division is somewhat arbitrary and dependent upon the authors' bias, it is helpful in determining the indications for cholecystectomy.

SYMPTOMATIC CHOLELITHIASIS

The first study of symptomatic gallstone patients[50] included all of the individuals from the city of Malmo, Sweden, who had a positive oral cholecystogram in the years 1951 and 1952. The mean age and sex ratio of these patients was not stated. Of the total of 1,501 patients, 128 underwent operation early after diagnosis and will not be further considered. The remaining 1,373 were followed until death, cholecystectomy, or 11 years. Twenty-four patients were excluded from analysis for various reasons, and 73 died of nonbiliary causes. Six hundred two patients underwent elective operation (429 in the first year; 173 thereafter). Biliary complications prompted operation in 210 patients (15.3% of the original 1,373), including 122 with acute cholecystitis, 82 with jaundice or pancreatitis, 5 with gallbladder cancer, and 1 with common duct obstruction. Complications occurred in 14.3% of the patients less than 60 years of age and 28.7% of those greater than 60 ($P<.001$). An important finding was that complications

TABLE 1
MORTALITY (%) OF CHOLECYCTECTOMY

	Elective*	Nonelective†
Patient younger than 50 years		
Functioning gallbladder	0.075	0.06
Nonvisualized gallbladder	0.075	0.12
Patient older than 70 years		
Functioning gallbladder	2.0	2.70
Nonvisualized gallbladder	2.0	4.80

* Based on data from the National Halothane Study.[26] Note: these are old data, and mortality figures are probably even lower today. Note also that mortality of cholecyctectomy does not increase with a nonfunctioning gallbladder.
† These figures are derived from the risk of developing a complication[50,74] (which is doubled with a nonfunctioning gallbladder) and the mortality of emergency operation of each age group.[36]

occurred nearly twice as frequently in patients with nonfunctioning gallbladders ($P<.001$). Stratification by age magnified the importance of a nonfunctioning gallbladder. Those patients greater than age 60 with nonfunctioning gallbladders were four times more likely to develop complications than those under age 60 with functioning gallbladders. Nineteen of the patients with complications died (9% of the complicated group; 1.3% of the original 1,373). It should also be noted that the 15.3% complication rate was a minimal estimate in that it was based on the entire 1,373-patient group and did not take into account the fact that nearly one-half of the patients underwent elective operation, were excluded, or died, thereby precluding them from the possible development of complications. Approximately one-third of the patients (464) did not undergo operation.

The second study[74] involved both symptomatic and asymptomatic patients. The latter will be addressed separately in the discussion of asymptomatic patients. The symptomatic group included 556 patients (372 females and 184 males), with an average age of 66.6 years, who were members of a health maintenance organization (HMO) in the New York City area. Gallstones were diagnosed in these individuals as follows: 519 underwent oral cholecystography (286 functioning; 233 nonfunctioning), 94 had ultrasound, and 60 had radiopaque stones. Clearly, several individuals had more than one diagnostic study, but precisely how the sets intersected is not stated. Follow-up from the time of diagnosis was an average of 82.9 months. During that time, 242 of the 556 patients underwent cholecystectomy. Of those operated, 47 (8.5% of 556) had acute cholecystitis, 9 others (1.6% of 556) developed jaundice, 36 additional patients (6.4% of 556) developed common duct stones, and 1 patient developed gallbladder carcinoma. The remaining 149 patients underwent operation on the basis of worsening symptoms or their doctors' recommendations. At an average of 68.6 months, 314 of the original 556 patients did not go undergo operation, including 25 who died of nonbiliary causes. In this study, then, a minimum of 16.7% of patients with symptomatic cholelithiasis developed complications. This does not include (because it is not stated in the paper) the patients whose pain worsened in the absence of a more serious complication, regardless of how frequent or severe the pain may have become. Neither does this figure exclude the patients who died of unrelated causes. Finally, it is quite unfortunate that the patients with functioning gallbladders and those with nonfunctioning gallbladders were not delineated with respect to the development of complications.

Summarizing the two studies, a minimum of 16% of patients with symptomatic gallstones will develop complications if followed over time. The risk is lowest in an individual younger than 60 with a functioning gallbladder (6%). It doubles with both age greater than 60 and a nonfunctioning gallbladder so that the risk in such an individual is approximately 27%. Combining these figures with the risk of death with urgent/emergent operations previously cited (approximately 1% if less than 60 and 20% if greater than 70 years of age),[36] the risk of death from emergency operation secondary to previously untreated symptomatic gallstones can be derived. Comparing these figures to the mortality rates for elective cholecystectomy in the two age groups provides the risk-benefit analysis necessary to decide whether or not cholecystectomy is indicated (*Table 1*).

Based on this assessment, it would appear that elective cholecystectomy is appropriate in patients with symptomatic gallstones (and without significant comorbid disease) in all but those individuals less than 50 years of age with functioning gallbladders. However, it must be remembered that these individuals, too, will continue to age, and that their gallbladders may become nonfunctional, thus placing them at ever-increasing risk for the development of complications and for operative mortality.

ASYMPTOMATIC STONES

The first study to be reviewed here[19] involves 123 healthy individuals (110 men; 13 women; average age, 54 years) with asymptomatic gallstones, who underwent oral cholecystogram as a part of a routine health screening. Followed 11 to 24 years, 35 underwent elective

operation at 97 patient-years (reportedly asymptomatic), 30 patients died at 352 patient-years (reportedly asymptomatic), 42 patients remained alive, unoperated, and asymptomatic, and 16 patients became symptomatic. Of the last group, three developed complications (each preceded by biliary colic), and 14 underwent operation, two emergently. The authors concluded that the probability of developing pain was 10% at 5 years, 15% at 10 years, and 18% at 15 years, and that thereafter it was unlikely stones would become symptomatic.

Although this article is extensively quoted and appeals for nonoperative management of gallstones, it is lacking in several areas that require comment. First, the study is retrospective. Second, the 10:1 male-to-female ratio is quite divergent from the usual 3:1 female preponderance in the gallstone population. Whether the natural history of gallstones in males is the same as that in females is not known. Third, 88% of these individuals had functioning gallbladders on oral cholecystogram. In most series, at least 30% of gallstone patients have nonfunctioning gallbladders, and as previously noted, the incidence of complications is at least doubled in the presence of a nonfunctioning gallbladder. Finally, over half of the patients were effectively excluded from study by elective operation or death.

The second study regarding asymptomatic stones[74] involves a second cohort from the same HMO that provided the previously cited study on symptomatic patients. It involved 135 patients (57 males; 78 females; average age, 73.6 years). Five patients had incidental cholecystectomy; 25 died of nonbiliary causes; 14 became symptomatic, of whom four developed complications (a total of 10 of the 14 underwent operated at an average of 46.8 months); and 91 patients remained asymptomatic at an average of 58 months. The authors therefore concluded that only about 10% of individuals with asymptomatic stones would become symptomatic in five years.

As in the previously cited study, there are some points in this series that raise serious questions as to its general applicability. Again, it was a retrospective study. This minimizes the reported incidence of developing symptoms or complications, in that with the passage of time, the living subjects and the relatives of the expired subjects may fail to recall them. The female-to-male ratio in this series again lacks the usual three-to-one preponderance and raises the issue as to whether the natural history of gallstones in males is that of gallstones in females. Finally, the methods by which stones were diagnosed in this study are again of interest. Radiopaque stones were found in 64% of the subjects. Radiopaque stones are usually found in 10%–15% of patients with gallstones, and it is unclear whether radiopaque (calcified) stones have the same natural history as radiolucent (cholesterol) stones. Also, only 80 of the 135 patients in this study underwent oral cholecystogram, and of those, 75% showed functioning gallbladders. Since nonfunctioning gallbladders correlate with an increased incidence of symptoms and complications, this group is clearly at lower risk for same than the usual gallbladder population. Finally, this group was followed, on the average, less than six years, which is a relatively short interval on which to base conclusions regarding natural history.

Summarizing these two most recent and widely quoted articles on asymptomatic gallstones, it would appear (based on their authors' interpretation of the data) that the risk of becoming symptomatic is only about 10% after five years, and that the risk of developing biliary complications is less than 3%. Using these figures and subjecting the data to the same risk analysis done for symptomatic stones, it does *not* appear that cholecystectomy is warranted for asymptomatic gallstones. It should be noted, however, that the benefit-to-risk ratio improves in individuals with nonfunctioning gallbladders in young patients and in patients with sickle cell disease.

SUMMARY

Cholecystectomy is indicated in cases of gallbladder trauma, gallbladder cancer (including "porcelain gallbladders"), gallstone complications, and acute cholecystitis. Cholecystectomy is also indicated in most patients with symptomatic cholelithiasis (chronic cholecystitis), especially those with nonfunctioning gallbladders. A minority (perhaps 20%) of patients with chronic cholecystitis are candidates for gallstone lithotripsy and an even smaller number for gallstone dissolution. In individuals with asymptomatic gallstones, cholecystectomy is usually not indicated (other than *en passant*), but special consideration should be given to the young, individuals with nonfunctioning gallbladders on oral cholecystogram, and patients with sickle cell disease.

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