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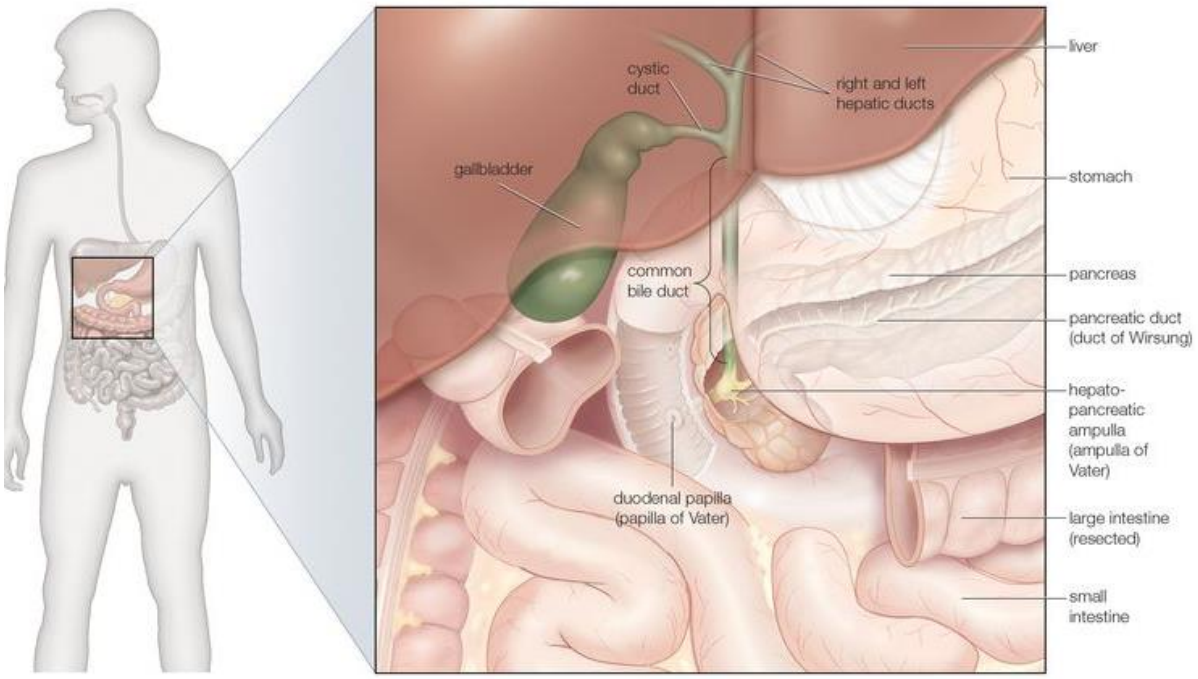
8.0 Acute Cholangitis and cholecystitis: definitions, pathophysiology, and epidemiology

Acute biliary infection is a systemic infectious disease which requires prompt treatment and has a significant mortality rate. The first report on acute biliary infection was Charcot's "The symptoms of hepatic fever" in 1877.2. This section of the Tokyo Guidelines defines acute cholangitis and acute cholecystitis and describes the incidence, aetiology, pathophysiology, classification, and prognosis of these diseases



8.1 Acute cholangitis

Definition: Acute cholangitis is a morbid condition with acute inflammation and infection in the bile duct.

8.1.1 Historical aspects of terminology

Hepatic fever. "Hepatic fever" was a term used for the first time by Charcot,2 in his report published in 1877. Intermittent fever accompanied by chills, right upper quadrant pain, and jaundice became known as Charcot's triad.

Acute obstructive cholangitis. Acute obstructive cholangitis was defined by Reynolds and Dargan in 1959 as a syndrome consisting of lethargy or mental confusion and shock, as well as fever, jaundice, and abdominal pain, caused by biliary obstruction. They indicated that emergent surgical biliary decompression was the only effective procedure for treating the disease. These five symptoms were then called Reynolds's pentad.

Longmire's classification.4 Longmire classified patients with the three characteristics of intermittent fever accompanied by chills and shivering, right upper quadrant pain, and jaundice as having acute suppurative cholangitis. Patients with lethargy or mental confusion and shock, along with the triad, were classified as

having acute obstructive suppurative cholangitis (AOSC). He also reported that the latter corresponded to the morbidity of acute obstructive cholangitis as defined by Reynolds and Dargan, and he classified acute microbial cholangitis as follows:

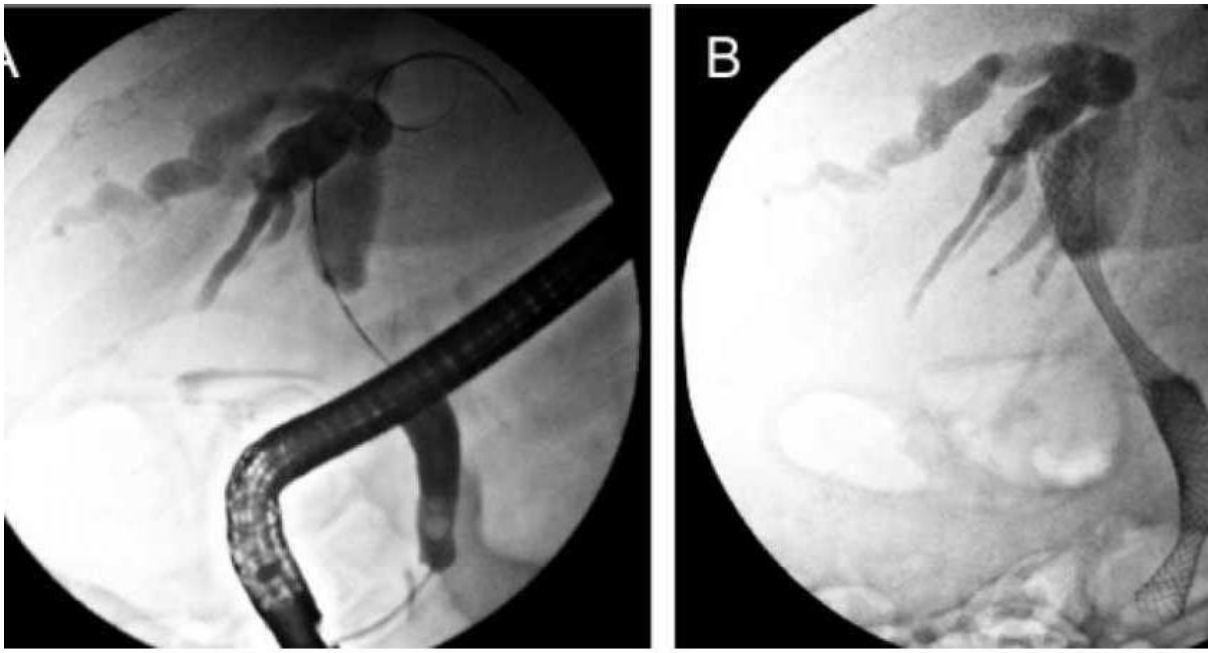
1. Acute cholangitis developing from acute cholecystitis
2. Acute non-suppurative cholangitis
3. Acute suppurative cholangitis
4. Acute obstructive suppurative cholangitis
5. Acute suppurative cholangitis accompanied by a hepatic abscess.

8.1.2 Aetiology

Acute cholangitis requires the presence of two factors:

(1) biliary obstruction

(2) bacterial growth in bile (bile infection).



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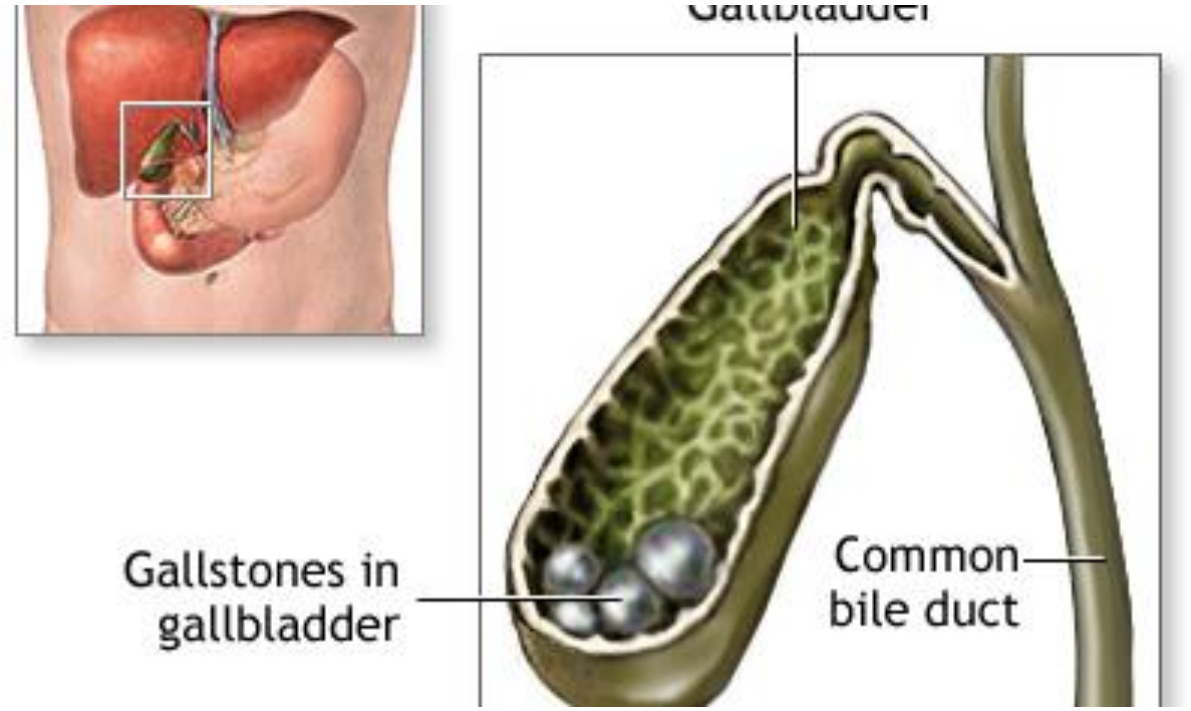
Frequent causes of biliary obstruction are choledocholithiasis, benign biliary stenosis, stricture of a biliary anastomosis, and stenosis caused by malignant disease. Choledocholithiasis used to be the most frequent cause of the obstruction, but recently, the incidence of acute cholangitis caused by malignant disease, sclerosing cholangitis, and non-surgical instrumentation of the biliary tract has been increasing. It is reported that malignant disease accounts for about 10%–30% of cases of acute cholangitis.

8.1.3 Risk factors

The bile of healthy subjects is generally aseptic. However, bile culture is positive for microorganisms in 16% of patients undergoing a non-biliary operation, in 72% of acute cholangitis patients, in 44% of chronic cholangitis patients, and in 50% of those with biliary obstruction. Bacteria in bile are identified in 90% of patients with

choledocholithiasis accompanied by jaundice. Patients with incomplete obstruction of the bile duct present a higher positive bile culture rate than those with complete obstruction of the bile duct. Risk factors for bacto – bilia include various factors, as described above. The incidence of complications after retrograde cholangiopancreatography (ERCP) ranges from 0.8% to 12.1%. Other aetiologies of acute cholangitis. There are two other aetiologies of acute cholangitis; Mirizzi syndrome and lemmel syndrome. Mirizzi syndrome is a morbid condition with stenosis of the common bile duct caused by mechanical pressure and/or inflammatory changes caused by the presence of stones in the gallbladder neck and cystic ducts. Lemmel syndrome is a series of morbid conditions in which the duodenal parapapillary diverticulum compresses or displaces the opening of the bile duct or pancreatic duct and obstructs the passage of bile in the bile duct or hepatic duct, thereby causing cholestasis, jaundice, gallstone, cholangitis, and pancreatitis.



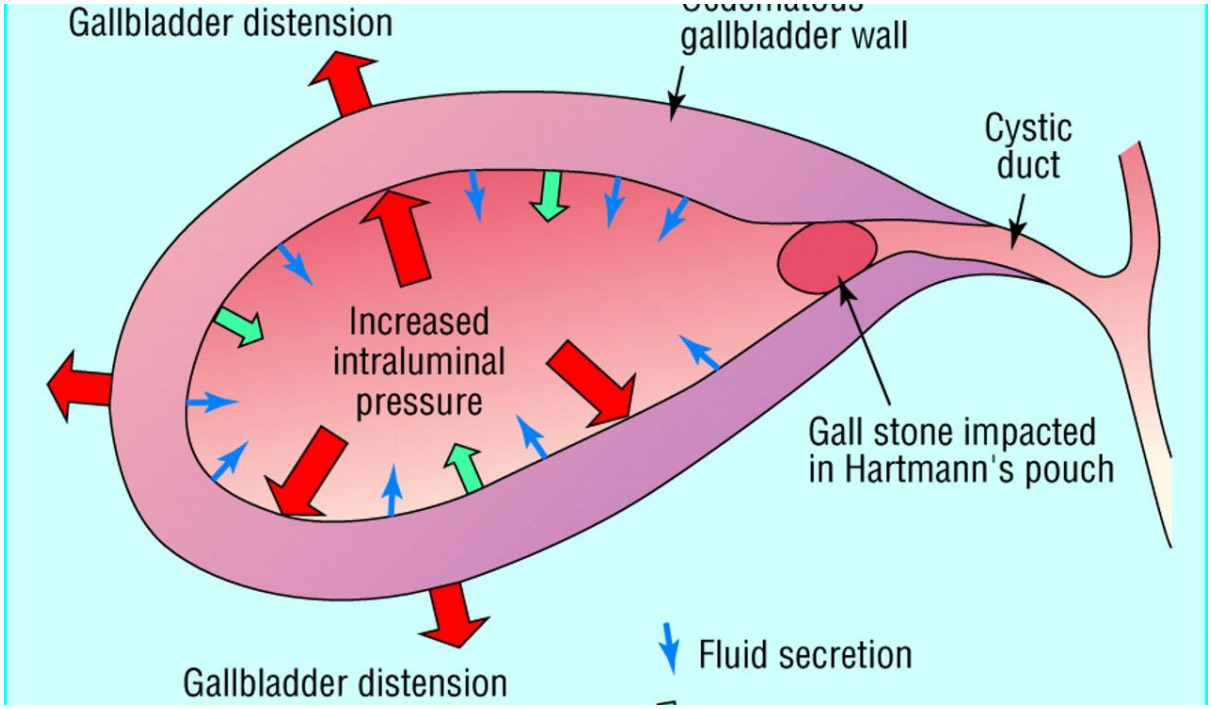
8.1.4 Pathophysiology

The onset of acute cholangitis involves two factors:

(i) increased bacteria in the bile duct

(ii) elevated intraductal pressure in the bile duct that allows translocation of bacteria or endotoxins into the vascular system (cholangio-venous reflux).

Because of its anatomical characteristics, the biliary system is likely to be affected by elevated intraductal pressure. In acute cholangitis, with the elevated intraductal biliary pressure, the bile ductules tend to become more permeable to the translocation of bacteria and toxins. This process results in serious infections that can be fatal, such as hepatic abscess and sepsis.



8.1.5 Prognosis

Patients who show early signs of multiple organ failure (renal failure, disseminated intravascular coagulation [DIC], alterations in the level of consciousness, and shock) as well as evidence of acute cholangitis (fever accompanied by chills and shivering, jaundice, and abdominal pain), and who do not respond to conservative treatment, should receive systemic antibiotics and undergo emergent biliary drainage. We have to keep in mind that unless early and appropriate biliary drainage is performed and systemic antibiotics are administered, death will occur.

8.1.6 Mortality

The reported mortality of acute cholangitis varies from 2.5% to 65%. The mortality rate before 1980 was 50%, and after 1980 it was 10%–30%. Such differences in mortality are probably attributable to differences in early diagnosis and improved supportive treatment. The major cause of death in acute cholangitis is multiple organ failure with irreversible shock, and mortality rates have not significantly improved over the years. Causes of death in patients who survive the acute stage of cholangitis include multiple organ failure, heart failure, and pneumonia.

8.2 Acute cholecystitis

8.2.1 Definition

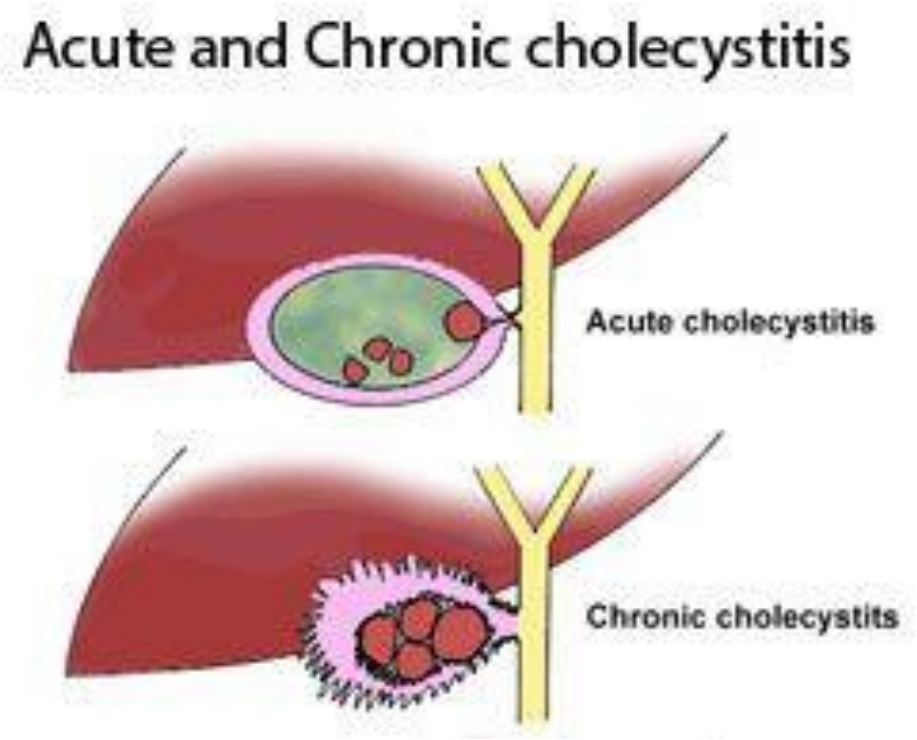
Acute cholecystitis is an acute inflammatory disease of the gallbladder. It is often attributable to gallstones, but many factors, such as ischemia; motility disorders; direct chemical injury; infections with microorganisms, protozoa, and parasites; collagen disease; and allergic reaction are involved.

8.2.2 Incidence

Acute cholecystitis cases account for 3%–10% of all patients with abdominal pain. The percentage of acute cholecystitis cases in patients under 50 years old with abdominal pain was low, at 6.3%, whereas that in patients aged 50 and over was high, at 20.9% (average, 10%).

8.2.3 Aetiology

Cholecystolithiasis accounts for 90%–95% of all causes of acute cholecystitis, while acalculous cholecystitis accounts for the remaining 5%–10%.



8.2.4 Risk factors.

Acute cholecystitis is the most frequent complication occurring in patients with cholelithiasis. The number of those with acute cholecystitis has increased, from 3.9 million in 1979 to over 10 million in 1993 (Public Welfare Index in Japan; 1933). Of the natural history of cholelithiasis, serious symptoms or complications (acute cholecystitis, acute cholangitis, clinical jaundice, and pancreatitis) were observed in 1%–2% of asymptomatic patients and in 1%–3% of patients with mild symptoms per year, and the risk of complications increased in the first several years after the discovery of gallbladder stones, but then decreased. Every year, 6%–8% of patients whose symptoms progress from minor to serious undergo cholecystectomy, but this percentage decreases year by year.

In a follow-up of cholelithiasis patients with mild or nonspecific symptoms, acute gallstone complication was observed in 15%, and acute cholecystitis was seen in 12%. According to another report, on the follow-up of the patients with asymptomatic cholelithiasis, 16% of them presented with some symptoms, during the follow-up period, while 3.8% presented with acute cholecystitis. The rate of change from asymptomatic to symptomatic cholelithiasis is highest during the first 3 years after diagnosis (15%–26%), but then declines. However, there is a report suggesting that there is no difference in the incidence of common symptoms such as heartburn and upper abdominal pain, in cholelithiasis patients between those patients with asymptomatic cholelithiasis and controls without gallstones.

8.2.4.1 AIDS as a risk factor.

Enlarged liver and/or abnormal liver functions are observed in two/thirds of AIDS patients, some of whom have biliary tract disease. The biliary disease may occur by two mechanisms in AIDS patients: via AIDS cholangiopathy (which is more frequent) and via acute acalculous cholecystitis; AIDS patients with sclerosing cholangitis are also seen.

8.2.4.2 Drugs as etiologic agents.

Regarding the association between drugs and acute cholecystitis, 90%–95% of acute cholecystitis cases are caused by cholelithiasis, and drugs promoting the formation of stones are indirectly associated with a risk of acute cholecystitis.

8.2.5 Pathophysiology

In most patients, gallstones are the cause of acute cholecystitis. The process is one of physical obstruction of the gallbladder by a gallstone, at the neck or in the cystic duct. This obstruction results in increased pressure in the gallbladder.

There are two factors which determine the progression to acute cholecystitis:

(i) the degree of obstruction

(ii) the duration of the obstruction

If the obstruction is partial and of short duration, the patient experiences biliary colic. If the obstruction is complete and of long duration, the patient develops acute cholecystitis. If the patient does not receive early treatment, the disease becomes more serious and complications occur.

8.2.6 Pathological classification

1. Oedematous cholecystitis: the first stage (2–4 days). The gallbladder has interstitial fluid with dilated capillaries and lymphatics. The gallbladder wall is oedematous. The gallbladder tissue is intact histologically, with oedema in the subserosal layer.
2. Necrotizing cholecystitis: second stage (3–5 days). The gallbladder has oedematous changes with areas of haemorrhage and necrosis. When the gallbladder wall is subjected to elevated internal pressure, the blood flow is obstructed, with histological evidence of vascular thrombosis and occlusion. There are areas of scattered necrosis, but it is superficial and does not involve the full thickness of the gallbladder wall.
3. Suppurative cholecystitis: third stage (7–10 days). The gallbladder wall has white blood cells present, with areas of necrosis and suppuration. In this stage, the active repair process of inflammation is evident. The enlarged gallbladder begins to contract, and the wall is thickened due to fibrous proliferation. Intra – wall abscesses are present and involve the entire thickness of the wall. Pericholecystic abscesses are present.
4. Chronic cholecystitis. Chronic cholecystitis occurs after the repeated occurrence of mild attacks of cholecystitis and is characterized by mucosal atrophy and fibrosis of the gallbladder wall. It can also be caused by chronic irritation by large gallstones and may often induce acute cholecystitis.

Specific forms of acute cholecystitis. There are four specific forms of acute cholecystitis:

1. acalculous cholecystitis, which is acute cholecystitis without cholecystolithiasis;
2. xanthogranulomatous cholecystitis, which is characterized by the xanthogranulomatous thickening of the gallbladder wall and elevated intra-gallbladder pressure due to stones, with rupture of the Rokitansky-Achoff sinuses. This rupture causes leakage and bile entry into the gallbladder wall. The bile is ingested by histocytes, forming granulomas consisting of foamy histocytes. Patients usually have symptoms of acute cholecystitis in the initial stage.
3. emphysematous cholecystitis, in which air appears in the gallbladder wall due to infection with gas-forming anaerobes, including Clostridium perfringens. This form is likely to progress to sepsis and gangrenous cholecystitis; it is often seen in diabetic patients.
4. Torsion of the gallbladder. Torsion of the gallbladder is known to occur by inherent, acquired, and other physical causes. An inherent factor is a floating gallbladder, which is very mobile because the gallbladder and cystic ducts are connected with the liver by a fused ligament. Acquired factors include splanchnoptosis, senile humpback, scoliosis, and weight loss. Physical factors causing torsion of the gallbladder include sudden changes of intraperitoneal pressure, sudden changes of body position, a pendulum-like movement in the anteflexion position, hyperperistalsis of organs near the gallbladder, defecation, and trauma to the abdomen.

8.2.7 Incidence of complications with advanced forms of acute cholecystitis

The incidence of complications with advanced forms of acute cholecystitis ranges widely, from 7.2% to 26%, in reports published since 1990. In patients with acute cholecystitis, the incidence of morbidity was 17%, with the incidences of gangrenous, suppurative, perforating, and emphysematous cholecystitis being 7.1%, 6.3%, 3.3%, and 0.5%, respectively.

8.2.8 Types of complications.

There are four types of complications:

1. Perforation of the gallbladder, which is caused by acute cholecystitis, injury, or tumours, and occurs most often as a result of ischemia and necrosis of the gallbladder wall.
2. Biliary peritonitis, which occurs with the entry into the peritoneal cavity of bile leaked due to various causes, including cholecystitis – induced gallbladder perforation, trauma, a catheter detached during biliary drainage, and incomplete suture after a biliary operation.
3. Pericholecystic abscess, a morbid condition in which perforation of the gallbladder wall is covered by the surrounding tissue, with the formation of an abscess around the gallbladder.
4. Biliary fistula, which can occur between the gallbladder and the duodenum following an episode of acute cholecystitis. The fistula is usually caused by a large gallbladder stone eroding through the wall of the gallbladder into the duodenum. If the stone is large, the patient can develop gallstone ileus, with the stone causing mechanical small bowel obstruction at the ileocecal valve.

8.2.9 Prognosis

The mortality in patients with acute cholecystitis is 0–10%. Whereas the mortality in patients with postoperative cholecystitis and acalculous cholecystitis is as high as 23%–40%. The mortality of elderly patients (75 years and older) tends to be higher than that of younger patients, and comorbidity such as diabetes may increase the risk of death. Many reports of the mortality and morbidity of acute cholecystitis are difficult to compare because there are significant variations in the diagnostic criteria, timing and type of operation, presence of comorbidities, and hospital support systems for critically ill patients, as well as variations in available surgical expertise. According to reports published in 1980 and before, most of the causes of death after cholecystectomy were related to postoperative infections, such as ascending cholangitis, hepatic abscess, and sepsis. Since 1980, postoperative mortality from infection has decreased and the major causes of death include myocardial infarction, cardiac failure, and pulmonary infarction. Cholecystostomy was a common form of treatment in 1970 and before, and the most common cause of death during that period was pneumonia and sepsis. Currently, the major causes of death following cholecystostomy include malignant tumour, respiratory failure, and cardiac failure.

8.2.10 Recurrence rate of acute cholecystitis after conservative treatment

Most patients with acute cholecystitis are treated with a cholecystectomy, and it is difficult to anticipate whether the outcome will show recurrence. Recurrences of clinical concern include

- acute cholecystitis after spontaneous recovery without the undergoing of any treatment
- acute cholecystitis while waiting for cholecystectomy after conservative treatment with diet modification and antibiotics
- acute cholecystitis when cholecystectomy is not performed for some reason, such as surgical risk or the patient's decision (with or without biliary drainage)
- cholangitis after cholecystectomy.

There are no data on the recurrence of acute cholecystitis after the resolution of the initial symptoms. The recurrence of acute cholecystitis, while patients are waiting for cholecystectomy following conservative treatment, ranges from 2.5% to 22%.

Long-term recurrence is reported to be 10%–50% in 6 months to several years of observation, though there are few reports. According to a randomized controlled trial comparing non-operative treatment and cholecystectomy for patients with acute cholecystitis, excluding those with severe cases, 11% had a history of acute cholecystitis, and 24% patients assigned to non-operative treatment underwent cholecystectomy during an observation period of 1.5–4 years. In patients with acute cholecystitis who were observed after treatment with percutaneous drainage, acute cholecystitis recurred once or more 47 % patients during an average observation period of 18 months, and it recurred once or more in 31% patients who were observed for 37 months on average.