

# Management of Cholelithiasis with Concomitant Choledocholithiasis

**Ardhitio Musthafa Akmal<sup>1</sup>, Budhiarko Pramana Putra<sup>1</sup>,  
Cokorda Istri Agung A. Darmaningrat<sup>1</sup>, I Gusti A. R. Chantika Nariswari<sup>1</sup>,  
Lalu Dio Srigede<sup>1</sup>, Catarina Budyono<sup>2\*</sup>**

<sup>1</sup> Faculty of Medicine Universitas Mataram, Nusa Tenggara Barat, Indonesia.

<sup>2</sup> Departement of Internal Medicine, Faculty of Medicine Universitas Mataram, Nusa Tenggara Barat, Indonesia.

## Corresponding Author:

Catarina Budyono, MD. Departement of Internal Medicine, Faculty of Medicine Universitas Mataram. Jl. Pendidikan No. 37, Mataram 83125, Indonesia. Email: catarina.budyono@gmail.com.

## ABSTRACT

*Cholelithiasis refers to a condition in which hardened deposits exist within the gall bladder. These deposits are also known as gallstones. Among other gastrointestinal diseases, Cholelithiasis is associated with the highest hospital admissions. Those with cholelithiasis are generally asymptomatic. However, symptoms may start to appear in the case of inflammation or the blockage of the bile duct, which occurs in 10-25% of patients with cholelithiasis. The condition in which gallstones are present in the common bile duct is known as choledocholithiasis. Surgery is a curative therapy for cholelithiasis concomitant with choledocholithiasis. Other available options include laparoscopy, endoscopy, percutaneous technique, and open surgery. These methods can be done gradually or in combination. Considering this, there have been controversies about the best management option for the case. Therefore, this article aims to analyze and compare each methods of management.*

**Keywords:** Cholelithiasis, choledocholithiasis, management.

## INTRODUCTION

Cholelithiasis refers to a condition in which the formation of stones occurs within the gallbladder system. These stones are called gallstones.<sup>1</sup> Cholelithiasis has become one of the most common gastrointestinal diseases with the most hospital admissions. Several data have shown that the occurrence of cholelithiasis is found in 10-15% of Caucasian population, 70% in American Indian population, and 20% in European population. Asia on its own has a relatively low prevalence of the disease.<sup>2,3</sup> As for now, there is no data found concerning the epidemiology of cholelithiasis in Indonesia. However, research by Tuuk *et al.* at the Provincial Public Hospital Prof. Dr. R.D. Kandou Manado revealed that there were 113 cases of

cholelithiasis between 2015 and 2016.<sup>4</sup> Another research conducted in Cipto Mangunkusumo Hospital between 2008 and 2010 revealed 63 out of 129 patients with jaundice gone through endoscopic cholangiopancreatography therapy suffered from gallstones.<sup>5</sup>

Generally, patients with cholelithiasis do not show clinical manifestations or are asymptomatic. Nevertheless, around 10-25% patients will develop symptoms if inflammation or obstruction of the biliary duct is involved. The condition in which the common biliary duct is obstructed by gallstones is called choledocholithiasis.<sup>1,2</sup> Therefore, the incidence of cholelithiasis and choledocholithiasis is often diagnosed altogether, which is predicted to be 5-19%.<sup>6</sup> Research conducted by Prasson *et al.* (2016) showed

that the development of choledocholithiasis is approximately around 3-10% of cholelithiasis cases.<sup>7</sup> Memba *et al.* (2019) have specified that generally, choledocholithiasis is unintentionally diagnosed in routine checkups and pre-surgery radiology with incidence up to 5-33%.<sup>8</sup>

Cholesterol stones have become the most frequent cause of cholelithiasis and choledocholithiasis.<sup>2</sup> Several risk factors trigger the formation of the stones. Sex, family history, pregnancy, and age older than 40 are nonmodifiable risk factors. On the other hand, modifiable risk factors include obesity, rapid weight loss, high calorie diet, drugs such as oral contraceptives, type II diabetes history, hemolytic anemia, metabolic syndrome, dyslipidemia, smoking, and sedentary lifestyle.<sup>1</sup>

The management of cholelithiasis with choledocholithiasis has been a topic of discussion. Curative therapy for this case is surgery. Laparoscopic cholecystectomy is considered the gold standard of symptomatic cholelithiasis management. In contrast, the best management choice for choledocholithiasis is yet to be decided. Several choices are available such as laparoscopy, endoscopy, percutaneous technique, and open surgery, whether they are done in combination of gradually.<sup>2</sup> This article aims to discuss management choices for cholelithiasis with choledocholithiasis patients, and compare the methods.

## PATHOPHYSIOLOGY

Gallstones are made from the elements in the gallbladder such as cholesterol, bile salts, bilirubin, and phospholipids. Its formation occurs when the concentration of each element is imbalanced and then it settles into a solid compound.<sup>1</sup> There are two types of gallstones, cholesterol stones composed of cholesterol and pigment stones mainly composed of calcium bilirubinate. Pigment stones are further divided into two types, black pigment and brown pigment. Black pigment stones are formed due to polymerization in the gallbladder and usually found in hyperbilirubinemia conditions. Brown pigment stones have a softer texture because they are more often found unpolymerized in the bile ducts. These stones can appear due to anaerobic

bacterial infection or due to static flow.<sup>1</sup>

About 80% of the stones found in cholelithiasis are cholesterol stones. These stones form when the concentration of cholesterol is higher than the bile's ability to store them in solution.<sup>1</sup> The formation is triggered by the hormones estrogen and progesterone which play a role in increasing cholesterol secretion, decreasing bile salt secretion, and relaxing smooth muscle which will result in gallbladder stasis. Other conditions such as diabetic neuropathy, elevated levels of non-HDL cholesterol, metabolic syndrome, obesity, and rapid weight loss can also trigger cholesterol stone formation.<sup>1</sup>

Gallstones, especially small ones, can migrate to the common bile duct due to gallbladder contraction.<sup>6</sup> When these stones begin to block the ducts, they can cause hepatocyte damage due to reflux of flow to the liver and damage to the pancreas. The patient will also have biliary colic or pain in the epigastrium.<sup>1</sup>

## CLINICAL MANIFESTATIONS AND DIAGNOSIS

Cases of asymptomatic and uncomplicated cholelithiasis patients are estimated to be between 60 and 80% of total cases.<sup>9</sup> However, the risk of becoming symptomatic increases by 1-2.3% annually.<sup>2</sup> The cardinal signs of cholelithiasis or choledocholithiasis are usually fever, jaundice, accompanied by biliary colic. Biliary colic is a constant and sharp pain lasting more than 15 minutes, with irregular intervals in the right upper quadrant or epigastrium.<sup>3</sup> This pain may radiate to the ipsilateral scapula called Collin's sign.<sup>1</sup> Other symptoms may include back pain, nausea, vomiting, dyspepsia, diaphoresis, and abdominal bloating.<sup>1,3</sup> In patients with choledocholithiasis, the stool produced tends to be oily and has a foul odor due to obstruction of fat digestion substance, bile, in the duodenum.<sup>1</sup>

The presence of cholelithiasis can be diagnosed by transcutaneous ultrasonography (US) examination with a sensitivity of 95% and a specificity of 100%. The purpose of this sonography is to completely visualize the gallbladder from various positions along with the appearance of gallstones. According to the National Institute for Health and Care

Excellence (NICE), patients who are suspected of cholelithiasis are advised to undergo US and blood tests to see liver function.<sup>3</sup> In patients with suspected choledocholithiasis, liver function tests such as total bilirubin, gamma-glutamyltransferase ( $\gamma$ -GT), alkaline phosphatase (AP), alanine aminotransferase and aspartate aminotransferase (ALT/AST), and lipase, should be checked together with US.<sup>3</sup> Direct and total bilirubin have the highest sensitivity and are therefore considered the most reliable predictors of suspected choledocholithiasis.<sup>2</sup>

US examination sometimes fails to confirm choledocholithiasis. So, further radiological examination with MRI or CT scan is required. Radiological examination with CT scan, in this case, is rarely chosen because of the lower diagnostic power compared to that of MRI and high radiation exposure. In order to confirm further choledocholithiasis, Magnetic Resonance Cholangiopancreatography (MRCP) or Endoscopic Ultrasonography (EUS) are the most common options. NICE confirmed that EUS and MRI are also highly effective in detecting choledocholithiasis.<sup>3</sup> Both EUS and MRCP have similar specificity. For sensitivity, EUS is significantly superior to MRCP, with a percentage of 97% vs. 87%.<sup>3</sup>

The results of clinical, laboratory, and sonographic findings can be used as a guide to establishing the probability of the cholelithiasis patient also has choledocholithiasis complications. The probability is divided into three categories, high, medium, and low.<sup>3</sup> The criteria for each can be seen in **Table 1**.

Patients with a high probability of choledocholithiasis will be treated

with Endoscopic Retrograde Cholangiopancreatography (ERCP). ERCP is very helpful in assisting clinicians, not only as a diagnostic tool but also for therapeutic uses, especially in pancreaticobiliary tract disorders which need stone extraction. Retrospective study by Abdullah *et al.* (2012) in Cipto Mangunkusumo Hospital about the effectiveness of ERCP in the treatment of 53 choledocholithiasis patients showed 81% successful stone removal. Baron TH and Harewoods GC7 also reported 94.3% overall successful stone removal.<sup>5</sup>

If the probability of choledocholithiasis is low or moderate, an EUS or MRCP is recommended to decide whether an ERCP is necessary or not. For patients with a high probability of choledocholithiasis, it is also advisable to check with EUS or MRCP first. This examination is to improve accuracy and allow ERCP-referred patients to avoid unnecessary invasive procedures.<sup>3</sup> Figure 1 shows the diagnosis and treatment algorithm for choledocholithiasis in cholelithiasis patients.

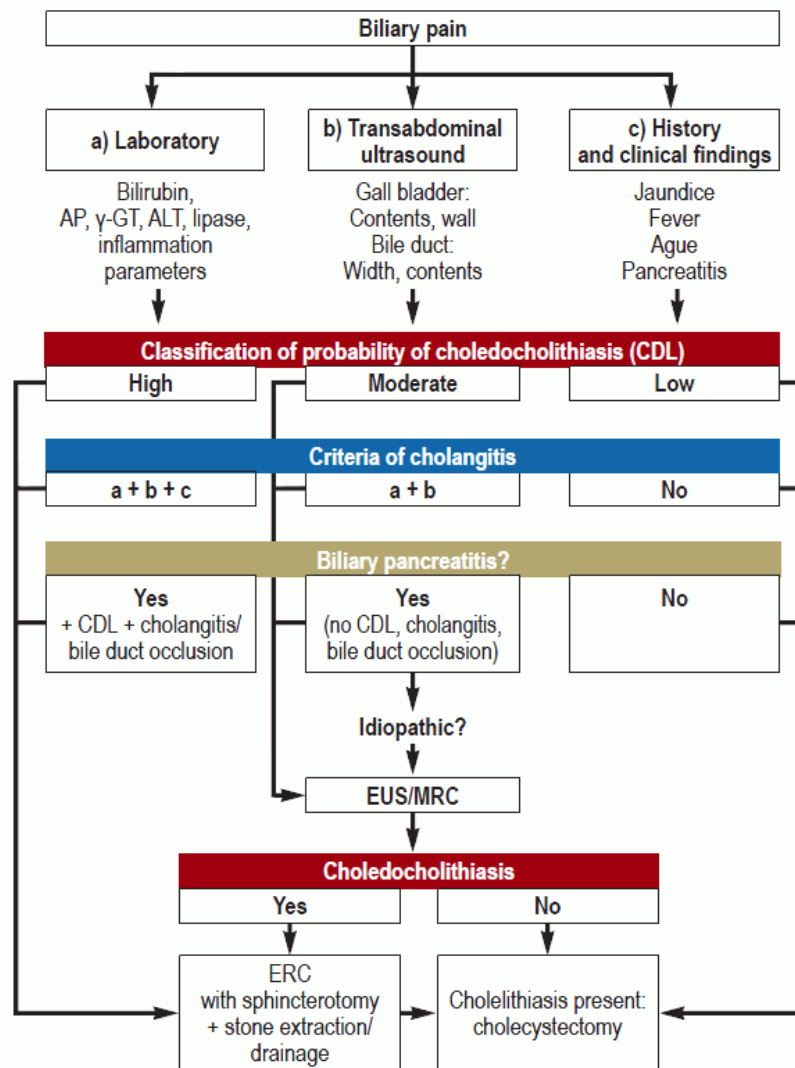
## MANAGEMENT

The principle of management of cholelithiasis is based on the presence or absence of symptoms and complications. Management generally includes changes in lifestyle, diet, and pharmacology. In asymptomatic patients diagnosed accidentally, the best treatment that can be done is expectant management. Pharmacological management is usually given to patients with mild symptoms.<sup>1</sup> Pharmacology provided consists of pain control, antiemetic,

**Table 1.** Criteria for simultaneous choledocholithiasis in a patient with cholelithiasis.

High likelihood of simultaneous choledocholithiasis (> 50%)
- Sonographically widened extrahepatic bile duct (>7 mm) + hyperbilirubinemia + elevation of $\gamma$ -GT, AP, ALT, or AST or
- Sonographic demonstration of bile duct concrements or
- Clinical and laboratory criteria of ascending cholangitis
Moderate likelihood of simultaneous choledocholithiasis (5–50%)
- Criteria for neither high nor low likelihood fulfilled
Low likelihood of simultaneous choledocholithiasis (<5%)
- Normal bile duct width (up to 7 mm)
- Total bilirubin, $\gamma$ -GT, AP, ALT, or AST not elevated during current pain episode
- Absence of episodes with biliary pancreatitis, acholic stools, and/or urobilinogenuria or bilirubinuria in recent past

Source: (Gutt *et al.*, 2020)



**Figure 1.** Algorithm for diagnosis and management of choledocholithiasis in cholelithiasis patients. Source: (Gutt et al., 2020)

and dissolution agent if needed. However, administration of a dissolution agent such as UDCA (Ursodeoxycholic Acid) to dissolve gallstones is not routinely recommended in all patients. Administration of UDCA is recommended in risk groups such as patients with rapid weight loss and patients with LPAC (low phospholipid-associated cholelithiasis). UDCA can also be administered to symptomatic patients with small cholesterol stones to avoid surgical intervention.<sup>1,3</sup> Surgical management is indicated in patients with symptomatic cholelithiasis, both complicated and uncomplicated, patients with asymptomatic cholelithiasis with gallstones >3 cm, polyps >1 cm, porcelain gallbladder, and patients with an increased risk of gallbladder

cancer.<sup>3</sup>

In cases of cholelithiasis accompanied by choledocholithiasis, surgical intervention is carried out to clear the tract and prevent more severe complications such as cholangitis and pancreatitis due to obstruction.<sup>2,9,10</sup> However, until now the best method for cholelithiasis patients accompanied by choledocholithiasis has not been determined.<sup>6</sup> Laparoscopic cholecystectomy is considered the gold standard for symptomatic cholelithiasis. On the other hand, the best method for choledocholithiasis is still uncertain.<sup>2</sup> Several guidelines such as the German Clinical Practice guideline, EASL, and SAGES provide treatment recommendations for cases of cholelithiasis accompanied by choledocholithiasis.

Management recommendations from each guideline are presented in **Table 2**.

Over time, new surgical methods have emerged with minimal invasion. The management of cholelithiasis with choledocholithiasis has now changed from open surgery to laparoscopy or endoscopic surgery.<sup>11</sup> This new surgical method can be divided into two, namely that which is carried out in stages (two stage treatment or two stages of therapy) and carried out simultaneously (one stage or single stage or one stage therapy).<sup>8</sup> The first category includes preoperative ERCP+laparoscopic cholecystectomy (LC) and postoperative LC+ERCP. The second category includes LC+ Laparoscopic Common Bile Duct Exploration (LCBDE) and rendezvous method.<sup>2</sup> However, open surgery in cases of cholelithiasis accompanied by choledocholithiasis is still performed in approximately 5-20% of cases.<sup>12</sup> The procedure consists of cholecystectomy by making a large incision, open exploration of the common bile duct by choledochenterostomy, and drainage with a T tube.<sup>2,12</sup> Currently, open surgery is performed when the stone clearance fails or the stone is difficult to extract by laparoscopic and endoscopic methods.<sup>2</sup>

ERCP followed by LC is the two-stage treatment most often chosen. ERCP is performed first to extract stones in the common bile duct using a sphincterotomy technique.<sup>8</sup> The second stage is followed by LC, which is removal of the gallbladder through four small incisions.<sup>13</sup> This second stage is carried out several days to

weeks after ERCP depending on the patient's condition.<sup>11</sup> The other two-stage therapy is the reverse of the previous method where the LC is performed first and then post-operative ERCP is followed. However, this method has a lower success rate than preoperative ERCP+LC. So, it is rarely chosen.<sup>2</sup>

In addition to preoperative ERCP + LC, LCBDE is also often recommended nowadays.<sup>6</sup> LCBDE includes single-stage therapy consisting of LC together with exploration of the common bile duct using intra-operative cholangiography (IOC) or ultrasonography (IUS). Stones in the common bile duct are then removed via a transistenic approach or choledocotomy under cholescopic direction.<sup>7,8</sup> As for the rendezvous method, LC and intra-operative ERCP were performed simultaneously. In this method, after cystic duct catheterization, cholangiography is performed to confirm the common bile duct stones. If the results are positive, then ERCP is performed, after which the LC is completed. However, the rendezvous method is rarely used because of the minimal availability of tools and experts.<sup>2</sup>

The three surgical methods for the management of cholelithiasis with choledocholithiasis have their respective advantages and disadvantages. Several RCTs and meta-analyses were performed to compare either two or all three methods of stone removal success, morbidity and mortality, complications, length of hospital stay, and cost of care. For comparison, the three methods are

**Table 2.** Recommendations for the management of cholelithiasis with choledocholithiasis.

Guideline	Treatment strategies in patients with choledocholithiasis with simultaneous cholelithiasis
<b>German Clinical Practice Guideline</b>	Therapeutic separation (pre- or intra-operatively) is recommended for patients diagnosed with choledocholithiasis and concomitant cholelithiasis (grade B recommendation, level of evidence I, strong consensus). After successful endoscopy of the bile ducts, cholelithiasis should be treated by cholecystectomy, ideally within 72 hours. Gallbladder that is still functional after stones are cleared (grade B recommendation, level of evidence I, strong consensus).
<b>EASL</b>	In patients found to have gallbladder and bile duct stones, early laparoscopic cholecystectomy should be performed within 72 hours after preoperative ERCP (moderate evidence, strong recommendation).
<b>SAGES</b>	ERCP with stone extraction that can be performed before, during, or after cholecystectomy, with little difference in morbidity and mortality rates, but the clearance rate is the same as for laparoscopic biliary tract exploration (level of evidence I, grade A recommendation).

Source: (Gutt *et al.*, 2020)

summarized in **Table 3**.

Meta-analysis by Singh and Kilambi (2018) compared the LCBDE+LC method with the ERCP+LC method to see which method is more ideal in cholelithiasis patients with choledocholithiasis.<sup>6</sup> There are several parameters for comparison. From the success rate of stone removal, LCBDE+LC had a higher success rate than ERCP+LC with a percentage of 88.1% and 82.2%, respectively. The failure rate of LCBDE+LC was also significantly lower (OR 0.59, 95% CI (0.38, 0.93),  $p=0.02$ ). There was no significant difference in mortality and morbidity rates, treatment costs, and stone recurrence rates between the two methods. LCBDE+LC had a shorter hospitalization time than ERCP+LC with a value of  $4.9\pm 1.6$  days compared to  $6.5\pm 3.4$  days. This meta-analysis concludes that single-stage therapy with LCBDE+LC is better than two-stage ERCP+LC therapy in terms of the success rate of the procedure and length of hospitalization.<sup>6</sup> Similar results were obtained from a retrospective study in 2015-2016 comparing single-stage rendezvous therapy with two-stage ERCP+LC therapy. It was concluded that patients who underwent one-stage therapy had a shorter hospitalization time than patients who underwent two-stage therapy ( $p < 0.026$ ).<sup>9</sup>

A study by Bayramov and Ibrahimova (2017) compared three procedures, namely open surgery, two-stage therapy, and one-stage therapy in 229 patients diagnosed with cholelithiasis with choledocholithiasis. The comparison parameters were seen from the length of the operation time, the success of removing all stones, the length of hospitalization, and complications. From the length of operation time, single-stage therapy and open surgery are not much different, but two-stage therapy requires a longer time. For

successful removal of all stones, single-stage therapy has higher effectiveness than two-stage therapy, and open surgery, with percentages of 97%, 85.7%, and 94.8%, respectively. Open surgery has the longest hospital stay. The highest complications were found in open surgery (52.5%), followed by two-stage therapy (33.3%), and single-stage therapy (19.4%). Increased mortality was also found in open surgery but not in the other two methods. The results of this study suggest that single-stage therapy can be used as the first choice for treating cholelithiasis patients with choledocholithiasis.<sup>12</sup>

Some guidelines such as EASL and SAGES still recommend two-stage therapy as the management of cholelithiasis with choledocholithiasis. This therapy is also still widely used. The advantage of this two-stage therapy is that the procedure is simpler or the tools are commonly available so that it can be carried out in various health facilities, especially with endoscopic facilities.<sup>8</sup> The results of various studies show the safety and effectiveness of this therapy, especially with the presence of MRI or EUS which increases the sensitivity and specificity of therapy in the preoperative diagnosis of choledocholithiasis.<sup>2</sup> The success rate, mortality, morbidity, cost of treatment, and length of treatment time of the two-stage therapy are quite good. However, two-stage therapy requires two separate procedures and two anesthetic procedures. So, it has a higher risk of complications than single-stage therapy.<sup>8</sup> The most common risks of complications are pancreatitis, sphincter of Oddi dysfunction, and duodenobiliary reflux due to retrograde procedures in ERCP.<sup>8,11,12</sup> The lag between the two stages also increases the possibility of the stone re-migrating to the common bile duct

**Table 3.** Comparison of the three operative methods in cholelithiasis with choledocholithiasis.

Parameter	One-Step Procedure (LCBDE+LC or rendezvous)	Two-Stage Procedure (ERCP+LC or LC+ERCP)	Open Surgery
Stone removal success rate	97%	85,7%	94,8%
Length of stay (days)	$2.3 \pm 0.65$	$6.5 \pm 1.5^*$	$8.2 \pm 2.7^*$
Mortality rate	0%	0%	3.8%
Complications	19.4%	33.3%*	52.5%*
Operating time (minutes)	$123 \pm 7$	$152 \pm 8^*$	$121 \pm 8$

\*  $p \leq 0.05$  compared to single-stage therapy (LCBDE+LC)<sup>11</sup>

before the LC can be performed.<sup>2,8</sup> Therefore, the implementation of LC should not be delayed too long to avoid stone recurrence.

From various comparison results, single-stage therapy has more advantages over the other two methods. Single-stage therapy is believed to be safe, effective, and efficient because two different pathological conditions can be resolved under one anesthesia and surgery. Complications due to two surgeries can also be minimized.<sup>2,6</sup> Despite these advantages, the choice of single-stage therapy needs to be considered. Adequate skills and instruments are required considering this therapy technique is quite complicated.<sup>6</sup>

## CONCLUSION

Choledocholithiasis is one of the complications of cholelithiasis. This condition requires immediate management by surgery intervention to avoid serious complications caused by obstruction. There are a variety of surgery methods at the moment, starting from the minimally invasive methods such as one stage and two stage treatment, to the extremely invasive methods such as open surgery. Based on the results of several studies comparing each method, it can be concluded that one stage treatment is significantly more effective in terms of the successful rate of stone removal, complications, and duration of hospitalization, while still considering instrument availability and masterliness. No research has determined the best management method for cholelithiasis with choledocholithiasis cases. Therefore, a subsequent study is required to determine the best method of management for the referred case.

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