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Successful Conservative Therapy in Patient with Cholelithiasis and Acute Cholecystitis with Elevated Liver Enzymes: A Case Report

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Abstract : Gallbladder disease has been a global medical burden. Acute cholecystitis is caused by stone either inside the gallbladder or in the bile ducts. Complications from the event could manifests as severe abdominal pain and may also cause elevated liver enzymes. We have long known cholelithiasis risk factors as 4F, which could also be found on young male patients. We report a young man with severe upper right quadrant-epigastric pain and nausea accompanied by the skin and sclera appeared jaundice. His laboratory showed elevated liver enzymes. Ultrasonography showed acute cholecystitis with sludge gallblader. In these patient, conservative care is carried out before further management. The liver function test was repeated and the results showed improvement. The repeated ultrasonography revealed cholelithiasis without signs of cholecystitis and sludge gallbladder. The purpose of this article is to discuss about cholelithiasis and cholecystitis, that cause elevated liver enzymes and its conservative treatment.

Keywords: acute cholecystitis, cholelithiasis, elevated liver enzymes, conservative therapy

1. Introduction

Cholecystitis is defined as gallbladder inflammation, which commonly caused by cystic duct obstruction from cholelithiasis. Ninety percent of cholecystitis is caused by stone in cystic duct (cholecystitis calculi), while the remaining 10% is acalculous cholecystitis. From all cholelithiasis cases in the United States, one third happens to have acute cholecystitis as well.

Cholelithiasis is more prevalence in developed countries than in developing countries. However the prevalence of cholelithiasis is decrease because of the socio-economic improvement, better diet and lifestyle, and diagnostic tools especially abdominal ultrasonography (USG).

Risk factors for gallstone formation includes obesity, diabetes mellitus, high estrogen level and pregnancy, hemolytic disease, and cirrhosis. Lifestyle, especially consumption of junk food, greasy food, and alcohol also contribute to early onset of gallstone formation. Where as, cholelithiasis is usually happen in the age of forty. Clinical presentations of gallstone are episodic pain (biliary colic), gallbladder inflammation (acute cholecystitis) or inflammation in the bile ducts (acute cholangitis). The migration of gallstone to common bile duct causes obstruction that can trigger some complications such as jaundice, elevated liver enzymes, pancreatitis and billiary cirrhosis. This case report will highlight an acute cholecystitis caused by cholelithiasis in a young male that causes elevated liver enzymes and its conservative therapy.[1,2]

2. Case Report

A 19-year-old male, with complaints of 5 days increasing epigastric and upper right quadrant pain. Pain is characterized as pulsating and constant, and worsen when patient was standing and walking. Pain is felt after eating and worsens especially after having greasy food. The patient denies of radiating pain to shoulder and right scapulae. Pain is accompanied with vomiting twice. Patient notices his eyeball and skin became yellowish. Patient also complaint of fever, 4 days before the abdominal pain started. The fever lasted for 3 days, constant and especially severe during the nights. Patient notices his urine is tea-like colored, and emerges together with the fever symptom. Patient also felt an itch all over his body. Patient denied pain and discomfort while urinating. Patient denied any discomfort in defecating, no bloody, clay-colored stool. Patient also denied any shortness of breath, chest pain, cold sweat, weight loss.

Since 2 years ago, the patient had history of alcohol consumption twice a month. The alcohol most frequently consumed is local alcohol drink from Bali. Patient frequently consumed fatty, oily, and junk food, and rarely consumes dietary fiber.

Physical examination revealed normal vital signs. The patient is 60 kg and 170 cm. When admitted to ward, physical examination revealed icteric sclerae, pain in right hypochondrium and epigastrium region with a positive Murphy's Sign, VAS scale is 6-7. Examination of other organs did not show any abnormalities. Routine blood count result: hemoglobin 14.7 g/dL, hematocrit 44.3%, leucocyte 5,820/μL, platelet count 211,000/μL. Blood biochemistry result: elevated ALT 2,030 U/L, elevated AST 930 U/L, elevated total bilirubin 8.81 mg/dL, elevated direct bilirubin 6.8 mg/dL, indirect bilirubin 2.01 mg/dL. Serology: negative Rapid Anti-HCV and HBsAg. Electrolyte and kidney functions are within normal range.

Table 1: Blood Examination Results (Day 1)

Parameter	Value	Unit	Normal value	Interpretation
Hemoglobin	14.7	g/dL	13.0-18.0	
White blood cell	5.82	10^3/uL	4.0-10.0	
Platelet	211	10^3/uL	150-400	
ALT	2,030	U/L	0-42	High
AST	930	U/L	0-37	High
Blood glucose	88	mg/dL	80-200	
Ureum	15	mg/dL	10-50	
Creatinin	0.8	mg/dL	0.3-1.2	
Total bilirubin	8.81	mg/dl	0.2-1	High
Direct bilirubin	6.8	mg/dl	0.1-0.4	High
Indirect bilirubin	2.01	mg/dl		
Sodium	137	mg/dl	136-145	
Potassium	4.1	mg/dl	3.5-5.1	
Chloride	98	mg/dl	97-111	
Anti HCV Rapid	negative		negative	
HBsAg	negative		negative	

Patient brought the results of the abdominal ultrasonography result before being treated in Wangaya Regional General Hospital. Abdominal ultrasonography showed enlarged liver (15 cm), smooth and sharp edges, homogenous echo liver parenchyma. Normal hepatica and portal vein, non-dilated intra biliary and extra hepatic ducts, no nodule, cyst, abscess was found on the liver. USG on gallbladder showed sludge, normal size gallbaldder, no thickness on the walls, no polyp or stone was seen. Conclusion: hepatosplenomegaly and acute cholecystitis with gallbladder sludge.

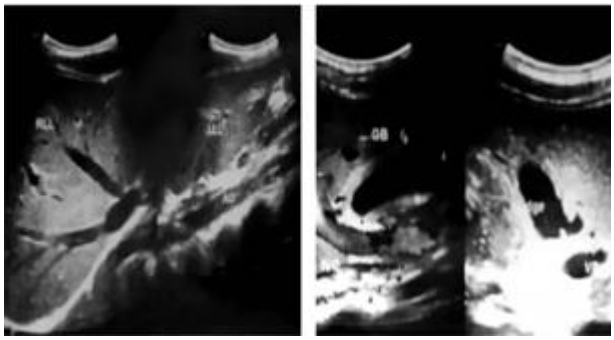

Figure 1: Abdominal Ultrasonography Before Admission in Wangaya Regional General Hospital.

Therapy given to the patient were cefoperazone injection (2x1 gram), Ursodeoxycholic Acid (UDCA) (3x1 tablet), curcuma (3x1 tablet). For symptomatic, the patient was given ranitidine injection (2x50 mg) for digestive complaints. Loratadine tables (1x10 mg) to ease the itch and dulcolax tablet (1x1) for constipation.

During hospitalization, patient experienced clinical and liver enzymes test improvement. Clinical evaluation was done to assess abdominal pain and jaundice on the patient. Abdominal pain is reduced, itchiness is resolved, jaundice on the skin and sclerae is reduced and no more occurrence of tea-colored urine. On day 5 admitted, blood works was repeated, and results shown reduced level of ALT (from 2,030 U/L to 718 U/L), reduced levels of AST (from 2.01 to 1.95 mg/dL), reduced levels of total bilirubin (from 8.81 mg/dL to 5.65 mg/dL), reduced levels direct bilirubin (from 6.8 mg/dL to 3.7 mg/dL), and reduced levels of indirect bilirubin (from 2.01 mg/dL to 1.95 mg/dL). On day 8 admitted, blood works was repeated again and more reduction was found: ALT 292 U/L, AST 60 U/L, total bilirubin 2.75 mg/dL, direct bilirubin 1.8 mg/dL and indirect bilirubin 0.94 mg/dL. Abdominal USG show no thickening and sludge was found on gall bladder. Abdominal USG shows enlarged liver (15 cm), homogenous echo liver parenchyma, smooth and sharp edges, no IHBD and EHBD dilation was seen. Gallbladder is normal in size, no sludge was seen, and a gallstone of 0.52 cm was found. Conclusion: hepatomegaly and cholelithiasis without signs of cholecystitis.

Table 2: Blood Examination Results (Day 5)

Parameter	Value	Unit	Normal value	Interpretation
ALT	718	U/L	0-42	High
AST	141	U/L	0-37	High
Total bilirubin	5.65	mg/dl	0.2-1	High
Direct bilirubin	3.7	mg/dl	0.1-0.4	High
Indirect bilirubin	1.95	mg/dl		

Table 3: Blood Examination Results (Day 8)

Parameter	Value	Unit	Normal value	Interpretation
ALT	292	U/L	0-42	High
AST	60	U/L	0-37	High
Total bilirubin	2.74	mg/dl	0.2-1	High
Direct bilirubin	1.8	mg/dl	0.1-0.4	High
Indirect bilirubin	0.94	mg/dl		

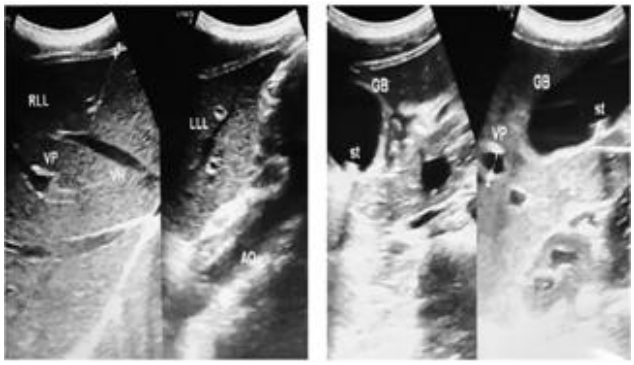

Figure 2: Repeated Abdominal Ultrasonography (Day 8).

3. Discussion

Patient came to the hospital due to severe upper right quadrant and epigastric pain that kept continously. Accompanied by skin and sclera appear jaundice. His laboratory showed elevated liver enzymes. His first ultrasonography revealed acute cholecystitis with sludge bladder and repetition ultrasonography revealed cholelithiasis without cholecystitis sign.

3.1 Acute Cholecystitis and Cholelithiasis

A hallmark symptom of acute cholecystitis is abdominal colic on upper right and epigastric quadrants, also tenderness, tachycardia and fever. Those symptoms might worsen progressively. The pain might radiate to shoulder or right scapulae and continuous up to 60 minutes without subsiding. The severity of symptoms rely on the degree of inflammation happening, from mild inflammation, gangrene, and even gall bladder perforation. Around 60-70% of patients reported self-resolving pain.[2] On this patient there are moderate abdominal colic on upper right and epigastric region also a positive Murphy's Sign, preceded by

a fever. On day 9 admitted Murphy's Sign is no longer positive.

Factors affecting an episode of cholecystitis are bile stasis, bacterial infection, and ischemia on gall bladder wall. The main cause of acute cholecystitis is gallstones (90%) and the rest (10%) is caused without the occurrence of stone (acalculous acute cholecystitis). Stones usually clog cystic duct causing bile stasis and gall bladder distension. This then causes blood and lymph flow disruption which resulted in ischemia and gall bladder wall necrosis. However, the exact mechanism on which stasis in cystic duct causing acute cholecystitis remains unclear until today. There are many factors that might cause inflammation response in cholecystitis, such as bile concentration, cholesterol, lysolecithin, and prostaglandins which irritates the gall bladder wall followed by inflammation and suppuration.[3] About 50-85% of acute cholecystitis is caused by bacterial infection, with the most common organism being *E. coli*, *Klebsiella* species, group D *Streptococcus*, *Staphylococcus* species, and *Clostridium* species. Endotoxins from these organisms causes loss of mucosal layer, bleeding, fibrin clotting, which resulted in ischemia and eventually gall bladder wall necrosis.[4] On this patient acute cholecystitis is caused by gallstone inside the gall bladder, as shown by repeated abdominal USG, where a 0,52 cm gallstone was seen inside the gall bladder, without gall bladder enlargement, no thickness on wall, no sludge. Liver was enlarged (15 cm), homogenous echo liver parenchyma, smooth and sharp edges, no IHBD and EHBD dilation was seen, a conclusion of hepatomegaly and cholelithiasis without signs of cholecystitis was noted. On the first USG, gall bladder was found to be normal in size with thickening walls, positive double layer and sludge without stones or polyp. Liver was found to be enlarged (15 cm), homogenous echo liver parenchyma, smooth and sharp edges, no IHBD and EHBD dilation was seen, and spleen was also enlarged (11,72 cm), homogenous echo spleen parenchyma, without any nodules, cysts, and calcification so it was concluded to be hepatosplenomegaly with acute cholecystitis and gall bladder sludge. Differences on the first and second USG was probably because of sludge covering the stone on the first USG or other factors, such as difficulties when the USG was done due to severe pain the patient was experiencing.

About a third until two thirds of cholelithiasis patient is asymptomatic. The symptoms might only manifests as dyspepsia accompanied with intolerance to fatty food. On symptomatic cholelithiasis, the main complaint is usually abdominal pain on epigastrium, right quadrant, or hypochondrium. The pain might also manifest as biliary colic which lasted for more than 15 minutes, and might subsided only after a few hours. Most cases reported of a gradual increasing pain, but about 30% of cases experience sudden pain.[1]

Cholelithiasis risk factors is categorized into modifiable and unmodifiable risks. Unmodifiable risks consist of ethnicity, female gender, age >40 years, family history, and pregnancy. Modifiable risks are obesity, which includes dyslipidemia, extreme weight loss (more than 15 kgs in a short period of time), high-calorie diet, lifestyle such as alcohol, type 2 diabetes, and metabolic syndrome. Nowadays, cholelithiasis is also seen on younger people and males. But females still have a higher risk. Early onset of cholelithiasis is caused by obesity and history of childhood obesity, extreme weight loss dieting, alcohol consumption, smoking, frequently consumes fatty and junk food, family history, and metabolic syndrome. On this patient, the risks factor found is related to lifestyle, the patient drink alcohol regularly and frequently eats fatty and junk food.[5]

3.2 Elevated Liver Enzymes

Normally, elevated liver enzyme are not found in gallstone-induced acute cholecystitis, except when it happened concomitantly with choledocholithiasis. But in biliary obstruction cases, usually the liver enzymes are elevated. It is caused by multiple reasons such as the increase in hepatocellular membrane permeability due to increased pressure in the biliary tract, elevated amino acid transcription enzymes, and hepatocellular toxicity from retained bile acids. A few studies have been done on using liver function tests to detect the presence of choledocholithiasis. Results show that alkaline phosphatase (ALP) and total bilirubin can be used to predict choledocholithiasis. However, liver enzyme test cannot single handedly be used to diagnose choledocholithiasis on account of its false-positive factors, such as Gilbert syndrome, general illness, and spontaneous stone passage. Also its false-negative factors, such as partial obstruction by common bile duct (CBD) stone. One study reported that a case of cholecystitis without choledocholithiasis show mild and transient acute hepatocellular injury and that hyperbilirubinemia and might be caused by changes in gallbladder from inflammation. A possible explanation is that severe acute inflammation of GB will disturb the bile flow, and bile stasis causes diffuse intrahepatic inflammatory change and bacterial contamination causing liver injury, Endoscopic Retrograde (ERCP), Magnetic Resonance Cholangiopancratography (MRCP), Endoscopic Ultrasonography (EUS), orintraoperative cholangiography, can be done to confirm choledocholithiasis diagnosis, however it is quite expensive and might cause complications as they are invasive examinations, and radiological examinations such as abdominal CT scan. A study by Videhult et al, found ALP and bilirubin were the most reliable factors, although their roles in the diagnosis were limited. Patients with severe inflammatory changes on histological examination, could also have elevated liver enzymes due to hepatocellular injury which is found by analyzing cholecystitis patients with elevated liver enzymes. Elevated liver enzyme by severe inflammation in gallstone disease could be explained such as: acute inflammatory change or fat metamorphosis was in gallstone disease including patients with cholangitis and acute cholecystitis, and these changes happened because of bacterial contamination through lymphatic or portal system. Hepatic and circulating cytokines such as TNF-a, interleukin-1 (IL-1), IL-6, and IL-8, which may be elevated because of bacterial endotoxin and lipopolysaccharides, might damage the liver tissues by activating immune response.Beside choledocholithiasis and CBD dilatation, it can be concluded that an elevated liver enzymes can be caused by liver

damage itself because of fatty liver (non-alcoholic fatty liver), and hepatitis.[6]

On this case, when abdominal USG did not found any gallstone an abdominal CT scan or ERCP should be done to ensure there are no stone in bile ducts, dilatation of IHBD and EHBD. We must admit of limited additional examination in this hospital, such as ALP, anti-HAV, abdominal CT, ERCP, MRCP, and EUS.

3.3 Treatments on Cholecystitis and Cholelithiasis

Even though surgery remains to be the main therapy for acute cholestasis and its complication, a stabilization period might be needed in the hospital pre-cholecystectomy. General treatments included bed rest, keeping check of patient's hydration status, parenteral nutrition, light diet, electrolyte correction, pain killers like pethidine and antispasmodic. Early administration of antibiotics is crucial to avoid complications such as peritonitis, cholangitis, and septicemia. Ampicillin, cephalosporin, and metronidazole is effective for usual causative bacteria for acute cholecystitis such as *E. coli, Strep. faecalis and Klebsiella*, however for diabetic patients with symptoms of sepsis caused by gram negative bacteria it is recommended to administer combination of antibiotics.[7] According to Sanford recommendation, a combination of intravenous ampicillin/sulbactam with a dosage of 3 gram/ 6 hour, third generation of cephalosporin, or metronidazole with a starting dose of 1 gram, and then 500 mg/6 hour IV may be administered. On severe cases, intravenous imipenem 500 mg/6 hour could be given. For nausea and vomiting, anti-emetics could be prescribed, or insertion of nasogastric tube. Intravenous CCK may help to empty the gall bladder and preventing further bile stasis. Before discharging any cholecystitis patients without complication, make sure there is no fever, stable vital signs, no signs of obstruction on laboratory results and USG, and other disease (such as diabetes mellitus) are kept in check. Upon discharged, prescribe antibiotics like levofloxacin 1x500 mg PO, and metronidazole 2x500 mg PO, anti-emetics, and analgesics. Timing for cholecystectomy is still a subject to be discussed, either as soon as possible (within 3 days), or delayed for 6-8 weeks after conservative therapy and patient's condition is generally better. About 50% cases is resolved without surgery interventions. Surgeons supporting early surgical intervention stated that gangrene and complication arising from conservative therapy failure could be prevented and shortens length of hospital stay. On the contrary, other surgeons stated that early surgical therapy might cause the infection to spread to peritoneum cavity, and more difficulties will be experienced during operation caused by anatomy blurring from inflammation. Nevertheless, emergency cholecystostomy or cholecystectomy might need to be done on acute cholecystitis complication, such as empyema, emphysematous cholecystitis, or perforation of gall bladder.[8]

When an asymptomatic gallstone is found during a patient examination, a prophylactic cholecystectomy is not needed. Only 30% patients with asymptomatic cholelithiasis need operation during their lifetime, and this proves that on some patients cholelithiasis is relatively a mild health problem and not harmful. However, there are few conditions that indicates the need to do a prophylactic cholecystectomy. These factors are, large gall bladder size (>2,5 cm), patient with congenital hemolytic anemia, unfunctional gall bladder, or patient under colectomy procedure. On symptomatic gallstones, it is commonly indicated for a definitive cholecystectomy to be done, with an exception on some cases when only medications are used to eliminate the gallstone. In non-complicated cholecystitis with biliary colic, medical treatment could be an alternative for some patients, especially to those with higher risks if operated.
For conservative treatment, medications suppressing the synthesis and secretion of cholesterol could be given, and also to inhibit absorption of cholesterol in the intestine. UDCA is the most commonly use medicine, and is indicated for radiolucent gallstones, with diameter less than 20 mm on patients unfit for cholecystectomy. This medication will inhibit endogen bile synthesis and secretion, and has jo effect towards phospholipid secretion in bile. After taking it for 3 weeks, the medication will reach a stable level. Commonly used dose is 8-10 mg/kg BB divided into 2-3 dosages per day. This intervention should be given for 6-18 months and usually will be successful with small sized stone, cholesterol-typed stones, and has a relapsing rate of 50% in 5 years.

3.4 Mechanisme of UDCA

Therapy with UDCA decreases the cholesterol secretion into bile which is proven by a reduction in cholesterol fraction of biliary lipids, it lowers biliary cholesterol by 40±60%. Also, UDCA either decreases absorption of cholesterol in intestine and/or increases cholesterol conversion into bile acids. Moreover, UDCA also affects bile acid metabolism, where UDCA increases the metabolic conversion of cholesterol to bile acids in healthy individuals, also in patients with hyperlipidemia and cholestatic liver diseases.

In cholestatic liver diseases, bile acids can be found in the liver, systemic circulation and peripheral tissues. Accumulation of hydrophobic (i.e. toxic) bile acids in hepatocytes leads to a cascade of cell damaging events starting from increased cell-membrane fluidity and permeability to apoptosis and necrosis. The damage on hepatocytes is related with the duration of exposure to hepatotoxic bile acids. A short exposure of bile acids inside the hepatocytes can cause reversible elevation of transaminases. However, on event like prolonged cholestasis, chronic exposure of toxic bile acids might result in liver fibrosis and cirrhosis. One of the main therapeutic effects of UDCA in cholestatic liver diseases is related toendogenous hepatotoxic bile displacement by expansion of the hydrophilic bile acid pool (i.e. enrichment by UDCA). Indeed, UDCA per oral may reduce the absorption of endogenous bile acids in ileum by competitive inhibition mechanism. Therapy with UDCA may improve hepatic excretory rates and transit time of a g-labeled bile acidanalog.

UDCA offers in hepatoprotective effects in multiple pathways such as maintaining cell structures (i.e. plasma membranes, mitochondria) and by promoting subcellular anti-apoptotic pathways as discussed below.

Hepatoprotective effects of UDCA was related to its direct interaction with liver cells plasma membranes and UDCA, through physical and chemical effects in reducing disruption of cholesterol-rich model membranes caused by toxic bile salts. By altering micelle's structure and composition UDCA prevents membrane disruption induces by hydrophobic bile acid. Evidence states that UDCA is capable of preventing destruction of cell-membrane. In cholangiocytes, we can distinctly see the protective effects of UDCA. Even though phospholipid-rich mixed micelles in canaliculi may be important to avert damage on the upper domain of cholangiocytes by hydrophobic bile acids, the direct protective effect of UDCA on these cells are very prominent. In hepatic epithelia, cell death mainly happens through apoptosis more than necrosis. Apoptosis (programmed cell death) is differentiate by morphologic and biochemical cell alterations causing inter nucleosome degradation and the development of apoptotic bodies (i.e. nuclear fragments and cell organelles contained by plasma membrane). Apoptosis facilitates selective elimination of senile, injured or diseased liver epithelia. Hepatocytes apoptosis caused by non-membrane damaging agents such as ethanol, transforming growth factor-b1 (TGF-b1), anti-Fas antibody and okadaic acid, could also be inhibited by UDCA.These broad mechanisms of UDCA in regulating a variety of apoptotic pathways may probably related to modulation of mitochondrial membrane stability and function.[9]

On this case, UDCA is given 3 times daily, and monitoring of the clinical symptoms and liver function. When first admitted, AST and ALT was elevated, with a value of 2,030 U/L and 930 UL/ respectively, accompanied with elevated total and direct bilirubin with a value of 8.81 mg/dL and 6.8 mg/dL respectively. Clinical improvement was seen on the patient, and it is proven when blood work was done again on the 5th day admitted. Levels of ALT and AST has decreased becoming 718 U/L and 141 U/L, total bilirubin is 5.65 mg/dL and direct bilirubin is 3.7 mg/dL. On the 8th day admitted, liver function test were done. ALT and AST became 292 U/L and 60 U/L, and decreased total and direct bilirubin concentration to 2.75 mg/dL and 1.8 mg/dL. Improvement of liver function is accompanied with improving clinical symptoms such as no more pain, jaundice on eyes and skin is reduced, and no tea-colored urine.

4. Conclusion

Existing theory supports that elevated liver enzymes is caused by stone formation on bile ducts. On this patient, USG only found gallstone inside the gall bladder and none on bile duct. Due to facility limitation further examination such as abdominal CT scan and ERCP could not be done. Tests for hepatitis B and C were done, but there was not a test for hepatitis A, so we could not find out whether the patients has hepatitis A or not. Impaired liver functions may also be caused by alcohol and related to the patient's age. Cholelithiasis risk factors are 4F. On younger population and outside 4F, lifestyle factors, like alcohol consumption and diet of fatty and junk food might also contribute to be risk factors. On this patient, a conservative treatment was done using cephalosporin class antibiotic and UDCA to suppress the synthesis and secretion of cholesterol, and to inhibit cholesterol absorption in intestines also for its cytoprotective effect, which fulfill therapy expectation.

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