INTRODUCTION

Gallstones, complex biomineralized deposits formed in the gallbladder, are still a major health problem all over the world. Cholelithiasis is common with the incidence ranging from 10% to 20% of the world population.

On the basis of their composition, gallstones can be divided into the three types: Cholesterol stones (CS) that vary in colour from light-yellow to dark-green or brown and are oval, and they must have at least 80% cholesterol by weight (or 70%, according to the Japanese classification system); Pigment stones (PS) which are small, dark stones made of bilirubin and calcium salts that are found in bile, and they contain less than 20% of cholesterol (or 30%, according to the Japanese classification system); and Mixed stones (MS) which typically contain 20% - 80% cholesterol (or 30% - 70%, according to the Japanese classification system).

Over the past two decades, a great deal has been learned about the epidemiology of and risk factors for gallstones. Ultrasonography has played a major role in this process, providing a rapid, risk-free method of screening large populations. Prior to the availability of ultrasound, most studies relied on highly selective autopsy data and limited oral cholecystography.
In our study by defining the pattern and type of the gallstone, and establishing correlation with severity of acute cholecystitis we will open new windows for further investigations in the future helping in implementing the non-surgical interventions measures. Gallstone disease is one of the most common and costly of all digestive diseases. The third National Health and Nutrition Examination Survey estimated that 6.3 million men and 14.2 million women aged 20 to 74 in the United States had gallbladder disease [1].
AIM

1) To determine the Biochemical analysis of Gall stones.
2) To study the clinical spectrum of acute cholecystitis.
3) To analyze the biochemical composition of gallstones and their association with severity of acute cholecystitis.
The malady of biliary tract stones is not just modern times, it dates back to 21\textsuperscript{st} Egyptian dynasty. Archeological evidence suggests that young Egyptian women had gallstones over 2000 years ago. The description about biliary tract calculi was given in the 5\textsuperscript{th} century AD by the Greek physician Altender Tralliamus. The surgical relevance of biliary tract disease was made obvious by the Islamic physician Ibusina (980 - 1037), who proved that the biliary cutaneous fistula could result from drainage of abdominal wall abscess. Hoffmann in 1793 described the presence of asymptomatic gallstones. In 1790, Jean Louis Peff recognized that a gallbladder could become adherent to abdominal wall and proposed that it could he punctured by a trochar through the abdominal wall.

It was Belzius in 1809 that recognized the bile acid fraction in bile. Later in 1863, Hoppe-Seyler postulated a continuous circulation of the bile acids in human system. Leberg in 1873 coined the term bile acid. In 1903 Buxom demonstrated the stones radiologically. The field had further developed by the performance of cholecystogram by Graham and Cole in 1924.

In 1882, Karl Langenbuck, a noted German surgeon, performed the first successful cholecystectomy. Innovations and new endeavors have
resulted in the evolution of new surgical approach, called minimally invasive surgery. Mouret, recently, in 1987, pioneered the technique of laparoscopic cholecystectomy in Lyon, France, which has grown ever since.

In 1966 – Maki proposed that bacterial infection plays a key role in the pathogenesis of pigment gallstones. In 1982 – National Institute of Health International Workshop classified most pigment gallstones as either black or brown. In 1991 PA grace – Lap cholecystectomy.

In 2002 Nakeeb and co-workers established that genetic factors were responsible for at least 30% symptomatic gallstone disease. In 2002 Schiffman and associates studied that there is decrease in gallstone formation in obese persons who is on low calorie diet for long periods. They also stated that previous gastric bypass surgery increases the incidence of gallstone formation.

**EMBRYOLOGY OF GALLBLADDER**

At 3rd week when the embryo is 3mm in length an endodermal bud arises from ventral aspect of between for foregut and midgut. It enlarges and becomes pars hepatica and pars cystica. It develops through the septum transversum and grows into ventral mesogastrium. The proximal portion is pars hepatica grows into the transverse septum and distal portion pars cystica develops into gall bladder and cystic duct. During the 12th week of gestation liver starts functioning and cystic duct
joins the hepatic duct to form common bile duct (CBD).

Figure 1. Drawing of the normal embryologic development of the gallbladder and bile ducts illustrates the foregut (A), the cranial end of the hepatic diverticulum, which represents pars hepatica (B) and the cystic diverticulum (C). The ventral (D) and dorsal (E) pancreas are also demonstrated.

ANATOMY OF GALLBLADDER

Gallbladder a pear shaped structure, hollow organ measuring 7.5 to 12 cm in long with normal capacity of about 25 - 30ml. It is able to distend to about 50 times. It lies in under surface of liver. It is divided anatomically into 1. Fundus 2. Corpus or body 3. Infundibulum 4. Neck
Figure 2: Anatomy of gall bladder

Cystic duct

It starts from gallbladder and joins with common hepatic duct at an acute angle to become common bile duct which enters the 2nd part of duodenum in its medial aspect at the summit of ampulla of vater. Cystic duct average length is 4 cm. Its mucosa is arranged as spiral folds known as valve of Heister.

Right, left and common hepatic duct

Right hepatic duct length is about 1 cm and it is vertical in course. The left hepatic duct arises from lateral & medial branches of II, III & IV segments. It is 1-3 cm in length & is partially extraperitoneal, which therefore dilates readily in distal obstructive disease.
**Common bile duct (CBD)**

The common bile duct begins from the junction of the cystic duct and common hepatic duct ends at the papilla of Vater in the second part of duodenum. It is 5-15 cm long with diameter of about 7mm, ranges from 4-10 mm. It acts as a conduit for bile from the liver & gallbladder to the duodenum. Four parts of CBD 1. Supraduodenal 2. Retroduodenal 3. Infraduodenal (intrapancreatic) & 4. Intruduodenal

**HISTOLOGY OF GALL BLADDER**

It has three layers- 1. The Serous layer 2. Fibromuscular layer  and 3. Mucous layer

![Histology of gall bladder](image)

**Figure 3: Histology of gall bladder**

**ARTERIAL SUPPLY OF GALLBLADDER**

Major blood supply is from right hepatic artery branch cystic artery. Its course in Calot’s triangle close to cystic duct. In superior
border of gallbladder neck it branches into superficial and deep branches. Rarely cystic artery arises from hepatic artery proper or a branch from gastroduodenal artery. Hepatic ducts and upper part of common bile duct is supplied by cystic artery. Venous drainage is by small veins that enter liver.

**Figure 4: Artery supply of gallbladder**

**LYMPHATIC DRAINAGE OF GALLBLADDER**

The lymphatic channels of the gallbladder communicate with those of Glisson’s capsule of the liver which in turn drain into the thoracic duct through several channels. Distally the lymphatics from gallbladder and extrahepatic bile duct drain into the cystic lymph node.
NERVE SUPPLY

Parasympathetic fibres of hepatic branch of anterior vagal trunk stimulate contraction of gallbladder and relax ampullary sphincter. Sympathetic fibres from cell bodies of coeliac ganglion inhibit contraction of gallbladder. The hormonal activity is much more important than neural function.

Afferent pain fibres pass mainly through the right sympathetic fibres into the spinal segments T 7-T9. This causes referred pain over the right infrascapular region. Some fibres may pass through the right phrenic nerve, C3-C5.

Fibers from the right phrenic nerve travel by way of the phrenic, celiac, and hepatic plexuses to reach the gallbladder. Many of these fibers are afferent and may account for the pain referred to the right hypochondrium and radiating the back between the shoulder blades in some patients with gallbladder diseases.

Burnett and associates demonstrated three nerve plexuses: subserous, muscular, and mucosal. The ganglion cells in each nerve plexus decrease in number from subserous to mucosal levels. In comparison with the myenteric plexus of the gut, the subserous plexus ganglia are larger and spaced farther apart.
PHYSIOLOGY OF GALLBLADDER

Bile secretion by liver is an active and continuous process. Its expulsion into duodenum, which is its site of action, is intermittent. Hence, it is necessary for bile to be stored and to be released when needed. Gallbladder serves this main function. Strictly bile is not a digestive secretion, because it doesn't possess any digestive enzymes. Liver secretes bile at the rate of 40ml/hr. The sphincter of Oddi dictates the flow of bile.

The functions of gallbladder are –

- Reservoir of bile
- Concentration of bile
- Pressure regulation
- Secretion of bile

Figure 5: Circulation of bile salts
MECHANISM OF STORAGE

The CBD is shut off from duodenum by sphincter of Oddi when pressure exceeds >70 mm H₂O, bile is directed from CBD into gallbladder. Because of inherent capacity of gallbladder to absorb water and inorganic constituents, bile is concentrated 4-10 times.

MOVEMENTS OF GALLBLADDER

Tonic contractions begin 5-30 minutes after food intake, intermittently till the gallbladder is empty. Normal emptying time varies between 2-5 hours. Rhythmic contractions, which are weak, not exceeding 50mmH₂O are not able to expel bile into duodenum. Since this pressure is less than the secretory pressure of liver, filling and evacuation is entirely dependant upon reciprocal sphincter of Oddi contraction and relaxation.

MECHANISM IN EXPULSION OF BILE

Expulsion of bile requires 2 factors

1) increased pressure of bile,

2) relaxation of sphincter of Oddi.

Pressure of bile is increased and secretion of bile is stimulated by bile acids and fatty meal. Gallbladder contraction is brought about by stimulation of right vagus, which is motor to gallbladder and inhibitory to sphincter. The second mechanism is hormonal which is more important
than neural reflex.

Cholecystokinin is secreted by duodenal mucosa, in response to food and low pH. The hormone has potent simulative action on gallbladder and inhibitory action on sphincter of Oddi.

**BILE SALTS AND BILE ACIDS**

These are steroid molecules, formed from cholesterol by hepatocytes and are major pathway of cholesterol excretion by body. To enhance their solubility in bile, bile acids are conjugated with glycine and taurine before excretion as sodium salts.

Bile acids - primary - cholic acid / cheno acid - secondary - deoxycholic / lithocholic / 7 ketolithocholic acid - tertiary - ursodeoxycholic acid

**BILE PIGMENTS**

Bilirubin is the chief bile pigment, produced by the breakdown of senescent RBCs in reticuloendothelial system. Biliverdin is produced from bilirubin.

![Figure 6: Bilirubin metabolism in liver.](image)
PATHOGENESIS OF GALLSTONES:

The earliest theories regarding the pathogenesis of gallstones focused on the gallbladder as the primary source of pathology. The notion was widely accepted until 1924, when Findlay introduce the concept that failure of the cholesterol to remain in solution was the critical factor initiating cholesterol gallstone formation. This fundamental concept was clarified by Admirand and Small who in 1968 described the critical nature of relation between the relative biliary concentration of phospholipids, bile salts and cholesterol liver biliary secretion gallstones are composed mainly of cholesterol, bilirubin, and calcium salts, with smaller amounts of protein and other materials. In western countries cholesterol is the principal constituent of more than three quarters of gallstones, and many of these stones are more than 80 percent cholesterol. Cholesterol stones often contain alternating layers of cholesterol crystals and mucin glycoproteins. Pure cholesterol crystals are quite soft, and protein contributes importantly to the strength of cholesterol stones.

Non-cholesterol stones are categorized as black or brown pigment stones, consisting of calcium salts of bilirubin. Black pigment stones are believed to consist of polymers of bilirubin, with large amounts of mucin glycoproteins. Brown pigment stones are made up of calcium salts of unconjugated bilirubin, with variable amounts of protein and cholesterol. Black pigment stones are more common in patients with cirrhosis or
chronic hemolytic conditions such as the thalassemias and possibly sickle cell anemia, in which bilirubin excretion is increased. Primary bile-duct stones, defined as stones that originate in the bile ducts, are usually brown pigment stones associated with infection, are found in elderly patients, in patients with congenital bile duct anomalies or obstruction. The high incidence of stones in patients with hemolytic disorders is due to loads of bilirubin presented to the liver for excretion. Bacteria in the biliary system release - glucuronidases, which hydrolyze glucuronic acid from conjugated bilirubin. The resulting unconjugated bilirubin precipitates as its calcium salts. Primary brown pigment stones of the bile ducts often occur in Asians, associated with decreased biliary secretory IgA. About 15 percent of gallstones are calcified enough to be seen on a plain abdominal radiograph, and of these two thirds are pigment stones. Calcification that is visible only on the rim usually occurs in cholesterol stones. In the simplest sense, cholesterol gallstones form when the cholesterol concentration in bile exceeds the ability of bile to hold it in solution, so that crystals form and grow as stones. Cholesterol is virtually insoluble in aqueous solution, but in bile it is made soluble by association with bile salts and phospholipids in the form of mixed micelles and vesicles. Micelles are aggregates of lipid with nonpolar hydrocarbon chains directed inward and polar phosphate or hydroxyl groups directed outward toward the aqueous solvent. Vesicles are spherical bilayers of
phospholipids with nonpolar hydrocarbon chains hidden inside the bilayer and polar groups directed outward toward the aqueous solvent. At higher cholesterol concentrations, increasing amounts of cholesterol are carried in vesicles. Single-layered (unilamellar) vesicles fuse into multilayered (multilamellar) vesicles, and cholesterol crystals can grow from their surfaces. These crystals presumably grow and agglomerate with mucin proteins in bile to form stones.

**Proposed Origin of Cholesterol Gallstones**

![Diagram of cholesterol gallstone formation](image)

**Aggregation of Unilamellar Vesicles into Multilamellar Vesicles**

![Diagram showing aggregation of vesicles](image)

**Figure 7: Pathology of gallstones**
The molar proportions of cholesterol, phospholipid, and bile acids in bile are often represented on triangular coordinates. In vitro studies of model bile mixtures show that cholesterol is most soluble in a mixture of lipids containing at least 50 percent bile acids, with smaller amounts of phospholipid. Bile acids that flow into the small bowel are recirculated by reabsorption in the terminal ileum and secretion into bile by the liver. Bile acids in the liver cause a decrease in the rate limiting step in bile acid synthesis. In general, the greater the degree of cholesterol supersaturation, the greater the risk of cholesterol gallstones. Lithogenic bile is most often the result of increased biliary cholesterol output, but in some ethnic groups there is decreased bile acid synthesis or a combination defect. The biliary output of cholesterol increases with age and as a result of estrogen treatment in men and women. Estrogen treatment also reduces the synthesis of bile acid in women. The association between serum lipids and gallstones is controversial. The risk of gallstones does not correlate with total serum cholesterol levels, but it does correlate with decreased high-density lipoprotein cholesterol and increased triglyceride levels.

In almost half of Americans the bile is supersaturated in the morning before breakfast because most total-body bile acids are sequestered in the gallbladder and the output of bile acid in hepatic bile is consequently reduced more than the output of cholesterol.
Each side of the triangle in figure 8 shows the molar fraction of total lipids represented by its constituent. As an example, the three dotted lines define a mixture containing a molar ratio of 15 percent cholesterol, 30 percent lecithin (phospholipid), and 55 percent bile salts. At higher saturations, cholesterol exists in multiple phases, as crystals, micelles, or vesicles. The phase diagram indicates that this cholesterol content is greater than that which can exist in a stable micellar liquid, or in a metastable saturated liquid. Eventually, therefore, cholesterol crystals will precipitate from this bile.

Figure 8: Triangular coordinates showing the solubility of cholesterol in a mixture containing phospholipid and bile salts

Cholesterol stones do not develop uniformly in persons with cholesterol supersaturated bile. When human bile supersaturated with cholesterol is filtered to remove crystals and allowed to incubate at 37°C, the first crystals appear after intervals of hours to more than a week. This represents the time required for the nucleation of cholesterol crystals --
i.e., the formation of the first microscopic collections that serve as a framework for further crystal growth. For a given degree of cholesterol supersaturation, bile from patients with gallstones forms cholesterol crystals more quickly than bile from patients without gallstones. These data point to the presence of factors in bile that inhibit or promote nucleation and the growth of gallstones. High biliary protein and lipid concentrations are risk factors for the formation of gallstones. Gallbladder sludge i.e., thickened gallbladder mucoprotein with tiny entrapped cholesterol crystals is thought to be the usual precursor of gallstones. Sludge can sometimes cause biliary pain, cholecystitis, or acute pancreatitis, but sludge may also resolve without treatment. Sludge frequently occurs with pregnancy, prolonged total parenteral nutrition, starvation, or rapid weight loss. The antibiotic ceftriaxone can precipitate in the gallbladder as sludge and, rarely, as gallstones. Efforts to understand the role of biliary proteins in the formation of gallstones led to the purification of proteins that either retard or promote the nucleation of cholesterol crystals. Gallbladder mucoprotein is a major component of stones, along with trace amounts of other proteins, and it may account for some pronucleation activity. At least five other bile proteins have been identified as putative nucleation proteins. The quantitative importance of these proteins is not clear, and the chief nucleation-promoting substance in bile may be a lipoprotein. High doses of aspirin reduce the incidence of
gallstones in a prairie-dog model, perhaps because they inhibit the synthesis of mucus in the gallbladder, but aspirin has had only variable success in other animal models and in humans. The biliary calcium concentration plays a part in bilirubin precipitation and gallstone calcification. Many patients with gallstones have increased biliary calcium, with supersaturation of calcium carbonate. Calcium salts of bilirubin and carbonate are more soluble at a lower pH. The gallbladder not only concentrates bile, but also acidifies it. Failure of acidification may promote the calcification of gallstones. Impaired motility of the gallbladder has been cited as another contributing factor in the development of gallstones. In theory, microscopic cholesterol crystals would regularly be washed out of the gallbladder if its contractions were effective enough. Evidence that gallbladder stasis causes the formation of stones is circumstantial in most cases, since the composition of bile is usually altered as well. Gallbladder stasis associated with high spinal cord injury or with the use of the somatostatin analogue octreotide may provide more convincing examples of stasis as a cause of gallstones.

**GALLSTONES CLASSIFICATION**

1) Pure gallstones  
   a) Cholesterol gallstones (cs) 70%  
   b) Pigment gallstones (ps) 30%  
   c) Calcium carbonate gallstones  
2) Mixed and combined stones (ms)
Figure 9 - types of gallstones

**CHOLESTEROL GALLSTONES:**

10% gallstones are cholesterol stones. They are usually solitary with smooth surface, oval or round in shape, pale yellow in colour. They are thought to be formed in aseptic static bile and commonly found in Hartman’s pouch. On section they shows radiating lines crossing the circular strata. In combined gallstone, the stone starts as pure cholesterol stones but ultimately receives mixed covering of pigment and cholesterol.

**PIGMENT STONES:**

May be pure or contain Calcium bilirubinate. They constitute about 80% of all gallstones. They are Dark or black brown in color, found exclusively in the gallbladder associated with excessive haemolysis like hereditary spherocytosis, sickle cell disease, thalassemia etc. Excessive
breakdown of hemoglobin resulting in increase bilirubin which are excreted in bile and forms pigment stones in the gallbladder. Stones are usually appear as small soft fatty like masses. Calcium bilirubinate stones are brown to orange in colour and soft in consistency. These stones are more often seen in bile ducts. These stones are often caused by infection (E.Coli and parasites).

**CALCIUM CARBONATE STONES:**

Calcium carbonate stones are rarest type of stone they are grayish white in colour with smooth surface or articulated surface. Increase alkalinity of the bile favours this stone formation.

**MIXED OR COMBINED STONES**

Mixed stones have varying proportion of all three of the stone forming constituents of the bile eg. cholesterol, bile pigment and calcium. They constitute about 10% of gallstones. Combined stones are those in which central core or external layers are pure and the reminder of the stone is mixture of constituents. Combined stones may be solitary but mixed gallstones are invariably multiple with faceted surface. Stones may vary in size few cm in diameter.

Colour of the stone depends on constituents of stones.

Pale yellow - Cholesterol
Black - Calcium bilirubinate
Grayish white - Calcium carbonate.

On section of laminated central nucleus may contain epithelial debris and bacteria. This suggests inflammatory origin of stones. Chemical inflammatory changes prepare the soil for bacterial invasion.

**EPIDEMIOLOGY OF GALLSTONES**

It provides information about the prevalence and incidence of the disease.

a. True incidence: 5 year incidence in women aged 30, 40, 50, and 60 are (4%), (3.6%), (3%) and (3.7%) years and the same incidence rate in men were 0.3%, 2.9%, 2.5% and 3.3% at the same age. This shows that the incidence is more in women.

b. Prevalence and incidence: Gallstones are two times more common in women than in men.

c. Ethnic predisposition: Several genes that are associated with gallstone formation and resistance are identified in mice. The importance of these genes in human gallstone formation has not been established. Pima Indians in southern Arizona are an example of an extremely high risk population in which 70% of women less than 25 years are affected by the disease.39 Populations at the lowest risk are sub Saharan Africans and Asians.
RISK FACTORS

In addition to the variability of gallstones in different ethnic populations, a number of other risk factors for this condition have been identified.

Age

Age is a major risk factor for the gallstones. Age 40 appears to represent the cutoff between relatively low and high rates of cholecystectomies. This observation was validated in the Sirmione study in which the incidence between the ages of 40 and 69 years was four times higher than that in younger subjects [14].

Sex

A higher prevalence of gallstones has been observed in women in all age groups [7,8,13]. The difference between women and men is particularly striking in young adults [20].

Pregnancy:

It is a major risk factor for the development of cholesterol gallstones. The risk is related to both the frequency and number of pregnancies. The incidence of new biliary sludge and gallstones was 31 and 2 percent, respectively. Supersaturation occurs as a result of an estrogen-induced increase in cholesterol secretion and a progesterone-induced reduction in bile acid secretion [23]. Pregnancy induces a qualitative change in bile acid synthesis characterized by relative
overproduction of hydrophobic bile acids such as chenodeoxycholate, thereby reducing the ability of bile to solubilize cholesterol [24].

**Oral contraceptive:**

It use also appears to cause a slight increase in the risk of gallstone formation. Women under the age of 40 years and those taking high-dose estrogen (>50 mcg) preparations have the greatest added risk [33,34].

**Family history and genetics:**

Family history studies suggest that genetics has a significant role in the development of gallstones. Investigators performed oral cholecystography in 171 first-degree relatives of patients with gallstones and 200 age matched controls [37]. Gallstones occurred more than twice as often in the family group: 20.5 versus 9 percent. A more recent study evaluated 330 first-degree relatives of 105 patients with gallstones using ultrasonography; cholelithiasis was found in 15.5 percent compared with only 3.6 percent of matched controls [38]. The risk was greater in female relatives in both of these studies.

**Obesity:**

Obesity (defined as weight greater than 120 percent of ideal body weight) is a well established risk factor for the development of cholesterol gallstones, presumably due to enhanced cholesterol synthesis and secretio [39-42]. The risk is particularly high in women [20,43,44], in
those with morbid obesity [42,45], and in younger age groups in which a threelfold increase in risk has been reported [14].

**Rapid weight loss:**

Rapid weight loss is also a risk factor for gallstone formation. High rates of gallstone formation have also been associated with very low calorie diets [46-48]. Gallstones which form in association with rapid weight loss appear to be more common in Caucasians and women.

In contrast to the general population in which the great majority of gallstones are asymptomatic, persons with weight loss related cholelithiasis are more likely to be symptomatic. In one series, for example, 28 percent of patients required urgent cholecystectomy within three months after a gastric exclusion procedure [45]. Prophylaxis with ursodeoxycholic acid (UDCA) has been shown to be effective at reducing the risk of stone formation during rapid weight loss. [48].

**Diabetes mellitus:**

Diabetes mellitus appears to be associated with an increased risk of gallstones[50]. Hepatic insulin resistance appears to be important [52,53]. Other contributing factors may be hypertriglyceridemia and autonomic neuropathy leading to biliary stasis due to gallbladder hypomotility [54].

**Serum lipids:**

The precise role of serum lipids on gallstone formation is not known. Gallstones appear to be positively associated with apolipoprotein
E4 phenotype and elevated serum triglycerides [55-57]. There is no conclusive evidence linking elevated serum cholesterol and gallstones [58].

**Serum bilirubin:**

Serum bilirubin levels may also be associated with the risk of developing gallstones. In a population-based study from Denmark that included 61,212 subjects, patients with mean bilirubin levels in the highest decile had an increased risk of symptomatic gallstone disease compared with patients who had lower mean bilirubin levels (hazard ratio 1.6, 95% CI 1.3-2.0) [59].

**Cirrhosis:**

Cirrhosis is a major risk factor for gallstones. [60]. The overall prevalence of gallstones was 29.5 percent. The increased risk of gallstone formation in these patients may be due to several factors, including reduced hepatic synthesis and transport of bile salts and nonconjugated bilirubin, high estrogen levels, and impaired gallbladder contraction in response to a meal [61-63].

**Gallbladder stasis:**

The conditions that result in bile stasis are associated with a higher prevalence of gallstones. Thus, if bile remains within the gallbladder for a prolonged period, it can become overly concentrated with cholesterol, thereby promoting stone formation. Gallstones are a frequent
complication of prolonged total parenteral nutrition [65,66]. Two factors are thought to contribute: biliary stasis due to lack of enteral stimulation; and, in patients with ileal resection, interruption of the enterohepatic circulation of bile acids results in a reduction in hepatic bile acid secretion and an altered composition of hepatic bile which becomes supersaturated with respect to cholesterol.

Other drugs:

- Clofibrate, a now rarely used cholesterol lowering agent, is strongly associated with gallstones. Fenofibrate has also been associated with gallstone formation [70]. Fibrates reduce bile acid secretion by inhibiting the rate limiting enzyme in bile acid synthesis, cholesterol 7-alpha-hydroxylase; this results in cholesterol supersaturated bile and stone precipitation [71]

- Ceftriaxone is a major cause of biliary sludge formation in hospitalized patients [73,74].

Decreased physical activity:

Physical activity is associated with a decreased risk of symptomatic [75]. The men in the lowest quintile of physical activity had a relative risk of 1.72 between the ages of 40 and 64 and 1.33 above age 64 compared with those in the highest quintile. It was estimated that 34 percent of cases of symptomatic gallstones in men could be prevented by 30 minutes of endurance-type training five times per week. In contrast, women who
had a sedentary lifestyle were at increased risk of cholecystectomy (relative risk 1.42).

**Crohn disease**

The prevalence of gallstones is increased in patients with Crohn disease [77-80]. Gallstones in patients with ileal Crohn disease (or those who have undergone ileal resection) are frequently pigment based, reflecting an increased concentration of bilirubin conjugates, unconjugated bilirubin, and total calcium in the gallbladder bile due perhaps to altered enterohepatic cycling of bilirubin [78].

**Hemolysis:**

Disorders associated with hemolysis increase the risk of pigmented gallstones.

**PROTECTIVE FACTORS:**

The use of statins, as well as a number of dietary factors, may protect against gallstone disease. Statins [81], Ascorbic acid [83], Coffee [84], Vegetable protein and nuts [87], Poly- and monounsaturated fats [89].

**NATURAL HISTORY:**

The majority of patients with gallstones are asymptomatic and will remain so throughout their lives. Of those with incidental (asymptomatic) gallstones, approximately 20 percent will develop symptoms over 15
years of follow-up, but their initial symptoms are typically not severe. The mortality rate related to incidental gallstone disease is significantly less than that associated with treatment, which is why most experts advise against a cholecystectomy for patients with asymptomatic gallstones [2].

Among patients who develop symptoms, a significant number will subsequently develop complications, which is why prophylactic cholecystectomy is advised once biliary symptoms develop. This is based on a variety of large population studies that, on the whole, indicate that once the initial uncomplicated biliary symptoms develop, the chance of recurring symptoms is approximately 30 percent per year in the first two years, and the chance of developing complications is approximately 2 to 3 percent per year. Once a complication develops, the chance of having additional, often more severe, complications is approximately 30 percent per year [2-7].

Complications that may develop in patients with gallstones include acute cholecystitis, choledocholithiasis with or without acute cholangitis, and gallstone pancreatitis. Acute cholecystitis is the most common complication. In a systematic review, it was seen in 6 to 11 percent of patients with symptomatic gallstones over a median follow-up of 7 to 11 years [8]. Rare complications include gallbladder cancer, gallstone ileus, and Mirizzi syndrome (impaction of a gallstone in the cystic duct, causing compression of the common bile or hepatic duct).
Patients with asymptomatic gallstones appear to have a slightly lower risk of complications than those with symptomatic gallstones. This was demonstrated in a study that followed 123 patients with asymptomatic gallstones and 298 patients with mild symptoms due to gallstones for up to 25 years [9]. It found that the cumulative probability of developing severe complications was lower among patients with asymptomatic gallstones compared with those with mild symptoms after 5, 10, 15, and 20 years of follow-up (4 versus 5 percent, 5 versus 12 percent, 10 versus 15 percent, and 16 versus 18 percent, respectively; p = 0.03).

**CLINICAL FEATURES**

Patients with uncomplicated gallstone disease typically present with biliary colic, normal physical examination findings, and normal laboratory test results. Patients often report associated diaphoresis, nausea, and vomiting.

While patients may present with atypical symptoms such as chest pain or nonspecific abdominal discomfort, the absence of biliary colic should prompt an investigation for alternative diagnoses. On the other hand, biliary colic that is associated with fevers, jaundice, or abnormal blood tests (leukocytosis, liver tests, pancreas tests) suggests the development of a complication of gallstone disease.

**Biliary colic** — Despite the name, the pain of biliary colic is usually constant and not colicky. The classic description is of an intense, dull
discomfort located in the right upper quadrant, epigastrium, or (less often) substernal area that may radiate to the back (particularly the right shoulder blade) [10,11]. The pain is often associated with diaphoresis, nausea, and vomiting. It is not exacerbated by movement and is not relieved by squatting, bowel movements, or passage of flatus [12]. The pain typically lasts at least 30 minutes, plateauing within an hour. The pain then starts to subside, with an entire attack usually lasting less than six hours [10].

Biliary colic is usually caused by the gallbladder contracting in response to hormonal or neural stimulation, forcing a stone (or possibly sludge) against the gallbladder outlet or cystic duct opening, leading to increased intra-gallbladder pressure. This increase in pressure then results in pain. As the gallbladder relaxes, the stones often fall back from the cystic duct, and the pain slowly subsides. In many patients, the pain is not severe, which is why patients often have had several attacks before seeking medical attention.

Eating a fatty meal is a common trigger for gallbladder contraction, and many patients report postprandial pain. However, an association with meals is not universal, and in a significant proportion of patients the pain is nocturnal [13,14]. The frequency of recurrent attacks is variable, ranging from hours to years, though most patients do not have symptoms
on a daily basis [12]. Typically, the pain has a characteristic pattern and timing for an individual patient.

**Atypical symptoms** — Numerous symptoms other than biliary colic have been reported in patients with gallstones, but their predictive value for the presence of gallstone disease is poor. In many cases they may coexist with biliary colic but may or may not be related to the gallstones [15-17]. Atypical symptoms seen in patients with gallstones include:

- Chest pain
- Nonspecific abdominal pain
- Belching
- Fullness after meals/early satiety
- Fluid regurgitation
- Abdominal distension/bloating
- Epigastric or retrosternal burning
- Nausea or vomiting without biliary colic

Whether atypical symptoms are due to the gallstones or due to a coexistent problem can be difficult to determine. Patients with atypical symptoms without associated biliary colic should be evaluated for alternative diagnoses, even if gallstones are demonstrated on imaging.
PHYSICAL SIGNS:

Physical examination results frequently are normal. Discomfort might be elicited on deep palpation of the right upper quadrant of the abdomen. Murphy sign (pain on palpation of the right upper quadrant when the patient inhales) might indicate acute cholecystitis. Other signs of cholecystitis include fever and tachycardia. An enlarge gallbladder may be palpated when there is a mucocele or emphyema of the gallbladder is present, the gallbladder is felt as tense globular swelling projecting downwards and lateral to the right rectus abdominus muscle.

Hyperaesthesia between the 9th and 11th ribs posteriarily on the right side is present in acute cholecystitis, is called as Boa’s sign. Complete or partial obstruction of the common bile duct manifests as jaundice. In all races, jaundice is detected most reliably by examination of the sclera in natural for yellow discoloration. Severe hemorrhagic pancreatitis occurs in 15% patients and carries a high mortality rate because of multisystem organ failure. In a few patients, the hemorrhagic pancreatic process and retroperitoneal bleeding induce discoloration around the umbilicus (Cullen sign) or the flank (Grey-Turner sign).
DIFFERENTIAL DIAGNOSIS:

Gallstone disease is usually considered as part of the differential diagnosis of patients presenting with upper abdominal symptoms. Other disorders in the differential diagnosis include:

- Esophageal chest pain
- Gastroesophageal reflux disease
- Peptic ulcer disease
- Nonulcer dyspepsia
- Hepatitis
- Functional gallbladder disorder
- Sphincter of Oddi dysfunction
- Chronic pancreatitis
- Irritable bowel syndrome
- Ischemic heart disease
- Pyelonephritis
- Ureteral calculi
- Complications of gallstone disease: acute cholecystitis, choledocholithiasis, acute pancreatitis, and acute cholangitis
CHOLECYSTITIS:

The term cholecystitis refers to inflammation of the gallbladder. It may develop acutely in association with gallstones (acute cholecystitis) or, less often, without gallstones (acalculous cholecystitis). It may also develop over time and be discovered histologically following cholecystectomy (chronic cholecystitis).

ACUTE CHOLECYSTITIS:

Acute cholecystitis refers to a syndrome of right upper quadrant pain, fever, and leukocytosis associated with gallbladder inflammation that is usually related to gallstone disease.

ACALCULOUS CHOLECYSTITIS:

Acalculous cholecystitis is clinically identical to acute cholecystitis but is not associated with gallstones and usually occurs in critically ill patients. It accounts for approximately 10 percent of cases of acute cholecystitis and is associated with high morbidity and mortality rates [2].

CHRONIC CHOLECYSTITIS:

Chronic cholecystitis is the term used to describe chronic inflammatory cell infiltration of the gallbladder seen on histopathology. It is almost invariably associated with the presence of gallstones and is thought to be the result of mechanical irritation or recurrent attacks of acute cholecystitis leading to fibrosis and thickening of the gallbladder [3-5]. Its presence does not correlate with symptoms since patients with
extensive chronic inflammatory cell inflammation may have only minimal symptoms, and there is no evidence that chronic cholecystitis increases the risk for future morbidity [6].

Some authors use the phrase "chronic cholecystitis" when referring to gallbladder dysfunction as a cause of abdominal pain [7]. It is more appropriate in this instance to refer to the condition based on the disorder present, such as pain due to gallstone disease, pain due to biliary

**PATHOGENESIS:**

Acute cholecystitis occurs in the setting of cystic duct obstruction. However, in contrast to biliary colic, the development of acute cholecystitis is not fully explained by cystic duct obstruction alone. Studies suggest that an additional irritant (possibly lysolecithin) is required to develop gallbladder inflammation. Once inflammation of the gallbladder begins, additional inflammatory mediators are released, further propagating gallbladder inflammation. In many patients, infection of the biliary system is also involved in the development of acute cholecystitis.

However, acute cholecystitis can be produced by blocking the cystic duct, followed by deliberate irritation of the gallbladder mucosa (either mechanically with an indwelling catheter or by infusion of an irritant).
One such irritant used in experimental models, lysolecithin, is produced from lecithin, a normal constituent of bile. The production of lysolecithin from lecithin is catalyzed by phospholipase A, which is present in gallbladder mucosa. This enzyme may be released into the gallbladder following trauma to the gallbladder wall from an impacted gallstone [9]. Supporting this hypothesis is the observation that lysolecithin (normally absent in bile) is detectable in gallbladder bile in patients with acute cholecystitis [10].

Inflammatory mediators are released in response to gallbladder inflammation and further propagate the inflammation [11]. Prostaglandins, which are involved in gallbladder contraction and fluid absorption, probably play a central role in this process. In experimental models using human gallbladder tissue, the main prostaglandins synthesized by inflamed human gallbladder microsomes were prostaglandin E2 and 6-keto-prostaglandin F1 alpha, the concentrations of which were increased four times above normal [12]. The prostaglandin hypothesis is supported by the observation that prostaglandin inhibitors relieve biliary colic and can reduce intraluminal cystic pressure [13-15]. Infection of bile within the biliary system probably has a role in the development of cholecystitis; however, not all patients with cholecystitis have infected bile. This observation was illustrated in a study of 467 subjects in whom bile samples were obtained from the gallbladder and
common bile duct for aerobic and anaerobic culture [16]. Patients with a variety of hepatobiliary diseases and a healthy control group were included. Patients with gallstones, acute cholecystitis, and hydropic gallbladder had similar rates of positive cultures in the gallbladder and common bile duct, ranging from 22 to 46 percent; cultures were generally sterile in healthy subjects. The main species isolated were Escherichia coli, Enterococcus, Klebsiella, and Enterobacter.

Histologic changes of the gallbladder in acute cholecystitis can range from mild edema and acute inflammation to necrosis and gangrene. Occasionally, prolonged impaction of a stone in the cystic duct can lead to a distended gallbladder that is filled with colorless, mucoid fluid. This condition, known as a mucocele with white bile (hydrops), is due to the absence of bile entry into the gallbladder and absorption of all the bilirubin within the gallbladder.

**CLINICAL MANIFESTATIONS:**

The clinical manifestations of acute cholecystitis include prolonged (more than four to six hours), steady, severe right upper quadrant or epigastric pain, fever, abdominal guarding, a positive Murphy's sign, and leukocytosis.

**HISTORY:**

Patients with acute cholecystitis typically complain of abdominal pain, most commonly in the right upper quadrant or epigastrium. The
pain may radiate to the right shoulder or back. Characteristically, acute cholecystitis pain is steady and severe. Associated complaints may include fever, nausea, vomiting, and anorexia. There is often a history of fatty food ingestion one hour or more before the initial onset of pain. The episode of pain is typically prolonged (greater than four to six hours).

**PHYSICAL EXAMINATION:**

Patients with acute cholecystitis are usually ill appearing, febrile, and tachycardic, and lie still on the examining table because cholecystitis is associated with true local parietal peritoneal inflammation that is aggravated by movement. Abdominal examination usually demonstrates voluntary and involuntary guarding. Patients frequently will have a positive Murphy's sign.

**MURPHY'S SIGN:**

To elicit for a Murphy's sign, the patient is asked to inspire deeply while the examiner palpates the area of the gallbladder fossa just beneath the liver edge. Deep inspiration causes the gallbladder to descend toward and press against the examining fingers, which in patients with acute cholecystitis commonly leads to increased discomfort and the patient catching his or her breath.

Patients with complications may have signs of sepsis (gangrene), generalized peritonitis (perforation), abdominal crepitus (emphysematous cholecystitis), or bowel obstruction (gallstone ileus).
INVESTIGATIONS:

To date there are no serum or other lab tests that are absolutely specific for the presence of gallstones. In acute cholecystitis due to gallstones patient will have leucocytosis. There may be mild elevation of transaminases and alkaline phosphatase.

Abdominal x-ray:

Only 10% gallstones are radio opaque and can be visualized.

Oral cholecystography:

For years this test was the mainstay and gold standard for the diagnosis of gallstone though now it has been replaced by USG except where function of the gallbladder has to be assessed. Cholecystography is more accurate than USG in terms of quantification of the number of stones and their sizes. The sensitivity for detection of radiolucent stones exceeds 90% but visualization of the ductal stones is obtained in only 20%.

Abdominal ultrasound:

This is the preferred investigation for suspected cholelithiasis or cholecystitis. Examination should be performed after overnight fast of 8 to 12 hours. Two types of transducers are used, 3.5 MHZ for most of the patients. 5MHZ provides superior imaging resolution and can be used in obese patients. Major signs of diagnosis of acute cholecystitis are demonstration of gallstones or edema or gas in the gallbladder wall. Non
visualization of the gallbladder is also a major sign. Simple wall thickening is a minor sign as is local tenderness, a round shaped or dilatation. Pericholecystitic fluid is also a minor sign. The demonstration of major and minor sign together gives an overall accuracy of over 90%. When the gallbladder is normal, ultrasound often indicates other pathologies.

In chronic cholecystitis the wall is also thickened but lacks the echo poor halo and there is no local tenderness. The gallbladder fails to empty after a meal or CCK Challenge. Stones are usually present. A mucocele appears as a large, sometimes enormous gallbladder which is non tender and thin walled. The contents are usually echo free, apart from stones, though debris may form.

In general ultrasonography has distinct advantages over conventional oral cholecystography. These include absence of radiation exposure, independent of patient compliance and the lack of requirement for an intact digestive and hepatic system. In addition to identifying stones within the gallbladder or bile duct, abdominal ultrasonography provides important ancillary information regarding the anatomy of bile ducts, pancreas, and other structures in the upper abdomen. The newer techniques of sonography include the endoscopic ultrasonography. It is more sensitive in identifying small gallstones and also common bile duct stone. Endoscopic ultrasonography is useful for detecting small
gallbladder stones missed on transabdominal imaging, especially those located in the neck of the gallbladder, where duodenal gas can obscure the image when scanning percutaneously.

Sensitivity of USG to detect cholelithiasis is 95-99%. They are seen as echogenic foci with accousting shadowing and move with change in posture. This can detected the gallstones of about 1mm in size. The difficulty in USG is its limitation in measuring large gallstones and quantifyying multiple gallstones.

**CT SCAN** (Computed tomography)

This test provides more useful information than USG when there is extrahepatic obstruction avoiding to causes other than choledocholithasis. **ERCP** (Endoscopic Retrograde Cholangio Pancreatography) ERCP is very accurate in the diagnosis of ductal calculi but is less accurate than USG and oral cholecystography in the diagnosis of gallbladder disease and gallstones.

**ORAL CHOLECYSTOGRAPHY:**

Visualization of gallbladder by giving radioopaque dye. This test is useful in patients in whom USG is unsatisfactory. Contrast media is given which is excreted by liver into the bile after its absorption in the intestine. (Contrast media – iodine containing preparation like telepaque or bioptin).

Uses:
Accuracy of gallstone detection is 80-95%, number, size of stones, patency of the cystic duct, ability of the gallbladder wall to concentrate the bile and contraction of the gallbladder wall.

Technique

- Initial control x-ray is taken prior to cholecystography.
- A fatty meal is given to the patient in the previous day.
- 6 tablets of telepaque is are given orally at 9-00 pm. The next day (after 12-16 hours) x-ray of abdomen is taken in erect and supine position. If gallbladder is visualized a fatty meal is given and one hour later another x-ray of the abdomen is taken to see the gallbladder contraction. If gallbladder is not visualized, double dose of the contrast is given.
- Gallstones are seen as filling defects in the form of translucent areas in opaque shade of gallbladder.

**CHOLANGIOGRAPHY:**

When IV route is used the entire biliary tree can be visualized. Biligraffin is the contrast media used (20ml of 20% biligraffin). After doing a sensitivity test, it is used in whom oral cholecystography is unsuccessful. It is also used with oral cholecystography to visualize gallbladder and intra and extra hepatic biliary apparatus.

**PTC**(Percutaneous Trans Hepatic Cholangiography)
It can be done in jaundiced patients. It is done by using chiba needle under fluoroscopy. Clotting time and platelet count should be done before PTC. Antibiotic cover is given before and after the procedure. Vitamin K infection is given if coagulation studies are abnormal. In supine position patient is sedated and under lumbar aspiration (LA) needle inserted in 8th intercostal space (ICS) in mid axillary line. Contrast media injected until it enters the biliary radicle to see intrahepatic pathology and biliary calculus. Complications are haemorrhage and sepsis.

**Liver function tests:**

Alterations in LFT may be due to long standing obstruction of CBD due to gallstone or due to repeated attacks of ascending cholangitis and hepatitis.

It includes –

1. Serum bilirubin
2. Van Den Berg’s reaction
3. Serum alkalinephosphatase
4. SGOT, SGPT
5. Serum proteins
6. Serum albumin
7. PT (prothrombin time)
Investigations other associated pathological states:

- Urine routine
- Random blood sugar, Renal function tests
- Serum cholesterol
- Upper GI endoscopy
- Serum amylase and urinary amylase for pancreatitis.

**DIAGNOSIS:**

Acute cholecystitis should be suspected in a patient presenting with right upper quadrant or epigastric pain, fever, and a leukocytosis. A positive Murphy's sign supports the diagnosis [18]. However, history, physical examination, and laboratory test findings are not sufficient to establish the diagnosis. Confirmation of the diagnosis requires demonstration of gallbladder wall thickening or edema, a sonographic Murphy's sign, or failure of the gallbladder to fill during cholecintigraphy. In most cases, the diagnosis can be confirmed with an abdominal ultrasound.
Figure 10 - Algorithm for diagnosis of acute cholecystitis

CRITERIA FOR THE SEVERITY ASSESSMENT OF ACUTE CHOLECYSTITIS

Acute cholecystitis has a better outcome/prognosis than acute cholangitis but requires prompt treatment if gangrenous cholecystitis, emphysematous cholecystitis, or torsion of the gallbladder are present. The progression of acute cholecystitis from the mild/moderate to the severe form means the development of the multiple organ dysfunction syndrome (MODS). Organ dysfunction scores, such as Marshall’s multiple organ dysfunction (MOD) score, and the sequential organ failure
assess-ment (SOFA) score, are sometimes used to evaluate organ dysfunction in critically ill patients. The Guidelines classify the severity of acute cholecystitis into three grades (Tables 3–5): “severe (grade III)”: acute cholecystitis associated with organ dysfunction, “moderate (grade II)”: acute cholecystitis associated with difficulty to perform cholecystectomy due to local inflammation, and “mild (grade I)”: acute cholecystitis which does not meet the criteria of “severe” or “moderate” acute cholecystitis (these patients have acute cholecystitis but no

**CRITERIA FOR MILD (GRADE 1) ACUTE CHOLECYSTITIS**

“Mild (grade I)” acute cholecystitis does not meet the criteria of “severe (grade III)” or “moderate (grade II)” acute cholecystitis. Grade I can also be defined as acute cholecystitis in a healthy patient with no organ dysfunction and only mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure.

**CRITERIA FOR MODERATE (GRADE 2) ACUTE CHOLECYSTITIS**

“Moderate” acute cholecystitis is accompanied by any one of the following conditions:
1. Elevated WBC count (>18 000/mm³)

2. Palpable tender mass in the right upper abdominal quadrant

3. Duration of complaints >72 h

4. Marked local inflammation (biliary peritonitis, pericholecystic abscess, hepatic abscess, gangrenous cholecystitis, emphysematous cholecystitis)

**CRITERIA FOR SEVERE (GRADE 3) ACUTE CHOLECYSTITIS**

“Severe” acute cholecystitis is accompanied by dysfunctions in any one of the following organs/systems

1. Cardiovascular dysfunction (hypotension requiring treatment with dopamine 5 μg/kg per min, or any dose of dobutamine)

2. Neurological dysfunction (decreased level of consciousness)

3. Respiratory dysfunction (PaO₂/FiO₂ ratio <300)

4. Renal dysfunction (oliguria, creatinine >2.0 mg/dl)

5. Hepatic dysfunction (PT-INR >1.5)

6. Hematological dysfunction (platelet count <100 000/mm³)
TREATMENT

There are various treatments available for treatment of gallstones but cholecystectomy still remains the gold standard.

NON INVASIVE TREATMENT OF GALLSTONES

1. Oral dissolution therapy
2. Extracorporeal shock wave lithotripsy. (ESWL)

INVASIVE PROCEDURE

1. Open cholecystectomy

MINIMALLY INVASIVE GALLBLADDER PROCEDURE

1. Percutaneous cholecystostomy
2. Contact dissolution therapy
3. Percutaneous cholecystolithotomy
4. Laparoscopic cholecystectomy
OPEN CHOLECYSTECTOMY

It can be performed either of two different approaches:

a) Retrograde b) Anterograde

Incisions: A right subcostal (Kocher) incision is the most often used incision. Alternatively, an upper midline incision can be used when other concomitant operations are planned and a wider exposure is needed. A right paramedian incision is another option.

Right Subcostal (Kocher) Incision:

The subcostal incision approximately 1cm to the left of the linea alba, about 2 fingerbreadths below the costal margin (approximately 4 cm). Extend the incision laterally for 10 cm. Incise the anterior rectus sheath along the length of the incision, and divide the rectus and lateral muscle (external oblique, internal oblique, and transversus abdominis) using electrocautery. Then incise the posterior rectus sheath and peritoneum and enter the abdomen. The gallbladder is retracted, allowing dissection of the cystic duct and artery. The cystic artery and duct are clipped and cut.

Dissection:

Grasp the dome of the gallbladder with a Kelly clamp and elevate it superiorly. Adhesions to the undersurface of the gallbladder from the transverse colon or duodenum are typically encountered; these can be lysed with sharp dissection or judicious use of electrocautery. Dissection
of the gallbladder can be performed in two ways: Fundus first or Duct first. Traditionally, dissection in open cholecystectomy is performed by duct first method.

In the anterograde approach, attention is initially directed to the porta hepatis. Grasp the fundus of the gallbladder and elevate it superiorly while the neck of the gallbladder is mobilized away from the liver laterally to expose the triangle of Calot. Dissect the cystic artery and cystic duct with careful attention to the potential for anatomical variations. Dissect the cystic duct and cystic artery completely till they are clearly identified entering directly into the gallbladder (the so called critical view popularized by Strasberg).

Cholecystectomy (Open) Cystic duct is tied close to the gallbladder with a 2-0 silk. Before division of the cystic duct, "milk" the duct from proximal to distal to deliver stones that reside in the cystic duct into the gallbladder lumen. When the cystic duct and artery are correctly identified and completely dissected, they are ligated. Nonabsorbable sutures are acceptable for use on the cystic duct stump; however, they are not recommended. Absorbable sutures, are used for ligation of the cystic duct. If the cystic duct is large and inflamed, mechanical staplers may be used. The cystic artery can be ligated with ties (absorbable or nonabsorbable), suture ligature, or clips. Following divisions of the cystic artery and duct, dissect the gallbladder away from the liver bed. The
dissection plane is typically avascular, with only small cholecystic veins that need to be divided. If significant bleeding occurs, the dissection has likely been too deep entering the liver parenchyma.

Complications:

Bleeding and infection - Inherent to any surgical procedure.

Biliary complications:

Complications related to the biliary system include bile leaks and common bile duct injuries, which can result in biliary strictures.

Figure 11 - Laparoscopic and open cholecystectomy
LAPAROSCOPIC CHOLECYSTECTOMY

A supra/infra umbilical midline incision was made and carried down to the fascia which was divided exposing the peritoneal cavity. ‘0’ vicryl sutures were used to place two stay sutures into the midline fascia. An open/closed technique was used to enter the peritoneal cavity with a Hassan/Verres needle and used to establish our pneumoperitoneum. The laparoscope was inserted into the abdomen under direct vision. Subsequently the following ports were inserted under direct visualization in the typical fashion: a 10/12 mm epigastric port and two 5 mm ports along the right costal margin. The peritoneal cavity was inspected and no abnormalities were found. The patient was placed in reverse Trendelenburg position with the right side up. Omental attachments to the gallbladder were gently swept away until an atraumatic grasper could be used to retract the fundus of the gallbladder superiorly over the dome of the liver. Filmy adhesions between the gallbladder and omentum or duodenum were also lysed sharply. The infundibulum was identified and subsequently retracted laterally towards the right lower quadrant using another grasper. This maneuver exposed Calot’s triangle. The peritoneum overlying the gallbladder infundibulum was incised with electrocautery anteriorly. Then the posterior peritoneum was dissected. The triangle was dissected to expose: 1) the cystic duct LN 2) cystic artery 3) cystic plate 4) cystic duct. Once these structures were carefully identified, the cystic
artery was divided first. Then further dissection of the triangle was completed.

**Figure 12 - Calot's triangle as seen in Laparoscopic cholecystectomy**

Once it was determined that the only structure remaining, entering the gall bladder was the cystic duct, it was doubly clipped and divided. The electrocautery was then used to separate the peritoneal attachments between the gallbladder and its bed in the liver. The gallbladder fossa and cystic artery were inspected to ensure no bleeding. Hemostasis was achieved with electrocautery. There was no leakage of bile from the cystic duct stump. The gallbladder, once freed easily removed from the abdomen through the epigastric port. The specimen was sent to pathology. The fascia at the supra-umbilical and epigastric ports were re-approximated using the 1-0 or 0’ (vicryl/biosyn) sutures in a figure-of-eight fashion. All incisions were closed using 4-0 (vicryl/biosyn) sutures in an (interrupted/continuous) subcuticular fashion. The operative field was cleaned and dried. Steri-strips/dressings were applied
Figure 13a: Laparoscopic cholecystectomy - Ports position

Figure 13b: Laparoscopic cholecystectomy - Steps
BIOCHEMICAL ANALYSIS:

The various physical parameters of stones such as number, shape, size, texture and cross-section were noted. The stones were powdered in a pestle and mortar and dissolved in different solvents depending upon the type of chemical constituent to be analyzed. To determine total cholesterol and total bilirubin, 30mg stone powder was dissolved in 3 ml chloroform in a test tube. The tube was kept in boiling water bath for 2 min. The stone solution thus obtained was used for determination of total cholesterol and total bilirubin. To determine calcium, oxalate, inorganic phosphate, magnesium, chloride, soluble protein, triglycerides, iron, copper, sodium and potassium, 30 mg stone powder was dissolved in 3 ml IN HCl in graduated 10 ml tube and its final volume was made up to 10 ml with distilled water. The tube was kept in boiling water bath for 1 hr. To analyze phospholipids, stone powder (20 mg) was dissolved in 15 ml CHCl₃+CH₃OH in 2:1 ratio, containing 1N HCl. To measure bile acids and fatty acids, the stones were dissolved in chloroform-methanol (2:1) mixture and ethyl alcohol-solvent ether in (3:1 mixture) respectively. Total cholesterol by enzymic colorimetric method (9), total bilirubin by colorimetric method , triglycerides by enzymic colorimetric method , soluble protein by colorimetric method of Lowry et al, oxalate as described by Satyapal and Pundir based on enzymic colorimetric method , calcium by OCPC kit method , phospholipid & inorganic
phosphate by colorimetric method, magnesium by colorimetric method, chloride by colorimetric method, iron & copper by Atomic Absorption Spectrophotometer sodium & potassium by Flame photometer, fatty acids by colorimetric method of Stern and Shapiro and bile acids by colorimetric method of Carey were estimated. The dissolved stone solutions were stored at 2-8°C, when not in use.
METHODOLOGY

About 50 consecutive cases were admitted, examined, investigated and diagnosed as calculous cholecystitis during the period of January 2016 to September 2016 are selected and detailed history of all the 50 cases were taken according to the proforma. Information regarding the age, nature of the symptoms, duration of the symptoms, diet history, history of ocp intake, Alcohol ingestion, diabetes were obtained. All patients undergone detailed examination, underwent investigations had haemogram, ECG, LFT, blood sugar, blood urea, serum creatinine, urine analysis, blood group, chest X-ray, ultrasound scan of the abdomen. Specialty consultations were taken for patients with associated medical illness and their control was achieved.

Risk and complications of the condition as well as surgery has been explained to the patients, concerned was taken. After cholecystectomy gallstones were analysed biochemically and correlation to severity of disease were assessed.

DURATION OF STUDY

9 months (Jan 2016 to Sep 2016)

PLACE OF STUDY

Department of General Surgery in Government Royapettah Hospital and Kilpauk Medical College hospital.
TYPE OF STUDY

Prospective study

SAMPLE SIZE

50 patients

SOURCE OF STUDY:

All patients with calculous cholecystitis who attend GRH during the study period.

INCLUSION CRITERIA:

1) All patients with calculous cholecystitis undergoing cholecystectomy in Government Royapettah Hospital
OBSERVATION AND RESULTS

In this study, 50 patients with cholelithiasis admitted in GRH, Chennai attached to Kilpauk Medical College, between January 2016 and September 2016 were included. Well known available literature on Cholelithiasis is reviewed. The results of our study are compared with those of well-known authors. After a detailed history, clinical investigations and treatment, following observations were noted.

1. AGE AND GENDER DISTRIBUTION:

Table 1 –Age and Gender Distribution Of Cholelithiasis

<table>
<thead>
<tr>
<th>AGE IN YEARS</th>
<th>GENDER</th>
<th>Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>21-30</td>
<td>3</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>31-40</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>41-50</td>
<td>6</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>51-60</td>
<td>3</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>&gt;60</td>
<td>1</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>
All cases fall between 22 and 75 years. There is an increased incidence in the 5th and 6th decade with the maximum incidence in the 5th decade.
2. PRESENTING SYMPTOMS:

Table 2 - Presenting symptoms of cholelithiasis

<table>
<thead>
<tr>
<th></th>
<th>Pain abdomen</th>
<th>Fever</th>
<th>Nausea/ Vomiting</th>
<th>Dyspepsia</th>
<th>Jaundice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>49</td>
<td>17</td>
<td>7</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>%</td>
<td>98</td>
<td>34</td>
<td>14</td>
<td>24</td>
<td>14</td>
</tr>
</tbody>
</table>

Figure 15 - Presenting symptoms of cholelithiasis

Pain abdomen was the most common presenting symptom in our study seen in 49 (98%) of the cases followed by fever in 17 (34%) cases. Dyspepsia was seen in 12 (24%) cases, 7 cases (14%) each presented with nausea/vomiting or jaundice.
3. SIGNS OF CHOLELITHIASIS

Table 3- Presenting signs of cholelithiasis

<table>
<thead>
<tr>
<th>Signs</th>
<th>No. of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenderness</td>
<td>45</td>
<td>90</td>
</tr>
<tr>
<td>Guarding</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Mass</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

Among the presenting signs seen in our study, tenderness was the most common sign seen in 45 cases (90%) followed by guarding in 10 cases (20%) and mass palpable in 5 cases (10%)
4. ULTRASONOGRAM FINDINGS

Table 4- Ultrasonogram findings of cholelithiasis

<table>
<thead>
<tr>
<th>Findings on ultrasonogram</th>
<th>No. of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stones in gall bladder</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Solitary Stone</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Multiple stones</td>
<td>38</td>
<td>76</td>
</tr>
<tr>
<td>Thickening of Gallbladder</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>Mass</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

Among the ultrasonographic findings of cholelithiasis most common finding was thickened gall bladder wall seen in 40 cases (80%). Ultrasonogram revealed 76% (38 cases) had multiple stones and 24% (12) has solitary stone. Mass was seen in 5 cases (10%).
5. TYPE OF CHOLECYSTECTOMY

Table 5- Type of cholecystectomy

<table>
<thead>
<tr>
<th>Type of operation</th>
<th>No. of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopic Cholecystectomy</td>
<td>43</td>
<td>86</td>
</tr>
<tr>
<td>Open Cholecystectomy</td>
<td>7</td>
<td>14</td>
</tr>
</tbody>
</table>

Figure 18 - Type of cholecystectomy

Out of the total 50 cases who underwent cholecystectomy 43 (86%) underwent laparoscopic cholecystectomy and rest 7 cases (14%) underwent open cholecystectomy
6. GALLSTONES IN CHOLELITHIASIS

Table 6- Type of gallstones in cholelithiasis

<table>
<thead>
<tr>
<th>Age</th>
<th>Cases</th>
<th>Cholesterol Stones</th>
<th>Pigment Stones</th>
<th>Mixed Stones</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-30</td>
<td>8</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>31-40</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>41-50</td>
<td>16</td>
<td>1</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>51-60</td>
<td>12</td>
<td>1</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>&gt;60</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>50</td>
<td>4</td>
<td>8</td>
<td>38</td>
</tr>
</tbody>
</table>

Figure 19- Type of gallstones in cholelithiasis

Of the total 50 cases with cholelithiasis 38 patients (76%) had mixed stones, followed by pigment stones in 8 cases (16%) followed by cholesterol stones in remaining 4 cases (8%).

Majority of the patients were in the age group 41-50 (32%) followed by the 51-60 age group (24%).
7. GALLSTONE AND SEVERITY OF CHOLECYSTITIS

Table 7: Correlation between type of gallstone and severity of cholecystitis

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol Stones</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mixed stones</td>
<td>29</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Pigment stones</td>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 20 - Correlation between type of gallstone and severity of cholecystitis

Of the total 50 cases with cholelithiasis 38 patients (76%) had mixed stones, followed by pigment stones in 8 cases (16%) followed by cholesterol stones in remaining 4 cases (8%). Majority of the patients were in the age group 41-50 (32%) followed by the 51-60 age group (24%).

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8. GALLSTONE AND SEVERITY OF CHOLECYSTITIS  
(CHI SQUARE TEST)

Table 8: Correlation between type of gallstone and severity of cholecystitis (CHI SQUARE TEST)

<table>
<thead>
<tr>
<th></th>
<th>Grade</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stones</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>Row Total</td>
</tr>
<tr>
<td>Cholesterol</td>
<td></td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>expected</td>
<td></td>
<td>3.120</td>
<td>.800</td>
<td>.080</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td></td>
<td>29</td>
<td>8</td>
<td>1</td>
<td>38</td>
</tr>
<tr>
<td>expected</td>
<td></td>
<td>29.640</td>
<td>7.600</td>
<td>.760</td>
<td></td>
</tr>
<tr>
<td>Pigment</td>
<td></td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>expected</td>
<td></td>
<td>6.240</td>
<td>1.600</td>
<td>.160</td>
<td></td>
</tr>
<tr>
<td>Columns Total</td>
<td></td>
<td>39</td>
<td>10</td>
<td>1</td>
<td>50</td>
</tr>
</tbody>
</table>

Chi square = 0.723  
P = 0.948

In our study we have found there is NO CORRELATION between the type of gall stones and severity of cholelithiasis by CHI SQUARE test.
DISCUSSION

In this study, 50 patients with cholelithiasis admitted in GRH, Chennai attached to Kilpauk Medical College, between January 2016 and September 2016 were included. The available literature on Cholelithiasis is reviewed and the results of our study are compared with those of well-known authors. After a detailed history, clinical investigations and treatment, following observations were noted.

Patients fall between 22 and 75 years. There is an increased incidence in the fifth and sixth decade with the maximum incidence in the 5th decade. Similar incidence is seen in the studies of Herman et al (fifth decade). Hanif series showed peak incidence in fifth decade. In western studies the peak incidence is in the fifth and sixth decades. Similar findings are noted in the studies of [89] Ganey et al and Moreaux et al.

In the present study 35 out of 50 cases were female while the rest were male.[91] Battacharya series showed 71.4% were female, 28.6% were male. Similar sex preponderance in the favour of females were noted by [92] Tamhankar AP, Ganey et al and Major Alok Sharma et al series showed that 70% were male and 30% were female.[93]

Pain was the predominant symptom in the present study with 98% incidence. The commonest site of pain was in the right hypochondrium, and the next commonest site was epigastrium. Similar presentations were noted in the series of Alok Sharma, Ganey series, Goswitz et al. series.
14% (7 patients) of cases in the present series had nausea/vomiting. Patients with vomiting in this study was similar to Ganey et al. series. In the present study 7 patients had jaundice. 24% (12 patients) of patients had dyspepsia. The endoscopic examination in these patients did not reveal any pathology. On ultrasound examination, these patients had gall stones.

The dyspepsia was relieved in these patients after cholecystectomy. The incidence of dyspepsia in present series was similar to Ganey series, Alok Sharma series. Fever was present in 17 cases in the present study. Tenderness in the Right Hypochondriam was present in 45 patients guarding was present in 10 patients. A positive Murphy’s sign was present in 7 patients. A mass was felt in five patients.

All the patients had undergone hematological and biochemical investigations. The hemoglobin of patients ranged from 8 to 15 gm%. Ultrasound scanning was done in all patients. Out of the 50 patients 12 had solitary stones, 38 were multiple, thickening of gall bladder was seen in 40 patients, mass detected in 5 patients. Many of the features in my study were similar to studies of Major Alok Sharma et al.

In the present study 7 patients had undergone open cholecystectomy and 43 patients had undergone Laparoscopic cholecystectomy. The most common incision used in open
cholecystectomy was right subcostal incision, which was used in 5 patients, 2 patients were operated through midline incision.

In the present study 76% had mixed stones and 8% had cholesterol stones, 16% had pigment stones, which is similar to the studies of Mathur SN et al.

Most of the gallstones patients were associated with grade 1 cholecystitis (78%), Grade 2 cholecystitis was seen in 20% of our study patients, Grade 3 was seen in 2% of our study patients.

In grade 1 cholecystitis 74.35 % patients were found to have mixed stones, 17.9% patients found to have pigment stones, 7.69 % patients found to have cholesterol stones. In grade 2 cholecystitis 80% patients were found to have mixed stones, 10% patients found to have pigment stones, 10 % patients found to have cholesterol stones. In grade 3 cholecystitis 100 % patients were found to have mixed stones.
SUMMARY

The study consists of only 50 cases of cholelithiasis therefore there may be some variations in the statistics as number of my cases is small for full statistical evaluation.

1. The highest age incidence of cholelithiasis was in 5th and 6th decade with maximum incidence in the 5th decade. There was an increased incidence in female.

2. Pain was the most common symptom present in 98% of the patients, fever was the second most common symptom presenting in 34% of patients, dyspepsia was present in 24% of patients, jaundice in 14% of the patients, 14% of patients had nausea/vomiting.

3. Tenderness in the right hypochondrium was the most common sign present in 96%, guarding was the next sign present in 20% of the patients and mass abdomen in 10% of the patients.

4. Ultrasonography was the investigation of choice in our hospital. All patients had gallstones, 24% solitary stone, 76% multiple stones, thickening of gall bladder is seen in 80% cases.

5. 86% of patients undergone laparoscopy cholecystectomy, 14% of patients undergone open cholecystectomy. Right subcostal incision
was the most common incision used in open cholecystectomy in our study

6. Gallstones analysis showed mixed stone in 76% of the cases and pigment stones in 16% of the cases, cholesterol stones in 2% of cases.

7. Most of the gallstones were associated with grade 1 cholecystitis (78%), Grade 2 cholecystitis was seen in 20% of our study patients, Grade 3 was seen in 2% of our study patients.

8. In grade 1 cholecystitis 74.35% patients were found to have mixed stones, 17.9% patients found to have pigment stones, 7.69% patients found to have cholesterol stones. In grade 2 cholecystitis 80% patients were found to have mixed stones, 10% patients found to have pigment stones, 10% patients found to have cholesterol stones. In grade 3 cholecystitis 100% patients were found to have mixed stones.

9. In our study we have found there is no correlation between the type of gallstones and severity of cholelithiasis by CHI SQUARE test.
CONCLUSION

1. The incidence of gallstones was high in 5th and 6th decades of life, with maximum incidence in the 5th decade. Gallstone disease is more common in females.

2. The commonest symptom was pain abdomen and the commonest sign was tenderness in the right hypochondrium. Ultrasonography was the investigation of choice. It showed multiple gallstones and thickening of the gallbladder in majority of the patients.

3. Subcostal incision was the most common incision used for open cholecystectomy.

4. Majority of patients underwent Laparoscopic cholecystectomy (86%) with reduced number of stay in the hospital, pain and disability as compared to open cholecystectomy.

5. The commonest type of stone was mixed stone.

6. Most of the gallstones were associated with grade 1 cholecystitis (78%), Grade 2 cholecystitis was seen in 20% of our study patients, Grade 3 was seen in 2% of our study patients.

7. In our study, there is NO CORRELATION between the type of gallstones and severity of cholelithiasis by CHI SQUARE test.

8. In grade 1 cholecystitis 74.35% patients were found to have mixed stones, 17.9% patients found to have pigment stones, 7.69% patients found to have cholesterol stones. In grade 2 cholecystitis
80% patients were found to have mixed stones, 10% patients found to have pigment stones, 10% patients found to have cholesterol stones. In grade 3 cholecystitis 100% patients were found to have mixed stones.