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Is the Gallbladder Really Unnecessary?
An Evaluation of Gallstone Treatment

DANIELLE WEINBERG

INTRODUCTION

The red numbers on your alarm read two o'clock AM, but you're wide awake. A dull ache below your ribs has tossed you from the blissful ignorance of sleep into the painful reality of another nocturnal attack. As the pale streaks of daylight appear, you grit your teeth in agony while the ambulance goes over yet another bump in its rush to get you to the emergency room. A blur of white coats, lab tests, and CT scans, and then you're staring into the bright lights above the operating table as the nurses prepare you for emergency gallbladder surgery. "Does it have to be this way?" you wonder, "Is there no other option?" The purpose of this paper is to answer just such a question. After clarifying gallbladder anatomy and the etiology of gallstone disease, it will evaluate surgical and nonsurgical options for the treatment of gallstones. In the course of the discussion, it will examine the mechanism of action, efficacy, and safety of each treatment option. Once the analysis is complete, it will be possible to conclude if there are nonsurgical therapies that may be preferred over surgical removal of the gallbladder for relief of gallstone disease.

Gallbladder Anatomy And Physiology

The gallbladder is a pear-shaped organ that can be found underneath the right lobe of the liver. Its function is to store the bile secreted by the liver and then, in turn, secrete this bile into the small intestine to aid in digestion of fats. Bile is composed of over 95% water with bile acids, phospholipids, cholesterol, bile pigments, and bicarbonate ions dissolved within (Portincasa et al, 2009). The general physiological purpose of bile acids is to emulsify dietary fats in the small intestine, thus aiding in the digestion process. This paper, though, will focus on the role of bile acids and phospholipids in solubilizing cholesterol in bile. While cholesterol is the building block of bile acids, it is also secreted unchanged into bile in order to maintain cholesterol homeostasis in the blood. The synthesis of bile acids and the danger of excessive amounts of cholesterol will be discussed in subsequent sections. Bile pigments are composed
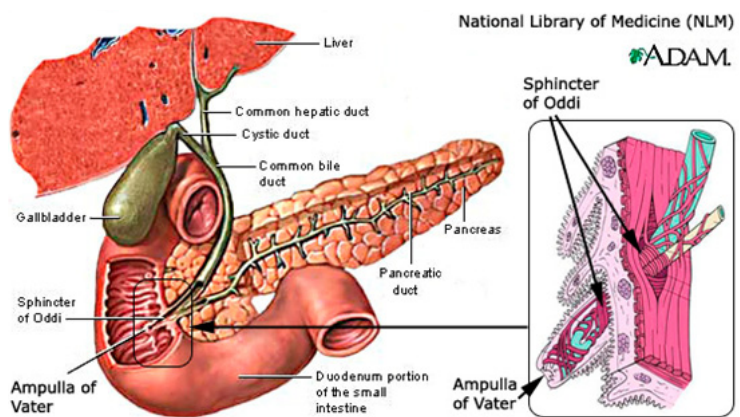

Figure. 1 Gallbladder anatomy

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primarily of bilirubin, which is a breakdown product of hemoglobin. By secreting bilirubin into bile, the liver ensures that toxic levels do not build up in the body and are instead eliminated in the feces. Finally, bicarbonate ions are secreted by the pancreas into the bile to neutralize the acid entering the small intestine from the stomach (Widmaier et al, 2008).

While the liver is always in the process of secreting bile, not all this bile travels directly to the small intestine. At the point where the common bile duct joins the pancreatic duct and empties into the duodenum, a ring of smooth muscle surrounds the duct and prevents the release of bile. As long as this ring of muscle, the sphincter of Oddi, remains contracted, bile secreted from the liver is shunted into the gallbladder for storage. In the gallbladder, the dilute hepatic bile is concentrated many times over as salts and water are reabsorbed into the blood. Bile secretion from the gallbladder is controlled by a hormone called cholecystokinin, or CCK. After a fatty meal, the presence of fatty acids and amino acids in the small intestine stimulate the release of CCK into the blood. From there, the hormone travels to the gallbladder to stimulate its contraction, and to the sphincter of Oddi to stimulate its relaxation. This dual action allows the gallbladder to release its store of bile into the cystic duct, and the bile continues through the common bile duct and sphincter of Oddi to its final destination in the duodenum (Widmaier et al, 2008). It is only when problems arise in this chain of events that normal physiology is interrupted and gallstone disease develops.

Bile Acid Synthesis And Metabolism

In order to understand the ensuing discussion of gallstone pathogenesis, a preliminary discussion of bile acid chemistry is necessary. Bile acid synthesis is the primary method by which cholesterol is catabolized, or broken down. However, bile acids are not simply metabolites of an organic substance. They have their own unique roles—numerous functions which scientists are continuously clarifying and expanding. The fascinating phenomenon of bile acid synthesis converts a completely hydrophobic molecule into an amphiphile which can solubilize and transport nutrients, fats, and vitamins while also functioning as a powerful receptor ligand in various signaling pathways. The process of synthesizing bile acids from cholesterol is a multistep sequence catalyzed by a host of different enzymes. The liver is the only organ in the body that boasts all fourteen enzymes required for this de novo synthesis of bile acids (Chiang, 2009).

The first step in the classic pathway of bile acid synthesis is to add a hydroxyl group to position 7 of the cholesterol steroid nucleus. This reaction is catalyzed by the rate limiting enzyme, cholesterol 7α-hydroxylase, abbreviated CYP7A1. At this point, the pathway diverges to form the two most common human bile acids, cholic acid (CA) and chenodeoxycholic acid (CDCA). To create the former, sterol 12α-hydroxylase (CYP8B1) is employed to add a hydroxyl group to position 8 of the steroid nucleus. The precursors of CDCA do not need an additional hydroxylation and proceed to the next step in the sequence. Once the cholesterol double bond is reduced by enzymes in the cytosol of the hepatocyte, mitochondrial sterol 27-hydroxylase (CYP27A1) can add a hydroxyl group to position 27 of the cholesterol side chain. This alcohol is then further oxidized to an aldehyde, and finally to a carboxylic acid, whereupon it is transported to the peroxisomes of the hepatocytes for
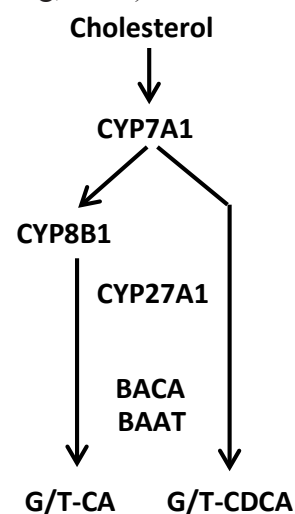
Figure 2. Bile acid synthesis (see text for explanation). (Adapted from Chiang, 2009)

side chain shortening. In the peroxisomes, a three carbon unit is cleaved from the original side chain to form the C-24 bile acid from the C-27 cholesterol molecule. The basic backbone of the bile acids has thus been created, but most are conjugated to hydrophilic side chains derived from amino acids to increase their solubility in bile. Glycine and taurine (derived from the amino acid cysteine) are conjugated to the carboxylic acid side chain of the bile acids by means of their amino groups. The enzymes BACA (bile acid-CoA synthase) and BAAT (bile acid-amino acid transferase) facilitate this process and create the glyco- or tauro-conjugated CA or CDCA (Monte et al, 2009).

An interesting point is that this developed synthesis pathway is only employed for 5% of the bile acids that are secreted into bile (Portincasa et al, 2009). This is due to the recycling effect known as enterohepatic circulation. The bile acids synthesized by the liver are termed primary bile acids and are further modified by intestinal bacteria to their secondary bile acid counterparts. Both primary and secondary bile acids are then actively absorbed in the distal ileum, the last part of the small intestine. A transport protein coupled to sodium reabsorption transports the bile acids across the epithelial cells lining the intestine to the hepatic portal vein (Chiang, 2009). Upon reaching the liver, bile acids are taken up by hepatocytes where they prevent further bile acid synthesis by inhibiting the rate limiting enzyme CYP7A1 (Monte et al, 2009). These recycled bile acids are then used again in the secretion of bile. While some bile acids are inevitably lost in the feces, over 95% are recovered via enterohepatic circulation, accounting for the minimal de novo synthesis of bile acids in the liver.

Figure 3. Chemical structures of cholesterol and the primary bile acids

Gallstone Pathogenesis

Gallstone disease is one of the most common and most costly digestive diseases affecting Western industrialized countries. In a large epidemiologic study, the third National Health and Nutritional Examination Survey (NHANES III) found that the overall prevalence of gallstones was 7.9% in men and 16.6% in women in the United States. The disease was more dominant among Native Americans than other ethnic groups, indicating that genetics may play a role. Incidence of gallstones was comparable in European countries but much lower among Asians and Africans (Paumgartner and Greenberger, 2009). With over one million new cases of gallstones being discovered every year, scientists continue to research the contributing factors of gallstone disease in the hopes of preventing future diagnoses (Portincasa et al, 2009).

All arrows seem to point to cholesterol as the primary culprit of gallstone disease, or cholelithiasis. Radiographic scans have enabled doctors and scientists alike to characterize 80% of diagnosed gallstones as cholesterol stones. The pathogenic mechanisms that contribute to the formation of gallstones, then, must be connected to cholesterol metabolism. Indeed, the hydrophobic cholesterol molecule is not soluble in bile and must be maintained in proper proportion with the other components of bile (namely, bile acids and phospholipids) in order to remain in solution (Portincasa et al, 2009).

Bile acids have been shown to be amphiphiles, that is, they are detergent-like molecules with both lipophilic and hydrophilic properties. As mentioned, the ringed steroid nucleus forms
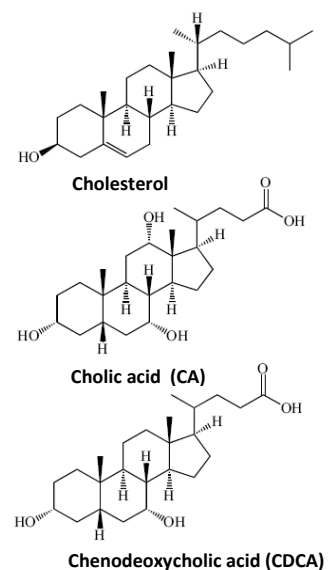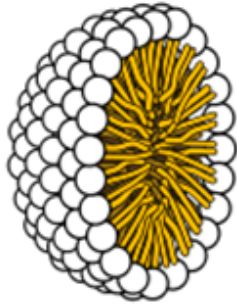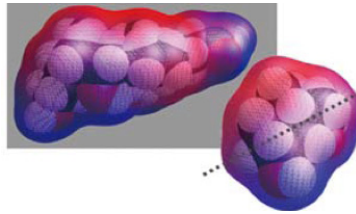
Figure 4. Micelle

Figure 5. Space filling model of cholic acid showing hydrophobic face(red) and hydrophilic face(blue). (Portincasa et al, 2009)
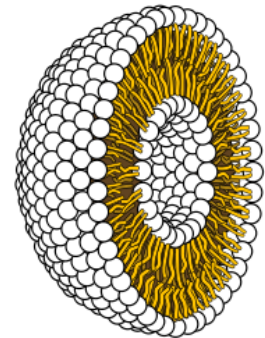

Figure 6. Vesicle

the lipophilic face of the molecule while the hydroxyl groups and conjugated side chain create a hydrophilic face. If the levels of bile acids exceed a certain value, termed the critical micelle concentration (CMC), they will self-assemble into simple micelles. These structures are sphere-like shapes consisting of a monolayer of bile acids surrounding cholesterol molecules sequestered within. The hydrophobic face of the bile acids faces inwards towards the lipophilic cholesterol, while the hydrophilic face is oriented outwards facing the aqueous medium of bile (Portincasa et al, 2009).

Phospholipids are another kind of amphiphile composed of long chain fatty acids bound to glycerol and polar phosphate groups on one end. They form a phospholipid bilayer that surrounds cholesterol molecules in unilamellar vesicles. These vesicles are unstable, but with the addition of bile acids, will form water soluble "mixed micelles" that can solubilize triple the amount of cholesterol that simple micelles solubilize (Portincasa et al, 2009). Thus, if all the biliary components are in proper proportion, cholesterol will remain in solution and no disease will occur.

Figure 7. Gallstone pathogenesis (Paumgartner and Greenberger, 2009)

The problem arises when bile is supersaturated with cholesterol so that the cholesterol exceeds the solubilizing capacity of bile acids and phospholipids. This can occur due to excess cholesterol or insufficient amounts of bile acids or phospholipids. Whatever the reason, if all the unilamellar vesicles cannot be converted into the more stable mixed micelles, unstable cholesterol-rich vesicles remain in the bile. These vesicles are in a state of delicate equilibrium and can easily aggregate to form large multilamellar vesicles. The multilamellar vesicles are even less stable than their counterparts and cannot prevent the cholesterol molecules they hold from precipitating and forming cholesterol crystals (Paumgartner and Greenberger, 2009). Cholesterol crystals have traditionally been described as rhomboid monohydrate crystals with a notch missing from one corner. Recent studies have shown that in the early stages of crystal formation, cholesterol may form anhydrous crystals shaped like needles, spirals, or tubules (Dowling, 2000). Cholesterol crystals that get stuck in a mucin gel lining the gallbladder will aggregate, giving rise to mature gallstones (Paumgartner and Greenberger, 2009).

Different proteins have been identified as being responsible for transporting each specific element of bile from the interior of the hepatocyte to the bile canaliculus. These proteins are part
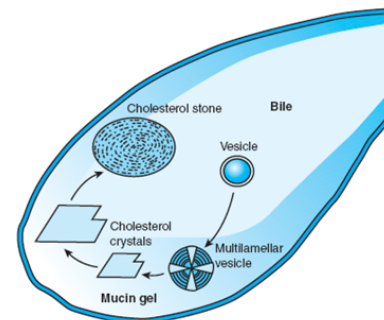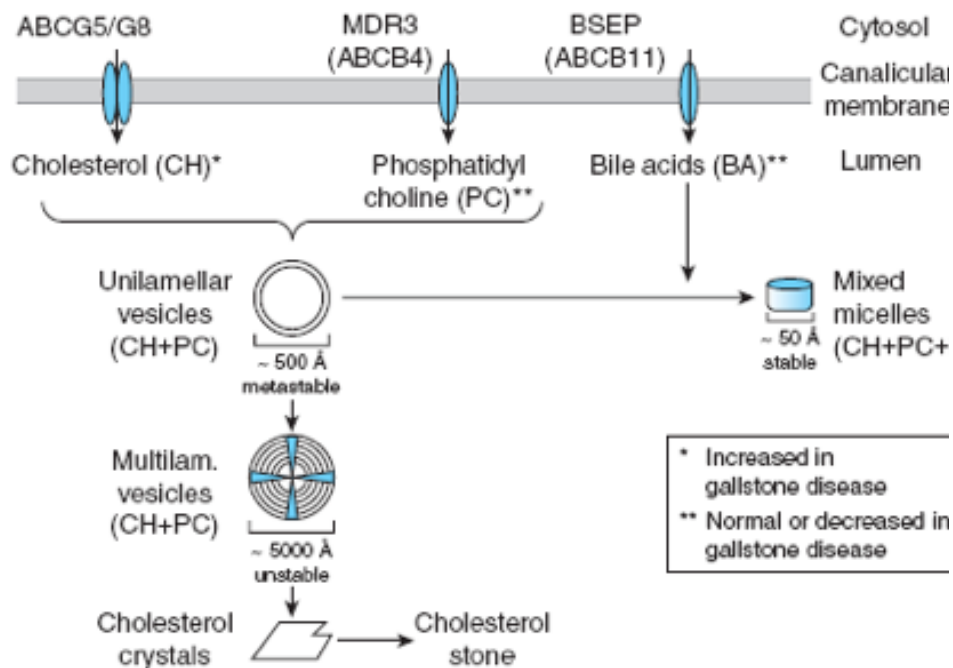
Figure 8. Biliary transport proteins and gallstone pathogenesis.
(Paumgartner and Greenberger, 2009)

of a superfamily of transport proteins called ATP-binding cassette transporters (ABC transporters) that use the energy from ATP hydrolysis for translocation of various substances across a biological membrane. Cholesterol secretion into bile is controlled by ABCG5/G8, while the bile salt export pump (BSEP; ABCB11) regulates the secretion of bile acids. Multidrug resistant p-glycoprotein 3 (MDR3;ABCB4) transports phosphatidylcholine, the primary phospholipid in bile, from the inner leaflet to the outer leaflet of the canalicular membrane. Emerging studies reveal that a genetic defect in the cholesterol transporter, ABCG5/G8, predisposes its carrier to gallstones (Paumgartner and Greenberger, 2009). Additionally, one team identified a mutation in the gene encoding the ABCB4 transporter protein (Wang et al, 2009). This mutation results in decreased phospholipid levels in bile and has been named "gallbladder disease 1" (GBD1). Other risk factors of gallstone disease include obesity, where excessive amounts of cholesterol supersaturate the bile, and pregnancy, where increased estrogen levels also result in elevated levels of cholesterol in bile (Paumgartner and Greenberger, 2009).

One final factor implicated in the pathogenesis of gallstones is impaired gallbladder emptying. The sequence outlined above that accounts for the formation of gallstones from cholesterol-rich unilamellar vesicles cannot occur if these vesicles and the cholesterol crystals they produce are expelled from the gallbladder in a timely fashion. Normally, the time required for gallstones to develop from supersaturated bile is longer than the amount of time the bile sits in the gallbladder! However, if the contractility of the gallbladder is diminished in a condition known as gallbladder stasis, then prolonged retention of supersaturated bile allows gallstones to grow. This condition is associated with fasting and parenteral nutrition, where there are no nutrients in the intestine to stimulate the release of CCK, which will, in turn, stimulate the gallbladder to contract. Additionally, increased levels of progesterone during pregnancy inhibit smooth muscle contraction, as do certain drugs, thereby impairing gallbladder emptying (Paumgartner and Greenberger, 2009). Later sections will discuss options that have been proposed to increase gallbladder contractility, and thus prevent the formation of gallstones.

To Treat Or Not To Treat?

Most patients that are diagnosed with gallstones do not require any immediate treatment (Lanzini et al, 1994). Since many gallstones are found during imaging studies done for other gastrointestinal conditions, and the patients are otherwise unaware of their gallstones, these gallstones are considered asymptomatic (Paumgartner and Greenberger, 2009). Patients with asymptomatic gallstones have a very low likelihood of developing any pain or complications from their condition. Only a small subgroup of asymptomatic patients are at increased risk of developing complications due to individual characteristics. This group of patients will not be discussed in this paper. In general, then, treatment of asymptomatic gallstones is ill-advised, as the risks outweigh any potential benefits. The only recommendations offered are that patients be monitored by observation alone to ensure that they remain asymptomatic (Lanzini et al, 1994).

Symptomatic gallstone disease, on the other hand, is a definite indication for treatment. Patients with symptomatic gallstones typically present with intense pain in the upper right quadrant of the abdomen that often radiates to the angle of the right scapula and/or shoulder (Portincasa et al, 2009). The pain is usually persistent despite its common classification as biliary colic, a misnomer suggesting intermittent pain. Rapid onset of pain is common and duration of symptoms ranges from fifteen minutes to a few hours after which the pain subsides gradually or rapidly. Patients may complain of associated nausea and other nonspecific symptoms of indigestion and may feel the urge to walk. Many patients are awakened by nocturnal symptoms, often after eating fatty foods. The pain of symptomatic gallstone disease is a visceral pain triggered by gallstones lodged in the cystic duct, common bile duct, or ampulla of Vater (the enlargement of the common bile duct and pancreatic duct as they enter the duodenum at the sphincter of Oddi). As the gallbladder contracts and releases bile, gallstones may migrate along with the bile into the aforementioned passageways. When they get stuck in the ducts, they block the normal flow of bile, thus causing distention of the biliary tract and gallbladder. Such distention activates visceral sensory neurons that communicate a feeling of pain to the patient (Paumgartner and Greenberger, 2009). Once pain sets in, patients should commence fasting to prevent release of CCK and further contraction of the gallbladder causing more pain. Narcotic analgesics, such as meperidine, or non-steroidal anti-inflammatory drugs (NSAIDs), such as ketorolac or ibuprofen, are indicated to relieve biliary pain (Portincasa et al, 2009). Although direct relief of biliary pain is a vital component of managing symptomatic gallstone disease, this paper will focus on methods of eliminating or reducing the gallstones themselves in an effort to relieve their associated pain.

Laparoscopic Cholecystectomy

As the opening paragraph suggests, surgical removal of the gallbladder is considered first line treatment for symptomatic gallstone disease. In the days of open cholecystectomy, many patients were understandably concerned about the mortality risks, prolonged hospital stay, extended recovery time, and unattractive scars of the operation. The tendency to seek alternative, medical options to treatment was therefore high. However, with the advent of laparoscopic cholecystectomies in the late 1980s, attitudes towards surgical treatment have dramatically improved (Lanzini et al, 1994).

As opposed to the large incision required for open cholecystectomy, laparoscopic technique only necessitates four small incisions (5-10 mm) in the abdomen. The surgeon then inserts a thin, lighted tube, called a laparoscope, connected to a video monitor, and the tools that he will use during the operation (Brandon et al, 1991). This technique requires considerable surgical skill,

but has not been shown to increase the inherent risks of mortality and complications involved in surgically resecting the gallbladder. One landmark study even noted decreased risks of some complications after laparoscopic cholecystectomy, as compared with its traditional counterpart. "Lap chole," as it is known, effectively reduces the hospital stay of open cholecystectomy patients by up to three days and recovery time by up to three weeks. By returning to work early, laparoscopic patients have reduced the overall costs of the operation by 18% (Paumgartner and Greenberger, 2009). This minimally invasive procedure has demonstrated cosmetic and economic appeal over the conventional open cholecystectomy but an obvious question remains. To what degree does the surgery guarantee relief of biliary pain, its primary indication?

One study evaluated 118 patients who had undergone cholecystectomies, whether laparoscopic or traditional, and found that 93% of participants were satisfied with the results of the procedure. Although a significant number of patients reported persistent abdominal pain even after the operation, Vander Velpen et al classified these symptoms as unrelated to gallstone disease. By comparing the number of patients with preoperative symptoms to the number complaining of postoperative symptoms, the researchers determined that fat intolerance, flatulent dyspepsia, and nagging abdominal pain were unrelated to gallstone disease. They claimed, in keeping with earlier studies, that these symptoms were caused by unrelated gastrointestinal disturbances prevalent in gallstone patients and were therefore unaffected by removing the diseased gallbladder. In contrast, nausea, vomiting, colicky abdominal pain, back pain, and heartburn appear to be secondary to gallstone disease and were more reliably relieved by cholecystectomy (Vander Velpen et al, 1993).

Postcholecystectomy diarrhea may be the most distressing symptom that develops as a result of cholecystectomy. Vander Velpen et al found that 18% of their patients complained of PCD and traced it to malabsorption of fats due to changes in release of bile (1993). In a recent published work, Fisher et al offered their own pathogenic factors for PCD, but admitted that they could not be substantiated (2008). They found a similar incidence of PCD and correlated this increased incidence with male patients, younger than 50 years of age, with elevated BMIs. Despite the disruptive nature of PCD, Vander Velpen et al have shown that most patients are nevertheless pleased with the outcomes of their cholecystectomies (1993).

Besides the specific nature of PCD, a persistence of nonspecific abdominal symptoms after surgical resection of the gallbladder is known as postcholecystectomy syndrome, or PCES. PCES is not well defined but may be associated with sphincter of Oddi dysfunction resulting from scarring during cholecystectomy. Patients who complain of continued abdominal pain also do not realize that gallstones may still be forming in the common bile duct, even though their gallbladder has been removed. Endoscopic tests must be performed to diagnose and treat PCES properly (Comstock, 2008).

In one study, a group of 100 patients awaiting laparoscopic cholecystectomy was followed over the course of their operation and beyond. After evaluating individual characteristics in patients that remained symptomatic after surgery, Luman et al were able to identify specific predictors of PCES (1996). They urged surgeons to reconsider accepting patients with preoperative constipation, bloating, or psychotropic medication histories. These patients seemed more likely to develop PCES, and for good reason. Histological studies of the resected gallbladders revealed that many of them were not inflamed. Therefore, the abdominal pain that was diagnosed as biliary pain may have been due to underlying gastrointestinal disorders, such as irritable bowel disease. This finding matches the opinion of Vander Velpen et al cited above, and is confirmed by a history of anxiety and depression among many IBD patients (Luman et al, 1996).

Just over a year ago, another analysis confirmed these results and advocated more individual patient assessment before lap chole is categorically advised. Mertens et al proposed the novel notion that expectant management of gallstone disease may be preferred to surgical treatment in a group of high risk patients (2010). As found previously, individuals with dyspeptic symptoms (bad taste, heartburn, under abdominal pain, diarrhoea and flatulence) and those using psychotropic medications are at increased risk of unsuccessful cholecystectomies and should therefore be evaluated differently (Mertens et al, 2010).

In general, then, lap chole is considered the safe and effective gold standard for treating symptomatic gallstone disease. However, the decision to undergo surgery has to be made on an individual basis. Health care practitioners must educate patients on the potential risks of unsuccessful relief of symptoms or the onset of new symptoms, such as PCD. This is especially the case in patient populations with characteristics known to predict PCES and the like. Patients can then weigh the pros and cons of laparoscopic cholecystectomy and decide whether or not to go ahead with the procedure. Since gallstone disease is relatively benign, and watchful waiting has no increased risk of complications, patients may prefer such an option (Konikoff, 2003). The rest of this paper will discuss medical alternatives that patients and providers may wish to pursue as alternative to surgery in the treatment of symptomatic gallstone disease.

Ursodeoxycholic Acid (UDCA)

In 1936, a Japanese team identified the structure of ursodeoxycholic acid, the 7β-hydroxy epimer of chenodeoxycholic acid (Hofman and Roda, 1984). Where the hydroxyl group on C7 of CDCA has an alpha configuration (dashed wedge) and faces down and out of the plane of the steroid nucleus, the C7 hydroxyl group in UDCA acid has a beta stereochemistry (solid wedge) in line with the steroid nucleus. This minor change in stereochemistry has led to major differences in clinical findings, which will be discussed shortly. Ursodeoxycholic acid is found to only a lim-

Figure 9. Chemical structure of UDCA

ited degree in the bile of healthy individuals (Portincasa et al, 2009). However, it is the major bile acid of the black bear, explaining the origin of its unusual name. The curative nature of bear bile has been known for centuries, thus the Japanese who first established UDCA sought to investigate its medicinal effects (Hofman and Roda, 1984). As UDCA became more popular, other scientists joined in this effort, in the hopes of finding a new oral therapy to treat symptomatic gallstone disease. While CDCA had been the oral bile acid in use since the 1970s, it was later proven to be associated with increased liver enzymes, elevated LDL, and the development of bile acid-induced diarrhea (Portincasa et al, 2009). The manufacturer's information for chenodiol, the generic name for CDCA, now contains a black box warning with this evidence ("Chenodiol"). Scientists hoped that UDCA would preserve the efficacy of CDCA in dissolving cholesterol gallstone, while minimizing its adverse effects.

Indeed, if patients are carefully selected for treatment with UDCA, complete dissolution of gallstones can be accomplished in about 90% of cases. Proper inclusion criteria for UDCA treatment include the presence of radiolucent cholesterol stones, preferably less than 5 mm, and a functioning gallbladder (Portincasa et al, 2009). Cholesterol stones are generally radiolucent, thus they allow the passage of x-rays and cannot be seen on regular x-ray films. If the gallstones are com-
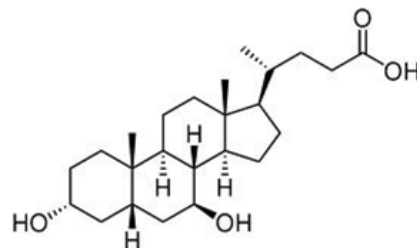
posed mostly of pigments or calcium, such radiopaque stones will show up on x-rays and are not indicated for oral dissolution with UDCA (Bouchier, 1983). Patients with smaller gallstones have a greater chance of complete dissolution in a reasonable time frame (around six months), because of the greater surface area and greater exposure to dissolving effects of the drug (Lanzini et al, 1994). Although patients with stones up to 10 mm are indicated for UDCA treatment, their length of therapy extends to one year and likelihood of complete dissolution drops to about 50% (Portincasa et al, 2009). Finally, a functioning gallbladder is necessary for UDCA treatment, to ensure that the drug will work properly and that its effects can be monitored radiologically (Bouchier, 1983). Thus, if patients meet the inclusion criteria for UDCA therapy, they can hope to benefit from the newer bile acid on the market. To confirm this hypothesis, Meredith et al established that UDCA is at least as effective as CDCA in treating gallstones, but that it does so at lower doses and with fewer side effects (1982). All that remains to be seen is the mechanism by which ursodeoxycholic acid succeeds in dissolving cholesterol gallstones.

If supersaturated bile is a prerequisite for gallstone formation, as discussed above, then unsaturated bile is a prerequisite for dissolution of preformed gallstones. Indeed, UDCA has been found to unsaturate gallbladder bile, although the exact mechanism is still unclear. It seems that by inhibiting cholesterol reabsorption from the intestines, cholesterol secretion into bile is decreased, and an unsaturated bile results (Portincasa et al, 2009). One team suggested that UDCA simply improves the incorporation of cholesterol into mixed micelles, thereby reducing biliary cholesterol saturation (Guarino et al, 2007). When cholesterol crystals are exposed to unsaturated bile in the

Figure 10. Cholesterol crystals (see text for explanation). (Portincasa et al, 2009)

gallbladder, they slowly dissolve over time. Fig. 9 compares typical cholesterol crystals in patients with gallstones(A,B) to the atypical crystals observed during UDCA therapy(C,D). The atypical nature of the bottom crystals indicates that they have been chipped away at by the unsaturated bile created by UDCA treatment (Portincasa et al, 2009).
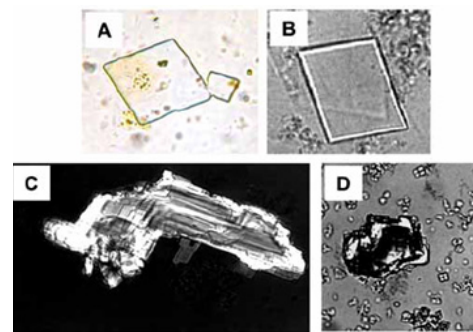
One interesting theory proposed to account for UDCA-dependent unsaturation of bile involves the ABC transporters mentioned earlier. The genes that regulate the expression of BSEP and MDR3 are in turn regulated by transcription factors. Transcription factors are receptors that bind to specific ligands, undergo a conformational change, and migrate to the nucleus where they regulate expression of specific genes. The ligand-activated transcription factor that is responsible for the expression of BSEP and MDR3 is known as farnesoid X receptor, FXR. FXR has been shown to upregulate BSEP and MDR3, thus creating increased levels of bile acids and phospholipids in gallbladder bile (Portincasa et al, 2009). Since UDCA is a ligand, albeit weak, of FXR, its binding to FXR may explain its unsaturation of gallbladder bile (Sauter et al, 2004). If the ratio of bile acids and phospholipids to
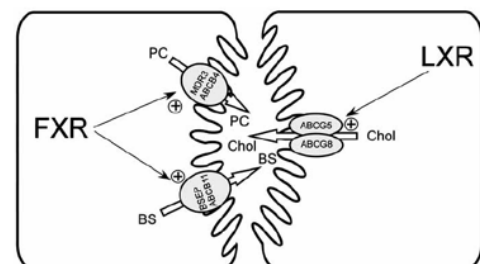

Figure 11. Transcription factors regulating biliary secretion. BS=Bile salts, PC=Phosphatidylcholine, Chol=Cholesterol. (Portincasa et al, 2009)

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cholesterol is increased, then more cholesterol can be dissolved in mixed micelles and the bile is considered unsaturated.

While supersaturation of bile certainly accounts for the pathogenesis of gallstones, gallbladder stasis is also implicated in this phenomenon. Therefore, improving the contractility of gallbladder can prevent gallstones from forming. In terms of UDCA therapy, its effects on the saturation of bile and gallbladder motility are related. By reducing cholesterol saturation in bile, UDCA prevents cholesterol from impairing gallbladder motility. Whatever the reason for UDCA-dependent unsaturation of bile, the end result is diminished levels of cholesterol in bile. Guarino et al proved that excess cholesterol in patients with gallstones tends to accumulate in the plasma membrane of muscle cells. The cholesterol molecules aggregate in caveolae, "high-cholesterol domains containing caveolin proteins and a variety of molecules involved in signal transduction pathways," and sequester receptors located in these regions (2007). When ligands such as CCK attempt to stimulate receptors in the caveolae to cause gallbladder contraction, they are blocked by the excessive of amounts of cholesterol surrounding the receptors. Reducing levels of cholesterol will therefore prevent the accumulation of cholesterol in the plasma membrane of muscle cells. This will allow CCK to bind to its receptors and restore normal gallbladder contractility (Guarino et al, 2007). In vitro studies have substantiated these theories, showing increased contraction with UDCA treatment, especially during long term therapy (Mas et al, 2007). Thus, by reducing levels of cholesterol, UDCA can effectively improve gallbladder motility.

Other authors have suggested a different mechanism by which UDCA improves gallbladder contractility. In this case, it not linked to a reduction of cholesterol saturation, but to a reduction of deoxycholic acid. DCA is secondary bile acid and is formed by dehydroxylation of the primary cholic acid. A hydrophobic bile acid, DCA is associated with impaired gallbladder emptying and cholesterol hypersecretion into bile (Dowling, 2000). Recent findings suggest that UDCA may prevent these detrimental effects of DCA (Portincasa et al, 2009). Specifically, UDCA has been shown to induce expression of CYP3A4, an enzyme responsible for bile acid metabolism. By increasing levels of CYP3A4, UDCA may increase breakdown of toxic, hydrophobic bile acids into less toxic, hydrophilic bile acids. UDCA can thus decrease levels of DCA and prevent gallbladder stasis and the attendant formation of gallstones (Paumgartner and Beuers, 2004).

The optimal dosage for UDCA therapy is 10-15 mg/kg/day. This dose is best administered at bedtime to maximize the effect of the drug (Portincasa et al, 2009). Normal physiology dictates that enterohepatic circulation is interrupted at night. This is will decrease the secretion of bile acids into the bile and increase the proportion of biliary cholesterol. However, UDCA maintains the secretion of bile acids overnight, thereby preventing secretion of supersaturated bile. It is therefore recommended to take a bedtime dose of UDCA in order to potentiate its effects (Lanzini et al, 1988).

As opposed to CDCA, treatment with UDCA has little if no side effects. In a comparative study of chenodiol and ursodiol, the incidence of hepatotoxicity with UDCA was low and none of the patients developed diarrhea (Meredith et al, 1982). However, other studies indicate that a small percentage of patients may develop calcified rims surrounding their cholesterol gallstones. This would render the stones radiopaque and incompatible with further UDCA therapy. The biggest disadvantage of oral dissolution of gallstones with UDCA is the high risk of recurrence. Up to 50% of patients treated with UDCA may find recurring gallstones as soon as 3-5 years after treatment. Therefore, UDCA therapy is only advised for patients who refuse surgery, are not candidates for surgery, or have transient risk factors such as pregnancy or rapid weight loss (Portincasa et al,

2009).

Extracorporeal Shock Wave Lithotripsy (Eswl)

Lithotripsy is the practice of using soundwaves to break stones into smaller fragments. This technique was originally developed for use in treating kidney stones but was pioneered for use in gallstone treatment by Paumgartner and colleagues in the 1980s (Paumgartner, 2010). The theory behind this treatment was to reduce larger gallstones to a diameter of less than 3 mm that would then be indicated for treatment with UDCA. Lithotripsy is therefore an adjuvant, or supplementary, procedure meant to improve the efficacy of UDCA therapy (Lanzini et al, 1994). Performing ESWL before UDCA also increases the amount of patients who eventually qualify for UDCA therapy. Indeed, the selection criteria for ESWL with subsequent UDCA therapy are broader than those for UDCA therapy alone. In order to qualify for ESWL + UDCA, patients must have one radiolucent gallstone less than 20 mm and a functioning gallbladder (Paumgartner, 2010). If these criteria are met and a high energy lithotripter is used, the treatment is effective in two-thirds of the cases (Lanzini et al, 1994).
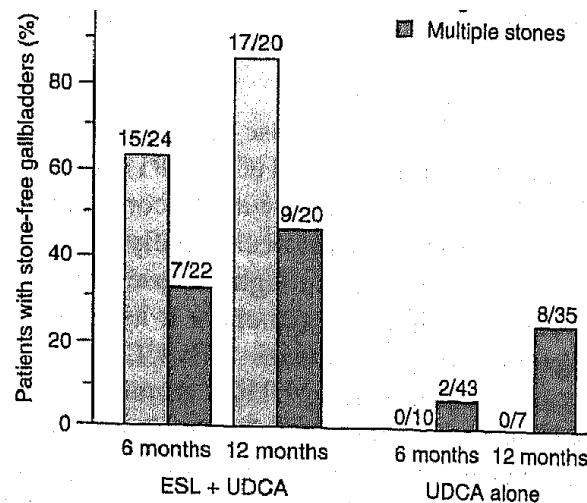

Figure 12. Percentage of patients with complete gallstone dissolution at 6 and 12 months after extracorporeal shockwave lithotripsy (ESL) plus UDCA therapy (left), and UDCA alone (right) for single and multiple stones. (Lanzini et al, 1994)

Before the advent of laparoscopic cholecystectomy, ESWL was preferred over traditional cholecystectomy because of its enhanced safety profile. However, like oral bile acid therapy, the recurrence rate was high. The incidence of recurrence of gallstones at two years and ten years after ESWL treatment was 11-29% and 60–80% respectively (Paumgartner and Greenberger, 2009). Darzi et al concluded that "while ESWL has minimal side-effects it is associated with more limited selection criteria, a more prolonged treatment time, a higher failure rate, and a higher recurrence rate when compared with laparoscopic cholecystectomy" (1994). Therefore, when lap chole became the gold standard for treating symptomatic gallstones and greatly reduced hospital stays and recovery time after surgery, ESWL became obsolete. Currently, ESWL is reserved for treating bile duct stones that have not responded to endoscopic treatment (Paumgartner, 2010).

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Ezetimibe (Ezt)

Ezetimibe is a potent member of a new class of drugs that inhibit intestinal absorption of cholesterol. Although it is currently only indicated for reducing LDL levels in hyperlipidemia, research is underway to determine its potential for preventing and dissolving gallstones. Cholesterol absorption from the intestine is a key step in the process of secreting cholesterol into bile. Although the liver can synthesize cholesterol from scratch, this de novo synthesis only contributes 15% to the overall biliary cholesterol (Porincasa et al, 2009). The majority of biliary cholesterol is derived from dietary and recycled biliary cholesterol that are absorbed in the small intestine. After absorption, cholesterol is packaged with triglycerides into lipoprotein particles called chylomicrons. These particles lose their triglycerides to tissues as they migrate through the bloodstream, and are finally absorbed by hepatocytes as cholesterol-rich particles (Malloy and Kane, 2009). By reducing intestinal absorption of cholesterol, ezetimibe can effectively reduce the amounts of cholesterol that reach the liver for secretion into bile.
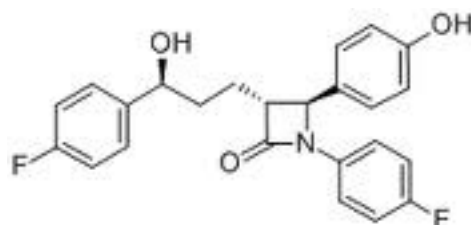

Figure 13. Chemical structure of ezetimibe

The mechanism of action of ezetimibe centers around a transport protein located in the brush border lining the small intestine. This protein has been recently characterized as NPC1L1 (Niemann-Pick C1-like 1) and facilitates intestinal absorption of cholesterol through a multi-step process (Fig. 14) (Portincasa et al, 2009). Ezetimibe binds to and inhibits NPC1L1, thereby effectively inhibiting absorption of dietary and biliary cholesterol. This, in turn, results in decreased
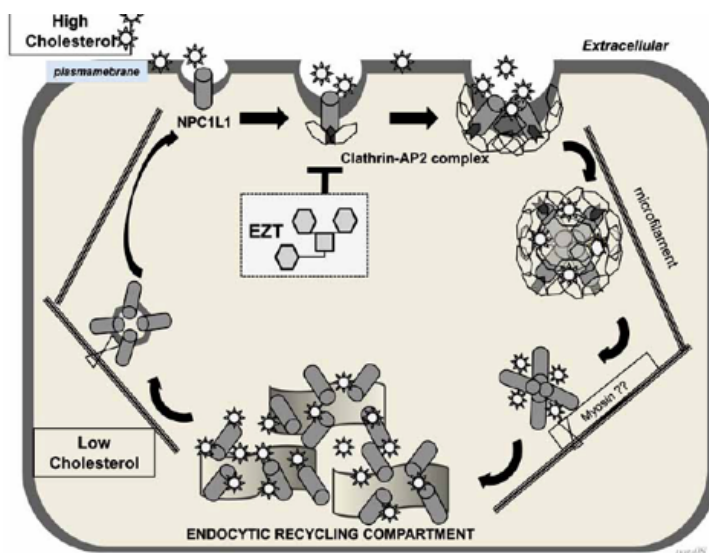

Figure 14. The NPC1L1 protein recycles between the plasma membrane facing the extracellular space and the endocytic recycling compartment. In the presence of high extracellular cholesterol, cholesterol is incorporated into the plasma membrane and is sensed by cell surface-localized NPC1L1. Both NPC1L1 and cholesterol are then internalized together through clathrin/AP2-mediated endocytosis and stored within the endocytic recycling compartment. If the intracellular cholesterol level is low, endocytic recycling compartment-localized NPC1L1 moves back to the plasma membrane along microfilaments and new cholesterol is absorbed. The key role of the inhibitor ezetimibe (EZT) is shown at the center of the cell. EZT prevents NPC1L1 from entering the AP2-mediated clathrin-coated vesicles. At this stage, the endocytosis of NPC1L1 is inhibited and cholesterol absorption is decreased (Portincasa et al, 2009).

secretion of biliary cholesterol and an unsaturated bile. Studies in mice proved that ezetimibe accomplishes dissolution of gallstones by forming unsaturated micelles. As cholesterol present in the preformed gallstones is transferred to the unsaturated micelles, the stones become smaller and eventually dissolve. Additionally, reduced levels of biliary cholesterol can improve gallbladder motility in the same way that UDCA achieves this goal (Wang et al, 2008). Although the effects of ezetimibe on cholesterol saturation of bile have yet to be corroborated by studies in humans, its effects in mice have shown potential for a novel therapy in the treatment of gallstone disease.

Dietary Phospholipids

Based on an understanding of gallbladder physiology and biliary secretion, studies have been conducted to evaluate the effects of phospholipids on formation of cholesterol gallstones. One experiment found that in vitro supplementation of gallbladder biles with disaturated phospholipids prolonged cholesterol nucleation time (Jungst et al, 1993). Nucleation time is understood as the number of days required for cholesterol monohydrate crystals to first appear in bile (Abeysuriya et al, 2010). Jungst et al proposed that this prolonged nucleation time was due to two factors (1993). Firstly, increasing levels of phospholipids serves to decrease the proportion of cholesterol in bile. This lowers the cholesterol saturation of bile and slows formation of cholesterol gallstones. The second interesting phenomenon Jungst and his colleagues discovered was that phospholipids stabilized cholesterol vesicles by shifting the phase equilibrium towards mixed micelles (1993). As mentioned earlier, cholesterol-phospholipid vesicles are considered unstable while mixed micelles consisting of cholesterol, phospholipids, and bile acids are more stable and therefore less likely to allow the cholesterol to precipitate into crystals. Thus, in vitro supplementation with phospholipids has been shown to create a biliary environment better able to solubilize cholesterol and prolong formation of gallstones. While other studies confirm these beneficial results, clinical practitioners cannot yet advise their patients to supplement their diets with phospholipids (Moschetta et al, 2001). Before such a recommendation can be made, further studies are needed in order to investigate whether the published results can be reproduced in vivo.
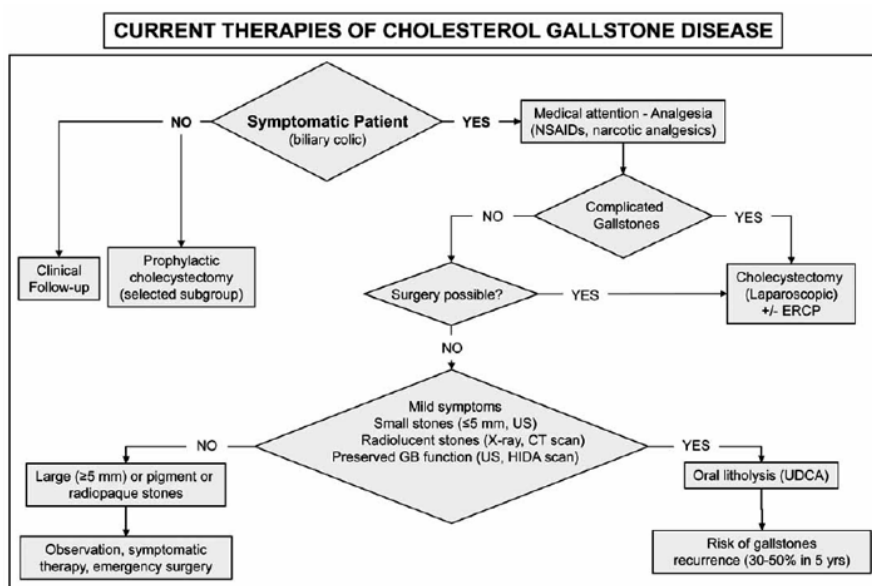
Summary Algorithm

Figure 15. Algorithm for the management of cholesterol gallstone disease. (Portincasa et al, 2009)

CONCLUSION

The high prevalence of gallstone disease in Western countries renders it an important topic of discussion. Unfortunately, many people can relate to the opening question of whether or not to consent to surgical removal of the gallbladder. In light of this paper's analysis of gallstone treatments, this decision is no doubt easier. Those with asymptomatic gallstones need no active treatment as long as they are routinely monitored and remain asymptomatic. It is clear that laparoscopic cholecystectomy is considered first line treatment for symptomatic gallstone disease. Although it poses a slight risk of mortality and complications, it is the most efficacious procedure for preventing recurrence of biliary pain and gallstones. Even the complaints of persistent abdominal pain following surgery have been shown to be associated with underlying conditions not related to gallstone disease. While UDCA and ESWL used to be standard alternatives to surgery, their prolonged length of therapy and high recurrence rate have rendered them virtually obsolete. They are reserved for patients who refuse surgery or for whom surgery poses increase risks. Novel therapies such as ezetimibe and dietary phospholipids are still being investigated and may prove to be mainstay treatments in the future.

The bottom line emerging from the clinical studies canvassed in this paper is the need to evaluate each individual case before recommending an option for treatment. Personal characteristics may indicate whether surgery is advisable or whether a medical option might be more successful. Effective communication between the informed patient and the well-versed physician is crucial for selecting the most beneficial treatment option. If the suggestions presented here are employed, we may yet see a decline in the incidence of gallstone disease.

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