# Chapter 2

**Modern Review**

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CHAPTER 2

Modern Review

Introduction:

Gall stones are the most common digestive disease leading to Hospitalization. Knowledge of the natural history and risk factors in patients with asymptomatic gallstones are therefore essential. This chapter will highlight the current knowledge on incidence, anatomy of biliary tract, composition of bile, etiology, pathogenesis, clinical features and treatment of gallstones.

1. Who 1st Mentioned\textsuperscript{11}?

Both Vesalius and Fallopius described gallstones found in the gallbladder of dissected human bodies at 16th century (Schwartz 1981).

2. Definition:

The presence of stone(s) in the gallbladder.

3. Prevalence:

Overall prevalence of the world is 11\%\textsuperscript{12}. Gallstones exhibits prevalence rates around 25\% in industrialized societies\textsuperscript{13}.

4. Anatomy of Biliary Tract:

Biliary apparatus having two parts i) Gallbladder with cystic duct and Bile ducts ii) hepatic part

4.1. Gallbladder:

4.1. i. Definition:

It is a sac for the storage and concentration of liver bile \textsuperscript{14}.

4.1. ii. Shape and Situation:

Pear shaped hollow viscous lying on the inferior surface of the right lobe of the liver in a fossa extending from the right end of the portahepatis to the inferior margin of the liver. The gallbladder is obliquely placed and its long axis is directed upwards backwards and medially\textsuperscript{15}. 


4.1. iii. Parts:
Gallbladder having 3 parts fundus, body and neck.

4.1. iii.a. Fundus:
Lies at the junction of the lateral border of the right rectus abdominis with the 9th costal cartilage at the level of the lower border of L1 vertebra.

4.1. iii.b. Body and Neck:
Lies on the inferior surface of the liver in the fossa for gallbladder.

4.1. iii.c. Size & Capacity:
Length- about 7-10 cm.
Breadth- about 2 cm.
Capacity- 30-50 ml, 1-2 ml/kg of the body weight.
Weight- 1.5 ounces.

4.1. iv. Development:
Develops from cystic diverticulum. Distal dilated part of this diverticulum forms gallbladder and narrow proximal part form cystic duct.

The gallbladder and the ducts that carry bile and other digestive enzymes from the liver, gallbladder and pancreas to the small intestine are called biliary system.
4.1. v. Blood Supply:
(a) Arteries: Cystic artery, a branch of right hepatic artery, occasionally by an accessory cystic artery, a branch of common or right or left hepatic artery.15
(b) Veins: Cystic vein draining into the portal vein and some veins from it enter liver directly.

4.1. vi. Lymphatics:
Drain into hepatic lymph nodes, few lymph vessels pass via cystic lymph node.

4.1. vii. Nerve Supply:
a). Vagus:
It is secretomotor nerve. It inhibits the sphincter of gallbladder. Pain via vagus may be referred to stomach.
b). Sympathetic:
From 9th thoracic segments of spinal cord. So pain may be referred to right 9th and 10th intercostals spaces.
c). Via right phrenic nerve C3, 4.14

4.1. viii. Structure:
a) Serous coat, b). Fibromuscular coat (muscle unstripped, longitudinal), c). Mucous coat- Thrown into minute folds. D). No submucuos coat and no muscularis mucosa. Epithelium is columnar.

4.2. Cystic Duct:
4.2. i. Length: 3-4 cm14.
4.2. ii. Extent:
It starts as a continuation of the neck of gallbladder descends parallel to common hepatic duct and ends by joining the right side of common hepatic duct, 3 cm below the porta hepatis to form bile duct.

4.2. iii. Interior:
Mucous membrane is thrown into 5-12 crescentic folds, arranged alternately in the walls and giving appearance of a spiral nerve.
4.3. Structure of bile duct:
Tube like structure for passage of bile from liver and gallbladder to second part of duodenum.

4.3. a. Length:
7.5 cm in length and 6mm in diameter

4.3. b. Formation with level:
Formed by the union of cystic duct with common hepatic duct, 3 cm below the porta hepatis.

4.3. c. End:
It pierces medial wall of 2nd part of duodenum in whose musculature unites with pancreatic duct form hepato- pancreatic ampulla.

4.3. d. Course:
It just passes downwards and to the right behind the 1st part of duodenum and head of the pancreas. It finally pierces medial border of 2nd part of duodenum where it joins with the pancreatic duct to form hepatopancreatic ampulla.

4.3.e. Structure:
i) Serous coat ii) Fibromuscular coat- the plain muscle fibres are arranged circularly. Muscle fibers are condensed around the duct near duodenum and are called “Sphincter of Boyden” iii) Mucous membrane is lined by columnar epithelium with tubulo- alvelor glands. No sub mucous coat is present.

4.3. f. Blood Supply:
(i). Arteries: Lower part is supplied by posterior division of superior pancreaticoduodenal artery. Middle part is supplied by right division of hepatic artery. Upper part is supplied by cystic artery.
(ii). Veins: From the upper part veins directly enter liver. From lower part veins enter the portal vein.

4.3.g. Lymphatics:
From upper part the lymph vessels go to the hepatic lymph nodes.
From lower part the lymph vessels go to the pancreatico splenic lymph nodes.

4.3.h. Nerve supply:
5. Physiology of Bile Formation:
Hepatocytes synthesize bile acids and transfer the bile acids to the bile canaliculi.

6. Function of Bile:
i). Plays an important role in fat digestion and absorption. Help to emulsify large fat particles of food into many minute particles that can be attacked by lipase secreted by pancreas. Also aid in the transport and absorption of digested fat end products to and through intestinal mucosal membrane.

ii). Bile serves as a means for excretion of several important waste product from the blood. These include bilirubin.

7. Function of Gallbladder:
Main functions of gallbladder are storage, concentration of bile absorption of some HCO₃⁻. It absorbs water and concentrates bile about 10 times. Also adds mucus to bile. Therefore gallbladder bile is less alkaline than hepatic bile. Gallbladder is not essential for life. Cholecystectomy is often done in patients from gallbladder diseases and patients do not suffer from any major disadvantages due to removal of gallbladder.

8. Composition of Bile:

Table 1: Difference between liver bile and gallbladder bile

<table>
<thead>
<tr>
<th>Composition</th>
<th>Liver Bile</th>
<th>Gallbladder Bile</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>About 8.0</td>
<td>About or little over 7.0</td>
</tr>
<tr>
<td>Water</td>
<td>98%</td>
<td>89%</td>
</tr>
<tr>
<td>Organic:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Bile acids</td>
<td>0.5 gm%</td>
<td>6.0 gms%</td>
</tr>
<tr>
<td>b) Bile pigments</td>
<td>0.05 gm%</td>
<td>0.3 gm%</td>
</tr>
<tr>
<td>c) Cholesterol</td>
<td>0.01 gm%</td>
<td>0.5 gm%</td>
</tr>
<tr>
<td>d) Lecithin</td>
<td>0.05 gm%</td>
<td>0.4 gm%</td>
</tr>
<tr>
<td>Inorganic:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Na⁺</td>
<td>150 mcq/liter</td>
<td>135 mcq/liter</td>
</tr>
<tr>
<td>b) K⁺</td>
<td>4 mcq/liter</td>
<td>12 mcq/liter</td>
</tr>
</tbody>
</table>
9. Bile acid pool:

Healthy adult contains a net amount of 2 to 4 gms. of bile acids in his body and this is total body ‘bile acid pool’. 600 mgs of bile acids from this pool is daily lost via feces and this amount is exactly replenished by new synthesis as mentioned above. During fasting or in the mid night or early morning most of the bile acids of the pool are found in gallbladder, where as during digestive phases most of the amount resides in the intestine.

10. Control of Secretion:

Nervous and humoral mechanisms affect biliary secretion. Vagal stimulation increases flow and this effect is abolished by atropine.

i). Presence of bile acids in the intestine or liver causes greater secretion of bile, called cholertic action.

ii). Secretin increases bile secretion. Actually secretin increases water and bicarbonate fractions of bile.

iii). Gastrin also increases secretion of bile.

11. Etiology of Gallstones:

The etiology of gall stones is still unclear. We have no power to prevent the formation of gallstones. It is noteworthy that the majorities of gallstones are asymptomatic and may remain as such for long period. Gall stones are uncommon before the age of 10 years and their incidence increases with age up to a certain limit. There are several folds more common in women than in man. The trends are strongest in women (less than 30 years of age) and those with more than two pregnancies.

11.1. Risk factors:

i). Geography:

Prevalence of gallstone varies worldwide. Gallstones are common in North America, Europe and Australia and are less frequent in India, the Far East and Africa.
ii). Ethnic-Heredity:
Pima tribe of the southern Arizona has the highest prevalence of the world (70% women over age 25 years). It is believed to be the racial tendency to secrete excessive amounts of cholesterol. Overall, the prevalence of gallstones was significantly higher ($c^2=14.52$, $P<0.001$) in the first-degree relatives. In particular, prevalence of gallstones was significantly higher in mothers, fathers, and sisters of index cases than that in the respective family members of index controls. Animal studies also implicate specific genetic susceptibilities from so-called lith genes to gallstone formation.

iii). Age:
Common after 40 years of age. The influence of age is attributed to increasing cholesterol secretions and decreased bile acid formation.

iv). Gender:
Female are at least twice lithogenic as males. Oestrogen increase biliary cholesterol secretion. Before puberty this risk is negligible.

v). Multiple Pregnancies:
During pregnancy the gallbladder does not empty in response to a fat meal and secrete more lithogenic bile. It is specially after 2 pregnancies. During pregnancies elevated oestrogen and progesterone levels increase biliary cholesterol secretions. Progesterone inhibits gallbladder contractility.

vi). Obesity:
Obesity particularly morbid obesity is a risk factor. This particularly notable for women and independently correlates with female-type fat distribution as judged by the waist-to-hip girth ratio. Increased cholesterol synthesis and excretion result in higher incidence of gallstones in obese patient.

vii). Hypertriglyceridemia:
High serum triglyceride (TG) and low high density lipoprotein (HDL) and cholesterol to be associated with increased gallstone formation.
viii). Disease of Terminal Ileum and Crohn's disease:
In contrast any disease that affects the terminal ileum, such as Crohn's disease, does lead to an increased incidence in gall stones by depleting the bile salt pool.

ix). Hypothyroidism:
There is an association between thyroid and gallstone disease with a gender-specific relation between hypothyroidism and cholelithiasis. It affects metabolic state.

x). Oral Contraceptives:
Oral contraceptives users were also found to have a greater risk of gallstones, particularly if they are younger than 40 years of age. Increases cholesterol levels in bile and decrease gallbladder movements.

xi). Cystic Fibrosis and Pancreatic Insufficiency:
The failure of patients with cystic fibrosis and pancreatic insufficiency to produce physiologic stimuli to empty the gallbladder reason these patients have a high incidence of gallstones.

xii). Cirrhosis:
It is associated with hyperbilirubinemia.

xiii). Prolonged Fasting:
Fasting decreases the gallbladder movement that helps bile to become over concentrated with cholesterol, which can lead to gallstones.

xiv). Total Parenteral Nutrition:
Gallbladder can not empty & leads to bile over concentration.

xv). Blood Dyscrasias:
Sickle cell anaemia, congenital spherocytosis increase the risk of gallstone formation.

xvi). Drugs:
A two-fold to 3.7-fold greater incidence of gallstones has been reported in women on Oestrogen replacement therapy, lipid lowering agent 'Clofibrate' is related to gallstone formation. Cholestramine might be expected to predispose to
gallstones by reducing the bile salt pool; this effect was not statistically significant in a large coronary disease prevention study: the same was true for nicotinic acid40.

xvii). Diet:
High- calorie diet may also be a responsible factor for gallstone formation. Consumption of simple sugar and saturated fat have been mostly associated with higher risk41. The vegetarians have a lower risk42.

xviii). Bacterial Infection24:
Produces β-glucuronidase that converts the bilirubinate into unconjugated insoluble form.

xix). Parasitic Infestations of the Biliary Tract43:
Dead parasite in biliary tract may become calcified in the length of time. e.g. Ascaris lumbricoides44.

xx). Malaria36:
Excess formation of bilirubin by haemolysis.

xxi). Rapid Weight Loss45:
As body metabolites fat during rapid weight loss, it causes the liver to secrete extra cholesterol into bile, which can cause gallstones.

xxii). Diabetes Mellitus44:
Incidence of gallstone complication is greater than normal. However, studies have shown that the natural history of gallstones in diabetics follows the same pattern observed in non-diabetics. A prospective study of non-insulin-dependent diabetics showed that after five years of follow-up, 15% of the asymptomatic patients developed symptoms47.

12. Types of Gallstones:
There are three types of stones that are as follows.

a. Cholesterol Stone
b. Pigment Stone
c. Mixed Stone

12.1 Pathogenesis of Cholesterol Gallstone:
Three main factors i) Altered hepatic bile, which becomes supersaturated with cholesterol, ii) Nucleation of cholesterol monohydrate crystals and iii) Impaired function of gallbladder. The normal ratio between cholesterol and bile salts in the bile varies from 1:25 when this ratio falls to 1:13. Solubilisation of cholesterol is critical to the formation of cholesterol gallstone and understanding the factors that regulate this process has provided new insights into gallstone disease.

i). Cholesterol saturation.

ii). Nucleation.


i). Cholesterol saturation:

Cholesterol super saturation is due principally to excessive hepatic secretion of cholesterol into bile. There appears to be 'biochemical mosaic' of several defects in most gallstone patients that results in an expansion of the hepatic cholesterol pool destined for biliary excretion. Alteration in the balance between cholesterol and bile salt that results in a relative increase in concentration of cholesterol as compared to other lipid components of bile may result in cholesterol saturation of bile and ultimately precipitation of it.

The major vehicle for transport and solubilisation of cholesterol in bile are micelles. If the micelles are saturated with cholesterol, the excess part would come out of solution and precipitate as crystals. This critical relationship between cholesterol, bile salts and phospholipids can be expressed by number of mathematical formulas.

More recent information indicates that perhaps no more than 30 percent of biliary cholesterol is transported in micelles, and that the majority is carried in a vesicular form. The supersaturated bile is secreted containing high number of unilamellar vesicles. All vesicles are made up of lipid bilayers similar to those found in cell membranes. These vesicles are able to solubilise more cholesterol saturation and precipitation.
Proposed Origin of Cholesterol Gallstone.

Current theory suggests that there is equilibrium between the physicochemical phases of these vesicles to such condition that the formation of the liquid crystals may or may not result in actual gallstone.

ii). Nucleation:

The first step in stone formation is referred to as nucleation. Nucleation refers to the process by which cholesterol monohydrate crystals form and agglomerate to become macroscopic. Although it is clear that, for bile from patients with cholesterol gallstones, the time required to nucleate is significantly shorter than that for bile from patients without gallstones. The factors responsible remain as yet unidentified. Several specific heat labile glycoproteins in the bile of gallstone patients have been identified as potential pronucleating factors. It has been proposed that specific proteins within cholesterol-saturated bile induce vesicular aggregation and ultimately promote stone growth.
Gall bladder mucus secretion can serve as a nucleating factor and as a matrix on which crystals agglomerate and cluster. Other factors presumed to be important in the nucleation process include increased concentration of biliary calcium, alteration in gallbladder prostaglandin metabolism, stasis in gallbladder and altered absorption process in gallbladder.

iii). Stone Growth:
Once cholesterol crystals begin to agglomerate and form clusters the stones are inevitable.

12.2. Pathogenesis of Pigment Gallstones:
Pigment gallstones are mixtures of insoluble calcium salts of unconjugated bilirubin along with inorganic calcium. Pigment stones can be further classified as either "brown" or "black" stones. Brown stones have a characteristic appearance and consistency and uncommon in developed countries, common in Asia. These stones presumably occur as a result of infection and are quite similar to primary bile duct stones. By contrast black stones are not typically associated by infected bile. These stones are found in haemolytic disorder or cirrhosis. Altered solubilisation of unconjugated bilirubin with precipitation of calcium bilirubinate and insoluble salts is presumed to be the common final pathway for the formation of all pigment stones, regardless of the clinical setting. Many years the presence of bacterial β-glucuronidase has been well documented. It was thought to be the critical factor in the enzymatic hydrolysis of bilirubin glucuronide into free bilirubin and glucronic acid. This free unconjugated bilirubin which is insoluble in water combines with calcium in bile to produce a calcium bilirubinate matrix that is the predominant component of most pigment stones. In patients with bilirubin overproduction due to haemolysis, deconjugation with a fixed portion of the bilirubin would explain the high incidence of stones. In cirrhosis of liver lower bile salt concentration may decrease the soluble bilization of the small amount of unconjugated bilirubin normally present as well as reduce the calcium buffering capacity of the bile. Gallstone growth is enhanced by the structural Framework provided by gallbladder mucin.

12.3. Pathogenesis of Mixed Gallstones:
Between the “pure” cholesterol and “pure” pigment stones there is a broad spectrum of so called mixed stones in essence “deviant” cholesterol stones they are multiple and often faceted.

12. **Symptoms:**

Patients having gallstones present in a number of different ways. Some patients remain asymptomatic.

i). **Asymptomatic Gallstones:**

Gallstones may be present for decades before symptoms develop, and 70% to 80% of patients remain asymptomatic throughout their lives. It appears that asymptomatic patients convert to symptomatic ones at the rate of 1% to 3% per year, and the risk diminishes with time.

ii). **Biliary Colic:**

Pain of biliary colic is produced by either distension or inflammation of gallbladder. It is the postprandial right upper quadrant but sometimes in other upper abdominal locations. Biliary colic is a steady rather than an intermittent pain, as suggested by the word colic. Pain precipitated by a fatty or protein rich meal occurs 30 minutes to several hours after eating and then resolves. The location of the pain is generally in the right upper quadrant, but many patients will have pain referred to inferior medial aspect of scapula, tip of the right shoulder or to the mid-epigastrium. Onset of pain is related to impaction of a stone in the cystic duct or Hartmann’s pouch, with obstruction to outflow of bile occurring secondarily.

This is a self-limited process and generally resolves within a few hours of onset. The frequency with which these attacks occur is unpredictable and does not appear to be linked to either the size or the number of stones present within the gallbladder. Once people begin to have attacks of biliary colic they tend to increase in frequency and intensity.

iii). **Nausea and Vomiting:**

They are frequently associated with attacks of biliary colic.

iv). **Gallbladder Dyspepsia:**
Dyspepsia is a general term used to refer to a group of ill-defined symptoms associated with gallstone disease and many other abdominal conditions. After fatty meal there is feeling of fullness associated with belching and heartburn, excessive belching or flatus, postprandial belching, fullness of abdomen, epigastric discomfort and episodic nausea and vomiting.

v). Low Grade Fever with Chills:
Indicate underline complication i.e. Cholecystitis, Cholangitis.

vi). Clay Coloured Stool:
It is the feature of obstruction in the biliary tree.

13. Signs:

i). Positive Murphy’s Sign:
To elicit tenderness in cholecystitis one may place the right hand just below the right costal margin on the lateral border of the right rectus. Moderate pressure is exerted with the fingers to palpate the fundus of the gallbladder. The patient is now asked to take a deep breath in the gallbladder immediately wince with a catch in the breath if the organ is inflamed. This is called Murphy’s Sign.

ii). Positive Boas’s Sign:
An area of hyperesthesia between the 9th and 11th ribs posteriorly on the right side is known as Boas’s Sign.

14. Complications:

A. In the gallbladder:
I. Acute cholecystitis:
Inflammation of the gallbladder due to gallstone 90% cases by obstruction of the neck or cystic duct.

II. Chronic Cholecystitis:
Patients with gallstone disease are often said to have chronic cholecystitis. Since it is associated with cholelithiasis in more than 90% of cases.

III. Gangrene:
It is dangerous complication producing where develop generalised peritonitis.

IV. Perforation:
Secondary to focal or diffuse gangrene of the gall-bladder in 10% cases of acute cholecystitis.

V. **Mucocoele:**
Dilatation of the gallbladder with mucous secretion.

VI. **Empyema:**
Gallbladder filled with pus. High fever with rigor and toxic features.

VII. **Hydrops:**
Chronic distension of the gallbladder due to hydrops may occur with chronic cystic duct obstruction²⁶.

VIII. **Cholesterosis:**
Cholesterol hypersecretion by the liver promotes excessive accumulation of cholesterol esters within the lamina propria of the gallbladder. The mucosal surface is studded with minute yellow flecks, producing the “strawberry gallbladder”³⁵.

IX. **Fistula:**
Rarely, fistula develops between the gallbladder and the duodenum, colon or stomach¹².

X. **Carcinoma:**
It is due to chronic cholecystitis and variable ranging from 2 to 10%⁶⁷.

A. **In the bile duct:**

I. **Obstructive jaundice:**
By obstruction in the biliary tract³⁵.

II. **Acute Relapsing Pancreatitis:**
If stone is impacted at ampulla of vater then is recurrent pancreatitis develops.

B. **Cholangitis:**
Intermittent high temperatures often accompanied by rigors indicate bacterial infection of biliary channel and usually follow the passage of a stone into the bile duct²².

B. **In the Intestine:**

I. **Gallstone Ileus:**
A gallstone in the intestine may be passed in the feces without causing symptoms. Occasionally, however, gallstone(s) in the intestine may cause intestinal obstruction called gallstone ileus.

15. Investigations for Gallbladder Diseases:

a. Skiagraphy of the abdomen:

Only 8 to 10% cases of gallstones are radio-opaque as compared to 90% of renal calculi.

b. Ultrasonography:

Many gallstones, especially silent stones, are discovered during investigation for other purposes. Now-a-days Ultrasonography is the first choice of investigation when clinical features appear. Nonspecific gallbladder wall thickening is often seen in conditions such as hepatitis, ascites, congestive heart failure, AIDS, hypoalbuminemia and renal failure.

c. Oral Cholecystography:

Certain radio-opaque dyes are excreted in the bile and concentrated with the bile in the gallbladder. When the gallbladder contains an adequate concentration of such dye, it can be visualized by x-ray. For determination of the gallbladder function i.e. capability of normal contraction, a fatty meal is fed.

d. Computed Tomography (CT) Scan:

The bile ducts may be seen on CT scan.

e. Magnetic Resonance Cholangiogram:

It may diagnose blocked bile ducts.

f. Cholescintigraphy (HIDA scan):
It is used to diagnose abnormal contraction of the gallbladder or obstruction. The patient is injected with a radioactive material that is taken up by the gallbladder, which is then stimulated to contract.

g. Endoscopic Retrograde Cholangiopancreatography (ERCP):

The patient swallows an endoscope, a long, flexible, lighted tube connected to a computer and TV monitor. The doctor guides the endoscope through the stomach and into the small intestine. The doctor then injects a special dye that temporarily stains the ducts in the biliary system. ERCP is used to locate and remove stones in the ducts.

h. Blood tests:

For signs of infection, obstruction, pancreatitis or jaundice.

Symptoms of gallstone are similar to those of heart attack, appendicitis, irritable bowel syndrome, hiatus hernia, pancreatitis, and hepatitis. So accurate diagnosis is important.

16. TREATMENT:

16A. Prevention:

Patients receiving total parenteral nutrition for longer than 3 months not only invariably develop biliary sludge in their gallbladders, but also have more complications than would be expected in conventional populations with choleliathiasis. Therefore prophylactic medical therapy with daily administration of intravenous cholecystokinin-octapeptide (CCK-OP) which prevents gallbladder stasis, sludge and gallstone formation is indicated. Standard ursodiol administration during the period of rapid weight loss prevents stone formation in patients undergoing more moderate weight loss to justify ursodial prophylaxis is unknown.
16.B. Curative:
16.B.i. Nonsurgical Treatment:

Nonsurgical approaches are used only in special situations such as a serious medical condition preventing surgery and only for cholesterol stones though usually recur (after nonsurgical treatment).


Medicinal treatment (Oral therapy).

Chenodeoxycholic Acid:

For gallstone dissolution chenodeoxycholate is used in a dose of 375 to 1500 mg/day. Chenodeoxycholate is converted to lithocholic acid by intestinal bacteria. The study showed stones dissolved in 14% of patients given 750 mg/day.

Adverse Effect:

It's administration induces abnormal liver function test in about one third of patients. Other side effect is diarrhoea.

Ursodeoxycholic Acid:

The 7 β-epimar of chenodeoxycholic acid, which is also found to reduce the cholesterol content of bile when fed to animals and humans. This compound is the major bile acid in the bear and have been used in traditional Asian medicine for hundreds of years. Ursodeoxycholic acid (UDCA) and impaired gallbladder motility reportedly reduce biliary pain and acute cholecystitis in patients with gallstones. However, the effect of UDCA in this setting has not been studied prospectively. UDCA does not reduce biliary symptoms in highly symptomatic patients. Early cholecystectomy is warranted in patients with symptomatic gallstones.
Adverse effects:

There are no potentially lethal toxic effects. Bile acids are thought to be one risk factor in the development of colonic carcinoma. UDCA treatment may be important. However studies of the co-carcinogenicity of UDCA indicate it is the only bile acid with no carcinogenic effects.

Symptomatic adverse effects:

Diarrhoea is a rare side effect of UDCA, unlike other bile acid therapy.

High risk groups:

Chronic liver disease or inflammatory bowel disease.

16.B.i.b. Contact Dissolution Therapy:

Diethyl Ether:

The organic composition of gallstones makes them tempting targets for direct dissolution with solvents. Though ether is an imperfect solvent because of its volatility and absorbability.

Methyle Tert-Butyle Ether (MTBE):

This experimental procedure involves injection a drug directly into the gallbladder to dissolve stones. The drug methyl tert-butyl ether can dissolve some stones in 1 to 3 days. The procedure is being tested in patients with symptomatic, noncalcified cholesterol stones.

Adverse effects:

It can cause necrosis of the villus tips of the gallbladder, but regeneration seems to be rapid. Its installation into the gallbladder often causes some pain, but this is
generally tolerable. If it escapes into the intestine, it causes a bad test in the mouth and some nausea and vomiting. Further its absorption has caused hemolysis and renal damage.

**Ethyle Propionate (EP):**

Ethyl propionate (EP), a C₅ ester, dissolves cholesterol gallstones rapidly in vitro, but differs from MTBE in being eliminated so rapidly by the liver that blood levels remain undetectable. Gallstone dissolution was assessed by chromatography, by gravimetric, and by catheter cholecystography.

**Adverse effects:**
Transient hypotension and pain at the infusion site; no patient developed somnolence or nausea. Gallstone elimination was associated with relief of symptoms. EP is an acceptable alternative to MTBE for topical dissolution of cholesterol gallbladder stones in high-risk patients. The lower volatility and rapid hepatic extraction of EP suggest that it may be preferable to MTBE in this investigational procedure.

**Copper vapor laser fragmentation of gallstones:**
Laser fragmentation is a promising new modality in management of retained CBD stones. A copper vapor laser (wave length, 510 nm; 5.6 W; 5 kHz; pulse length, 30 ns) was attached to a 650-micron quartz fiber. A stone was "impacted" in the tubing and the laser fiber was pushed against the stone while making multiple pieces to fragment it.

16.B.ii. Surgical Treatment:

Surgery to remove the gallbladder is the most common way to treat symptomatic gallstones.

16. B.ii.a. Cholecystectomy (Open or Laparoscopic):
Laparoscopic cholecystectomy is successful in about 95% of patients. In the remainder, the operation has to be converted to open cholecystectomy. This is more likely if there is acute cholecystitis particularly with empyema. Laparoscopic cholecystectomy reduces the number of hospital days, pain, and disability, as compared to open cholecystectomy.

Complication:
The complication rate is 1.6-8%, including wound infection, bile duct injury (0.1-0.9%).

Recurrence after Medical Therapy:
After stoppage of treatment abnormal bile will again be secreted and stone will recur. Indeed, in about 50% of people who have had successful dissolution with bile salts, gallstones recur within five years.

16.B.i.b Endoscopic Retrograde Cholangiopancreatography (ERCP):
The patient swallows an endoscope a long, flexible, lighted tube connected to a computer and TV monitor. The doctor guides the endoscope through the stomach and into the small intestine. The doctor then injects a special dye that temporarily stains the ducts in the biliary system. ERCP is used to locate and remove stones in the ducts. Its therapeutic application has also revolutionized the treatment of patients with choledocholithiasis.

16.B.i.c. Special Therapy:

Extracorporeal Shockwave Lithotripsy:
Extracorporeal gallstone lithotripsy uses focused high-amplitude sound waves to fragment stones. These waves create stresses that fragment the stones and pass relatively harmlessly through soft tissues. Shock waves are created in water by one of three methods and are focused by a parabolic reflector. Stones must be imaged by ultrasonography or fluoroscopy during the procedure to focus the shock waves
on them and monitor their fragmentating activity. A functioning gallbladder is
necessary to permit the evacuation of the fragments.\textsuperscript{83}

\textbf{Adverse effects:}

The fragments pass into the common bile duct and small intestine, sometimes
causing biliary pain if they are larger than 3 mm. Acute pancreatitis has not been a
common problem. Shock waves can damage soft tissues, such as lung or kidney,
causing self-limited gross hematuria in up to 9\% of patients.\textsuperscript{84} The long-term effects
of repeated lithotripsy are unknown.