New Trends In The Treatment Of Calculus Disease Of The Biliary Tract

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Background: **New treatment methods for calculus disease of the biliary tract offer options that can benefit a variety of patients. Laparoscopic surgery, for example, has revolutionized biliary surgery and is now the preferred approach for the majority of patients.**

Methods: **Using the key words "biliary tract," "calculus disease," and "cholecystectomy," MEDLINE files were searched from 1982 to the present. Articles dating before 1982 were accessed from the reference lists of the more recent articles.**

Results and Conclusions: **This review describes the various procedures that could be effective options for patients with biliary stone disease, including an algorithm showing a proposed scheme for evaluating and treating this disease. Cholecystectomy — either laparoscopic or open — will likely remain the treatment of choice for most patients. The newer options, however, for treatment of both acute and chronic cholecystitis have proved effective in select cases. (J Am Board Fam Pract 1995; 8:22-8.)**

The treatment of patients with calculus disease of the biliary tract has changed dramatically during the past 20 years. Today a variety of new techniques offer effective and safe treatment for patients with biliary stone disease. Although surgery will likely remain the best option for the majority of patients, physicians and surgeons should be aware of the other options so they can carefully select the treatment that will best suit each patient's needs.

Methods

Using the key words "biliary tract," "calculus disease," and "cholecystectomy," MEDLINE files were searched from 1982 to the present. Articles dating before 1982 were accessed from the reference lists of the more recent articles.

Results

Gallstones are a frequently occurring medical problem affecting approximately 10 percent of men and 20 percent of women older than 55 years of age in the United States.[1] It is estimated that 20 million Americans currently have gallstones and that 1 million additional cases are diagnosed each year. Understandably, a great deal of interest has been directed toward the development of new treatment methods.

Approximately 80 percent of biliary tract stones are composed of cholesterol. Many factors predispose patients to the development of biliary calculi. Female sex, obesity, the use of oral contraceptives, multiparity, anticholesterol-lowering drugs, and hypercholesterolemia have been linked to the development of biliary calculi. In addition, diseases of the terminal ileum — whether an inflammatory disease or a disease resulting in resection of that part of the intestine — can predispose a patient to the development of cholesterol gallstones.

The development of the less common pigmented gallstones has been linked to cirrhosis of the liver, congenital anomalies of the biliary tract, and hemolytic disease, possibly because of a primary hereditary deficit, such as spherocytosis, or an acquired condition, such as replacement of a heart valve.

Cholecystectomy is the reference standard for treatment of calculus disease of the biliary tract. An estimated 500,000 cholecystectomies are performed each year, making cholecystectomy the second most common abdominal operation, following Cesarean section. The procedure is safe and effective and is associated with a very low incidence of morbidity and mortality. The overall incidence of mortality ranges between 0.5 percent and 1.5 percent, and the morbidity ranges from 3.7 percent to 6.9 percent. The incidence of

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both morbidity and mortality has declined during the past 25 years.

There are several published series with morbidity rates of less than 3 percent. Gilliland and Traverso[2] reported a series of 671 elective cholecystectomies with a 0 percent mortality rate and a 3.9 percent morbidity rate. Ganey, et al.[3] reported a 0 percent mortality rate and a 3.9 percent morbidity rate in a series of 1035 patients who underwent elective cholecystectomy.

Reports of the effectiveness of cholecystectomy vary widely. In cases in which the disease can be attributed directly to the biliary tract — such as acute cholecystitis, gallstone pancreatitis, cholangitis, biliary colic, and gallstone ileus — surgery is very effective. In patients with less specific symptoms, such as dyspepsia, flatulence, bloating, fatty food intolerance, or nonlocalized pain, the efficacy could be much lower, probably because the surgery is sometimes performed to alleviate symptoms unrelated to the biliary tract. For example, a condition that has been described as post-cholecystectomy syndrome probably does not exist and most likely occurs because the initial symptoms are related to other gastrointestinal problems rather than problems directly associated with the biliary tract. Thus, proper patient screening and careful selection are necessary to optimize the efficacy of this procedure.

The main advantages of cholecystectomy are that it is highly effective in not only relieving symptoms but also halting the progression of calculus biliary tract disease, as the calculi and the primary site of their formation are removed. In most cases cholecystectomy can be performed with minimal risk to the patient, no long-term follow-up treatment is required, and no long-term adverse effects have been documented. The primary disadvantage of this procedure is that it is a major, intra-abdominal procedure requiring several weeks of recovery.

For any new treatment to become accepted, its efficacy and safety must be compared with those of the reference standard treatment, in this case, cholecystectomy. The new treatments are usually performed on carefully selected patients who are otherwise healthy. Because the sickest patients (who will have the worst outcomes) will not be candidates for these new treatment methods, the results of cholecystectomy and those of the new treatments must be compared carefully to avoid drawing incorrect conclusions.

Oral Dissolution with Bile Acids

Oral dissolution of biliary calculi is performed with chenodeoxycholic and ursodeoxycholic acids (Actigall, Ciba-Geigy). First performed in 1937, this technique gained popularity in the 1970s and 1980s. There are several reports of results achieved with chenodeoxycholic acid, most notably, the National Cooperative Gallstone Study.[4] Both drugs are now available, with Actigall being the most recent.

Bile is composed mostly of water, along with conjugated bilirubin, organic and inorganic ions, small amounts of protein, and three lipids (bile salts, cholesterol, and lecithin). When the percentage of bile acids and lecithin is adequate, cholesterol will remain in solution. Bile acids keep cholesterol in solution by forming a micelle. Cholesterol is kept in suspension by the bile salts and the lecithin. When the amount of cholesterol in bile exceeds the capacity of the micelle to keep it in solution, however, the cholesterol precipitates out, and there is a chance for the formation of cholesterol gallstones.

At some point during the day the vast majority of persons have bile that is supersaturated with cholesterol. Nevertheless, most persons do not form gallstones, suggesting that other factors, which are not completely understood, contribute to the formation of gallstones. These factors can include (1) defective biliary secretion (vesicles with excess cholesterol, defective bile acid flow, deficient bile flow); (2) a rapid nucleating factor that begins the precipitation of these cholesterol stones (calcium has been implicated); and (3) a diseased gallbladder, either because of some abnormality in the mucosa of the organ or because of poor contractility.

The primary effect of bile acids is to decrease the amount of cholesterol that is secreted into the bile. Ursodeoxycholic and chenodeoxycholic acids both reduce the amount of cholesterol in the bile by blocking the action of the HMG-coenzyme-A-reductase, which controls cholesterol formation. Also, it has been proposed that ursodeoxycholic acid plays a role in stopping the transport of cholesterol from within the hepatocytes to the bile. Once bile has micelles that are not saturated with cholesterol, those micelles are able to act at the bile-stone interface, slowly remove small particles of cholesterol from the stone, and, during months to years, dissolve it

into small particles. Ursodeoxycholic acid has another effect. There is a poorly understood liquid crystalline phase that causes removal of cholesterol from stones to the bile, where it can be removed.

Because these agents have slightly different actions, it has been proposed that using them together might have some type of synergistic effect. This view is held by German investigators, although it is not practiced routinely in the United States.

Ursodeoxycholic and chenodeoxycholic acids have been shown to be equally effective in dissolving cholesterol gallstones; however, the side effects associated with chenodeoxycholic acid have often required discontinuation of treatment. Patients receiving therapeutic doses of chenodeoxycholic acid often experience severe diarrhea. In addition, chenodeoxycholic acid causes elevations of liver enzymes, specifically the transaminases, which cause as many as one-third of the patients to discontinue treatment. Ursodeoxycholic acid, while having the same efficacy, does not have the same side effects. There is no documentation of liver enzyme elevation, and there is only a 5 percent incidence of clinically important diarrhea, rarely leading to discontinuation of treatment.[5-7] Another side effect of chenodeoxycholic acid is that it tends to raise the level of low-density lipoprotein cholesterol, known to be atherogenic. This side effect is not associated with ursodeoxycholic acid.

Approximately 20 percent to 30 percent of the patients who have gallstones meet the following criteria for bile acid treatment:

1. They have chronic cholecystitis
2. They have cholesterol gallstones (bile acids have no effect on pigmented or calcified gallstones)
3. They have a functioning gallbladder, so the bile acids can gain access to the stones
4. Their stones are less than 1.5 to 2.0 cm in diameter
5. Their stones are radiolucent
6. They are not pregnant and have no renal or hepatic disease

Using chenodeoxycholic acid, The National Cooperative Gallstone Study reported a 13.5 percent overall dissolution rate,[4] and the Sunnybrook Study in Canada reported a 10.9 percent dissolution rate.[8] It is now realized that suboptimal doses were administered (8 mg/kg/d to 10 mg/kg/d). At the optimal dose (15 mg/kg/d for chenodeoxycholic acid and 8.5 mg/kg/d for ursodeoxycholic acid), an overall dissolution rate of 15 percent to 20 percent could be achieved.

These studies found a subgroup of patients with a high (greater than 50 percent) chance of having their gallstones dissolved in 1 to 3 years. Such patients can be characterized as female, at or below ideal body weight, who have gallstones that are smaller than 2 cm in diameter, radiolucent, and shown to be floating by oral cholecystogram, thus indicating that the stones have a cholesterol content of more than 80 percent.

Because these oral agents are effective only on cholesterol stones, the higher the cholesterol content, the higher the chance for dissolution. In addition, patients with a serum cholesterol above 227 mg/dL also have a greater chance of dissolution with these oral agents.

The advantage of oral dissolution with bile acids is that it avoids an abdominal surgical procedure, and no recovery time is required. The chief disadvantage of this medical therapy is that approximately one-half the patients will experience a recurrence within the first 5 years. After 5 years the incidence of recurrence decreases and becomes rare. Another disadvantage is that medications must be taken for a long time to dissolve the stones. Chances for biliary complications developing during treatment remain unchanged.

Direct Contact Dissolution

Gallstones can be dissolved by the direct infusion of monooctanoin or methyl-tertiary-butyl-ether (MTBE) into the gallbladder or common bile duct. Monooctanoin, which will dissolve only cholesterol gallstones, was first used in 1978 to dissolve stones in the common bile duct. This treatment is effective approximately 50 percent of the time. Side effects, which include primarily abdominal pain, nausea, and vomiting, can result in the discontinuation of treatment in approximately 10 percent of the patients. This solvent can be instilled into the gallbladder or common bile duct by a variety of routes: a T-tube left in place after common bile duct exploration where a retained stone has been found, a cholecystectomy tube, a

transhepatic catheter, or a nasobiliary tube. This slow-acting agent requires an average of 5 days to dissolve a 1- to 2-cm cholesterol stone.

MTBE was first used in 1985. As will monooctanoin, it will dissolve only cholesterol stones. The toxic side effects of this agent prohibit its use in the common bile duct, because the agent will overflow into the duodenum and cause anesthesia, hemorrhage, and, if it enters the vascular system, massive intravascular hemolysis with associated renal failure. This sequence of events has been documented in experimental models, but we are not aware of it occurring in humans. The advantage of MTBE is that it acts rapidly, dissolving some stones in a few hours and most stones within 12 to 14 hours. There are very few stones that cannot be dissolved in 24 hours if they are composed primarily of cholesterol.

Direct contact dissolution is effective in patients who have chronic cholecystitis, a functioning gallbladder, radiolucent cholesterol stones (any size or number), and a patent cystic duct to allow any remaining fragments to pass out of the gallbladder. Contraindications to this procedure are coagulopathy, pancreatitis, or pregnancy. To perform direct contact dissolution, the gallbladder is first located using sonography, and a catheter is placed percutaneously, transhepatically into the gallbladder. Approximately 3 to 5 mL of MTBE is injected and withdrawn from the gallbladder every 5 minutes until the stones are dissolved. Dissolution of the stones is monitored either fluoroscopically by injecting contrast medium into the gallbladder or by sonography. The primary disadvantage of this direct contact dissolution is that it requires the uninterrupted time of a physician for a period of hours to inject and withdraw the agent. A mechanical exchange unit is under development, but its cost is expected to be high.

The advantages of direct contact dissolution include avoiding open abdominal surgery and minimal recovery time. This procedure is invasive, however, and there is potential for serious complications, especially with MTBE. With monooctanoin, treatment can be prolonged. Furthermore, as with all treatments in which the gallbladder remains in situ, there is approximately a 50 percent chance of recurrence of the stones. The long-term effectiveness of this treatment remains to be determined.

Percutaneous Drainage

This procedure is relatively new and useful for patients with acute cholecystitis who are at high risk for a surgical procedure. The ideal patient can be characterized as a patient in the intensive care unit who might be intubated, who has multiple injuries, and who develops acute cholecystitis. The gallbladder is located using sonography, a needle is placed percutaneously, and a drainage catheter is inserted. In effect, this procedure can be compared with draining an abscess. The gallbladder can then be removed when the patient's condition improves.

Percutaneous Cholecystolithotomy

Percutaneous cholecystolithotomy is an extension of percutaneous drainage. After the tract is established in the same manner as with percutaneous drainage, the tract is dilated and an operating scope is inserted. The stones can then be removed through the scope. Stones too large can be fragmented by ultrasonic beams (intracorporeal lithotripsy) or by a contact laser. The advantage of percutaneous cholecystolithotomy is that it is effective with all types of stones, the hospital stay and recovery period are shortened because only a small incision is required, and no long-term treatment is required. The patient must be anesthetized, however, and the procedure is invasive (although minimally, when compared with a standard cholecystectomy). Because the gallbladder is not removed, the stones will recur in approximately 50 percent of the patients.

Laparoscopic Cholecystectomy

Cholecystectomy is the reference standard for treatment of gallbladder disease, and laparoscopic cholecystectomy is an alternative method of accomplishing the procedure. The procedure is unchanged in that the gallbladder is removed; however, laparoscopic access to the abdominal cavity reduces postoperative pain and recovery time.

The earliest literature reports on laparoscopic cholecystectomy appeared in 1989, and since that time the procedure has grown in a manner unequaled in surgical history.[9,10] The procedure is carried out by viewing the gallbladder through a high-resolution video camera placed through the umbilicus. Operating ports are placed beneath the xiphoid and costal margin, and the gallbladder is removed as in the open procedure using laparo-

scopic instrumentation. The angle viewed by the operating surgeon is different, and a two-dimensional rather than three-dimensional view is obtained. These factors, together with the additional laparoscopic instrumentation, require a period of relearning before the procedure can be carried out safely.

It has been proved that laparoscopic cholecystectomy is a safe and effective treatment for cholelithiasis,[11] although there is a higher incidence of common duct injury.[12] It is likely that mortality and morbidity will decrease as surgical experience is gained with the technique.

The National Institutes of Health recently approved laparoscopic cholecystectomy as a safe and effective technique for the treatment of gallbladder disease. Laparoscopic cholecystectomy is the procedure of choice for patients with chronic cholecystitis at this time and, with increasing experience, will undoubtedly be used for the treatment of acute cholecystitis with increasing frequency.

Of all the techniques described, laparoscopic cholecystectomy is the most widely applicable and once again firmly establishes surgery as the primary treatment for calculus biliary tract disease. All types of stones can be treated, and gallbladder function does not affect the ability to carry out the procedure. Hospital stay is usually less than 24 hours, and patients can return to normal activities in 3 to 4 days.

Extracorporeal Shock Wave Lithotripsy

Pioneered by West German researchers for the treatment of renal calculi, lithotripsy was developed in 1960, and actual clinical studies were undertaken in 1974. Biliary lithotripsy experimentation began in 1976 with clinical trials beginning in the mid-1980s.

The principle of lithotripsy can be described as follows: (1) An explosive force is followed by (2) an expansion of gaseous elements, generating (3) a high-velocity shock wave, which is followed by (4) transmission of this shock wave to the patient, resulting in (5) an impact on variable density (the stones).

The elements of the lithotripter are an energy source (either spark cap, electromagnetic, piezoelectric ceramic, or microexplosive), a focusing device (to focus the shock wave on the stone), a method of coupling the patient to the shock wave (water immersion or dry methods), and a method of imaging the stone (sonography or fluoroscopy).

Coupling can be achieved by water immersion or by dry methods. Water immersion is cumbersome, because large amounts of water have to be prepared for each treatment, and if an emergency occurred during treatment, rapid access to the patient is difficult. Most lithotripters today use the dry method, which involves applying a mineral oil barrier to the skin. Sonographic imaging is most effective for biliary lithotripsy, whereas fluoroscopic imaging is most effective in locating common bile duct stones.

To be eligible for biliary lithotripsy, patients must have from one to three gallstones, 5 mm to 30 mm in diameter, a functioning gallbladder as demonstrated by oral cholecystogram, no calcified stones, and only minor medical problems. With these criteria, approximately 10 percent to 20 percent of gallstone patients are eligible. The patient is sedated for the procedure, the stone is located using sonography, the computer directs the focusing, the shock waves are generated, and the stones are fragmented. Although lithotripsy does not fragment the stones into pieces small enough to pass from the gallbladder spontaneously, it fragments them into smaller stones so there is a larger surface area allowing the stones to be dissolved more rapidly with ursodeoxycholic acid, which is the final part of the treatment.

Sackmann, et al.[13] reported the landmark study of the first 175 patients treated in this manner. The majority of patients had solitary stones smaller than 2 cm in diameter. Overall, 30 percent of the patients were stone-free 2 months following the procedure, 48 percent at 4 months, 63 percent at 8 months, and 91 percent at 18 months. For the patients with solitary stones smaller than 2 cm in diameter, success was improved, with the corresponding values of 45 percent, 69 percent, 78 percent, and 95 percent, respectively. The treatment was less effective in those patients with large (larger than 2 cm) or multiple stones.

To date there have been no serious or life-threatening complications associated with this treatment. Approximately 30 percent to 50 percent of patients will continue to have biliary colic, however, and 25 percent will have skin ecchymosis; transient nausea and vomiting and gross

hematuria have also been reported. Currently biliary lithotripsy is an experimental treatment with final Food and Drug Administration approval pending.

For the 10 percent to 20 percent of eligible patients, biliary lithotripsy eliminates the pain and risk of surgery, can be performed as an outpatient procedure, and minimizes recovery time. The disadvantages are that long-term medical dissolution is required, some patients require re-treatment with the lithotripsy, and there is the same chance of stone recurrence found with other medical treatments (50 percent at 5 years).

Summary of Treatment Options

Figure 1 diagrams a suggested treatment scheme encompassing all new treatment modalities. Patients with biliary calculi can be divided into two basic categories: those with chronic or those with acute cholecystitis. The treatment options available for chronic and acute cholecystitis can be summarized as follows:

Acute Cholecystitis

For patients with acute cholecystitis, primary cholecystectomy, either laparoscopic or conventional open, is the treatment of choice. Patients who are considered to be at high-risk for an intra-abdominal surgical procedure can now be treated with percutaneous drainage if medical treatment is not successful. If percutaneous drainage is unsuccessful, traditional cholecystectomy can then be performed.

Chronic Cholecystitis

For patients with chronic cholecystitis, the stones must be characterized by type and number, and gallbladder function must be assessed before treatment options can be determined.

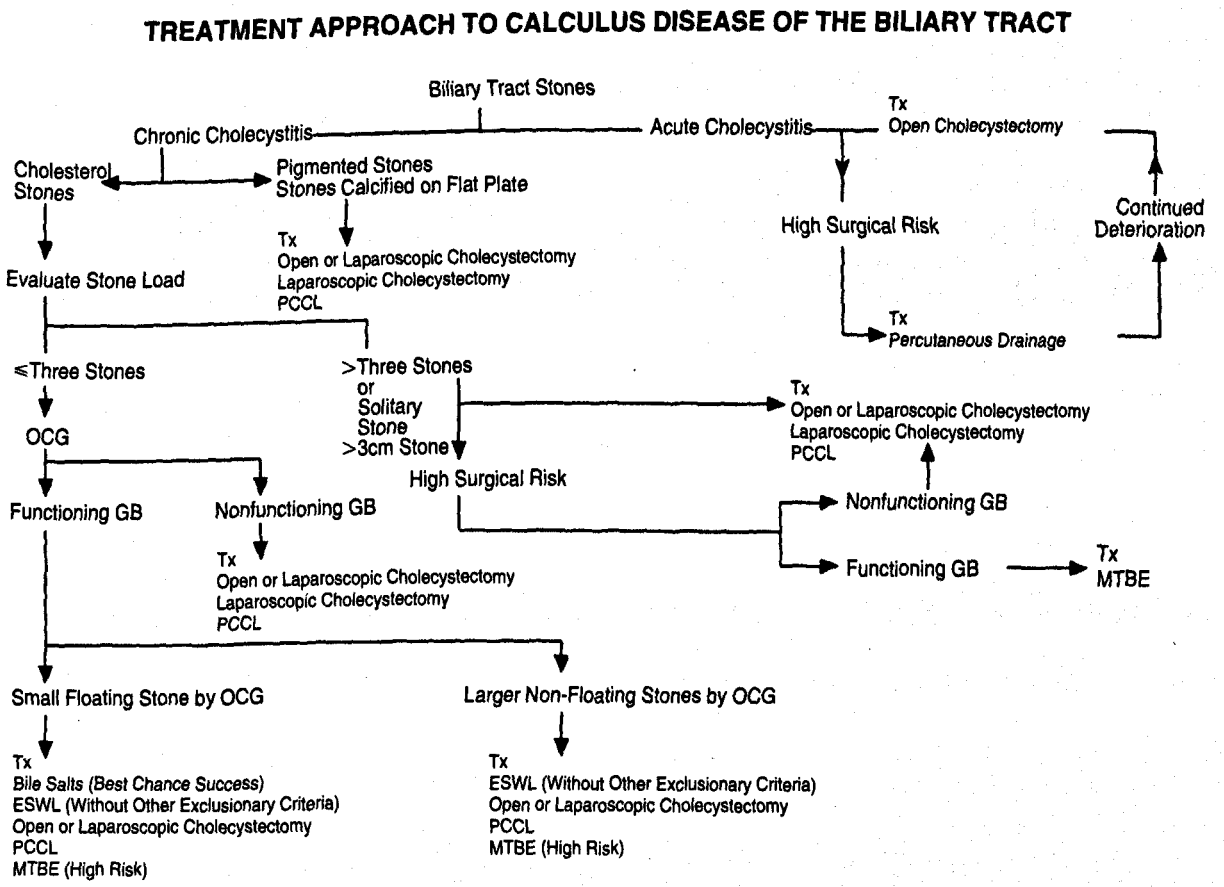

Figure 1. Treatment approach to calculus disease of the biliary tract. GB = gallbladder, Tx = treatment, PCCL = percutaneous cholecystolithotomy, MTBE = methyl-tertiary-butyl-ether, ESWL = extracorporeal shock wave lithotripsy, OCG = oral cholecystogram.

Cholesterol Stones

Because 80 percent of all gallstones are cholesterol stones, a wide variety of options are available. If there are more than three stones or a solitary stone larger than 3 cm in diameter, the first treatment choice will be one of the surgical procedures (open or laparoscopic cholecystectomy or percutaneous cholecystolithotomy). If the patient is at high risk for surgery, however, and oral cholecystogram shows that the gallbladder is functioning, the patient will be a candidate for MTBE treatment, because the stone load has no effect and the only requirement is that the stones are cholesterol gallstones. If the gallbladder is not functioning, however, the patient must be treated with one of the surgical options. If there are fewer than three stones and an oral cholecystogram shows a functioning gallbladder, the patient is eligible for all three treatments, and the choice is best determined by the patient and the physician.

For patients with larger, nonfloating stones, treatment options consist of extracorporeal shock wave lithotripsy, cholecystectomy (open or laparoscopic), percutaneous cholecystolithotomy, or MTBE for patients who are at high risk for surgery. For patients with nonfunctioning gallbladders, one of the three forms of cholecystectomy should be used.

Noncholesterol Stones

For patients with pigmented or calcified stones, one of the three surgical options must be used: (1) open cholecystectomy, (2) laparoscopic cholecystectomy, or (3) percutaneous cholecystolithotomy.

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