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Review Article

A Review of Ursodeoxycholic Acid Therapy for Cholelithiasis and Choledocholithiasis

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Abstract

Cholelithiasis and gallstone-related complications remain one of the most prevalent gastrointestinal diseases globally. Age, gender, body mass index, physical activity, dietary factors, and genetics play a role in the development of gallstones. More than 20% of patients with gallstones will develop symptomatic disease during their lifetime, which can often lead to complications and significant morbidity. Laparoscopic cholecystectomy is considered the standard of care for symptomatic gallstone disease. Still, in select patient populations and in those who are non-surgical candidates, medical management, with bile acid therapy such as ursodeoxycholic acid (UDCA) or mechanical therapy such as extracorporeal shock wave lithotripsy, is preferred. UDCA is a hydrophilic bile acid that lowers biliary cholesterol saturation and aids in dissolving small, cholesterol-rich gallstones. UDCA appears to be well tolerated in the populations studied. While serious adverse events were uncommon in the available literature, UDCA's efficacy is limited by a high recurrence rate. The aim of this review is to summarize the current evidence and developments regarding the role of UDCA therapy in the management of cholelithiasis and choledocholithiasis.

Introduction

Gallstone disease is defined as the development of symptoms or complications due to gallstones in the gallbladder or bile ducts. Cholecystolithiasis, or cholelithiasis, is the presence of stones in the gallbladder, which can lead to biliary colic and complications such as acute cholecystitis, whereas choledocholithiasis, which is the presence of stones in the common bile duct (CBD), can lead to acute cholangitis and biliary pancreatitis.[1] Age, gender, body mass index, physical activity, dietary factors, and genetics play a role in the development of gallstones.[2,3] More than 20% of people with gallstone will develop mild to severe symptoms in their lifetime, and this subset of the population is at an increased risk of developing serious complications.

Gallstones are caused by abnormally high levels of cholesterol or bilirubin in the bile. More than 75% of gallstones are cholesterol gallstones, while less than 20% are other types, consisting of black pigment gallstones (composed of polymerized calcium bilirubinate), brown pigment gallstones (composed of bilirubin and calcium fatty acid soaps), or mixed stones.[1,4] Cholecystectomy is currently considered the gold standard treatment for symptomatic gallstone disease, whereas endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy and stone extraction is performed for symptomatic CBD stone disease.[3] Though cholecystectomy is first-line management with a good success rate in the younger population, older patients are often considered high-risk surgical candidates, given extensive comorbidities and frailty.[5] In this cohort, there is a higher tendency to lean toward non-operative management.

The non-surgical modalities of treatment for cholesterol stones include gallstone dissolution through medical/bile acid therapy, such as ursodeoxycholic acid (UDCA), and biomechanical therapy, such as extracorporeal lithotripsy, with a success rate ranging from 25% to 60%. However, these treatments usually have a high recurrence rate.[3]

The aim of this review is to summarize current evidence on the mechanisms, clinical applications, limitations, and roles of UDCA in the management of cholelithiasis and choledocholithiasis across different patient populations, comparative effectiveness, and practical management considerations. The review focuses specifically on UDCA rather than chenodeoxycholic acid (CDCA), as CDCA is no longer widely used due to its higher rate of gastrointestinal

Keywords: Cholelithiasis; Choledocholithiasis; Cholestasis; Ursodeoxycholic acid; Gallbladder disease; Common bile duct disease; Drug therapy; Bile acid and salt; Stent; Cholecystectomy; Endoscopic retrograde cholangiopancreatography; ERCP.

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adverse effects, hepatotoxicity concerns, poorer tolerability, and limited availability in many regions.

Mechanism of action of UDCA

Bile acids are steroid-based molecules synthesized from cholesterol by hepatocytes, and they aid in the digestion and absorption of dietary fats. Bile acids exist in two main forms: primary bile acids (cholic acid and CDCA), which are synthesized in the liver, and secondary bile acids (deoxycholic acid and lithocholic acid), formed in the intestine through deconjugation and dehydroxylation of the primary bile acids by the gut microbiota. UDCA is a type of secondary bile acid that is produced in very small amounts naturally and comprises around 4% of bile acids in humans. It is not synthesized by hepatocytes but is instead produced by the colonic bacteria, which are then absorbed into the portal circulation.[6] In comparison to the naturally synthesized bile acids, UDCA is more hydrophilic.[6]

The mechanism of action of UDCA on the liver and biliary system involves several overlapping pathways, such as altering the composition of bile acids, promoting bile flow, and immune regulation, with a cytoprotective effect on hepatocytes and cholangiocytes. With respect to the management of gallstones, UDCA primarily works by altering the cholesterol-to-bile ratio. It decreases cholesterol secretion into the bile by almost 40–60%. Based on human and animal studies, UDCA does this by reducing cholesterol absorption in the gut and increasing the conversion of cholesterol to bile acids.[2,6] This may be beneficial in patients with hyperlipidemia and cholestatic liver disease. Studies in patients receiving UDCA for the dissolution of gallstones have failed to show any significant change in serum cholesterol or low-density lipoprotein. However, some studies have shown a triglyceride reducing effect of UDCA.

Intracellular accumulation of hydrophobic bile acids in the liver leads to the formation of reactive oxygen species, which induce inflammation, cell damage, apoptosis, and necrosis. This plays a significant role in the pathophysiology of cholestatic liver diseases, such as primary biliary cholangitis (PBC), and ongoing damage and inflammation within the gallbladder can lead to cholecystitis.[7] One proposed mechanism for the cytoprotective nature of UDCA is that it enriches the bile pool with hydrophilic bile components, displacing toxic hydrophobic bile acids at the hepatocellular level, thereby decreasing inflammation. Upon oral administration, it competes with the enterohepatic reuptake of endogenous bile acids at the level of the terminal ileum, altering the bile acid composition. Eventually, UDCA accounts for 20% to 65% of the total biliary bile acids.[6,8,9] This was observed in many animal models; however, in clinical studies of patients with cholestatic liver disease, it did not affect endogenous bile acid synthesis, and there was no change in serum bile acid levels before and after therapy.[10]

Experimental models have demonstrated an additional immunomodulatory effect of UDCA on the humoral immune system, characterized by a reduction in the levels of IgM and IgG antibodies, as well as a decrease in T cell-mediated hepatocellular injury. This can be beneficial in patients with autoimmune cholestatic diseases such as PBC. UDCA further protects hepatocytes by stabilizing cell structures and inducing anti-apoptotic pathways.[2,6] It also limits the production of reactive oxygen species by Kupffer cells, thereby keeping oxidative stress within hepatocytes under control.[9]

Furthermore, UDCA has a choleretic effect, provoking the secretion and flow of bile. This is confirmed in experimental models as well as clinical trials, in which patients with cholestatic liver disease showed increased excretion and lowered transit time of gamma-labelled bile acid analogues. Some studies also suggest that UDCA may cause impaired gallbladder motility, characterized by increased fasting and residual postprandial gallbladder volumes, fewer cholesterol crystals, or decreased mucin content in bile, which may lead to improved symptom control.[6,11] Figure 1 summarizes the proposed mechanisms of UDCA.

Indications for UDCA therapy

UDCA has been approved and used for managing symptomatic gallstone disease, as well as several cholestatic and other liver diseases. In 1975, Makino *et al*.[12] first published a study showing dissolution of gallstones after UDCA treatment. Since then, several prospective studies have reported variable response rates to UDCA treatment. Additionally, biliary sludge has been found to respond well to UDCA. It is also used in the treatment of persistent biliary colic after cholecystectomy, as in post-cholecystectomy syndrome. Some of the cholestatic liver diseases for which UDCA is considered the treatment of choice for cure or slowing disease progression are PBC, intrahepatic cholestasis of pregnancy (ICP), primary sclerosing cholangitis (PSC), cystic fibrosis, and familial cholestatic diseases.[6] Especially with PBC, studies have shown long-term treatment with UDCA slows disease progression and decreases the need for liver transplantation.[13,14] UDCA has been used in other situations, including graft-versus-host disease affecting the liver, liver allograft rejection, and TPN-related cholestasis, among others.[6]

Efficacy of UDCA in cholelithiasis

The effectiveness of UDCA in dissolving gallstones is significantly influenced by meticulous patient selection. The most substantial evidence supports its use in patients with radiolucent, non-calcified gallbladder stones smaller than 20 mm in diameter, particularly in those who are poor surgical candidates due to comorbidities, advanced age, anesthesia risks, or refusal to undergo surgery.[15,16] Pre-treatment imaging, including computed tomography to evaluate stone density, is recommended to enhance patient selection. Gallbladder motility can be evaluated using ultrasonography. A reduction in gallbladder volume exceeding 60% after a stimulating meal indicates proper gallbladder function. Large clinical trials and regulatory reviews have demonstrated that age, sex, weight, degree of obesity, and serum cholesterol levels do not significantly influence the likelihood of stone dissolution.[16]

Stone size and composition are the most critical determinants of UDCA effectiveness. Radiolucency on imaging is a surrogate marker for cholesterol-rich composition, which is essential for UDCA responsiveness. During the mid-to-late 1900s, several randomized controlled trials (RCTs) comparing the effects of placebo versus CDCA and UDCA on gallstone dissolution were published. A meta-analysis published in 1993 evaluating bile acid therapy in gallstone disease showed that in studies lasting more than six months, high-dose UDCA (>7 mg/kg/day) completely dissolved stones in 37.3% of patients (95% confidence interval (CI) 33–42 %), low-dose UDCA (<7 mg/kg/day) in 20.6% (95% CI 15–26%), and high-dose CDCA (>10 mg/kg/day) in 18.2% (95% CI 15–21%).[17] The authors concluded that bile acid therapy can be considered in a specific subset of patients, such as elderly patients, poor surgical candidates, or those with small stones.[17] Later, one

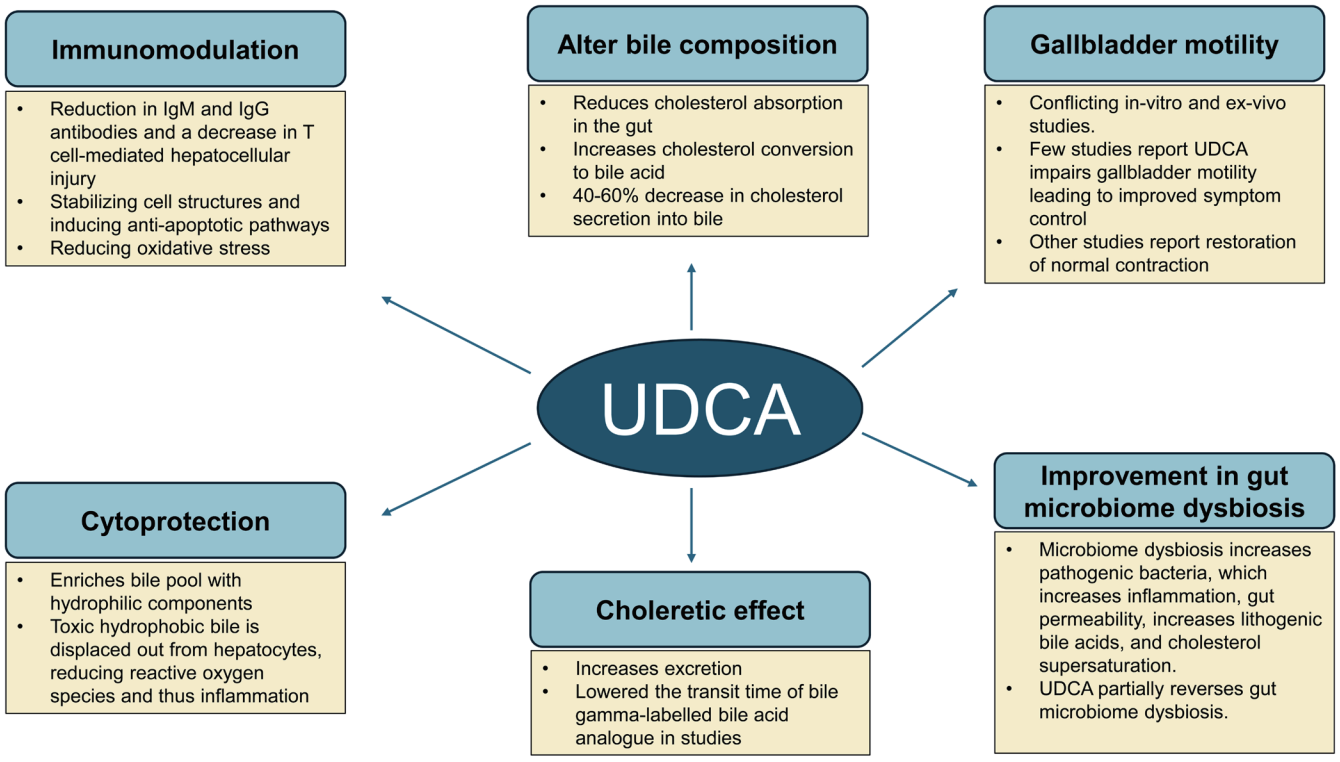

Fig. 1. Illustrative summary of the proposed mechanisms of UDCA. IgM, immunoglobulin M; IgG, immunoglobulin G; UDCA, ursodeoxycholic acid.

study reported an 87.1% response rate for isodense (cholesterol-rich) stones identified on computed tomography, compared to only 6.2% for hyperdense or calcified stones.[18] Complete dissolution was observed in 81% of patients with stones measuring ≤5 mm in diameter, whereas stones exceeding 20 mm in maximal diameter rarely dissolve with ursodiol therapy alone. These findings are based on pooled results from eight clinical studies (three in the U.S., one in the U.K., and four in Italy) involving 868 patients with radiolucent gallstones treated with ursodiol at 8–10 mg/kg/day for up to two years.[16] Table 1 summarizes the response and dissolution rates of gallstones with UDCA therapy across different studies.[16–19]

UDCA therapy is also linked to symptom improvement, including a reduction in biliary pain and acute cholecystitis, especially in patients with uncomplicated gallstones and those at high surgical risk. Long-term cohort data indicate a significant decrease in biliary pain and the need for cholecystectomy in both symptomatic and asymptomatic patients, regardless of complete stone dissolution.[20] However, previous studies have suggested no beneficial effect in patients with symptomatic gallstones awaiting cholecystectomy.[21]

The absence of partial dissolution within the first six to twelve months of therapy is a poor prognostic factor. Partial dissolution at six months is associated with a greater than 70% chance of eventual complete dissolution, whereas a lack of response at one year indicates a low likelihood of success.[16] Recent studies have identified the gut microbiome as a potential modulator of the response to UDCA therapy. Specifically, a low abundance of the Erysipelotrichi lineage and reduced overall abundance of the Firmicutes phylum have been correlated with a favorable therapeutic response.[22]

UDCA and endoscopic treatment for choledocholithiasis

When combined with endoscopic treatment and biliary stenting, UDCA reduces the size of large and multiple CBD stones, potentially aiding in stone clearance without increasing adverse events. In an Iranian study, 64 patients with multiple or large CBD stones (>3 or >15 mm) received standard endoscopic therapies with UDCA and CBD stenting (group B), while the controls received only standard endoscopic therapies with CBD stenting. The mean reduction in stone size was significantly greater in group B than in group A (3.22 ± 1.31 mm vs. 4.09 ± 1.87 mm) ($P = 0.034$). No significant differences were observed in the incidence of complications, such as pancreatitis, cholangitis, bleeding, or perforation, between the two groups ($P > 0.05$).[23]

In a South Korean multicenter prospective study involving elderly patients with challenging-to-remove CBD stones, a regimen combining a 10-French plastic biliary stent, 600 mg of UDCA, and 300 mg of a terpene preparation daily for six months resulted in a significant reduction in the average stone size. This approach enabled complete stone removal in 92.8% of patients, with an average of 1.7 procedures required. The intervention was well tolerated and appeared effective in managing retained CBD stones in this high-risk population. However, the study was limited by a small sample size and the absence of a control group.[24] Table 2 summarizes the efficacy and safety of UDCA combined with endoscopic treatment for choledocholithiasis/CBD stones.[23-26]

UDCA's role in recurrent stone disease

Although UDCA is not recognized as a primary treatment for choledocholithiasis, several studies have explored its role as an adjunctive agent to reduce stone recurrence after endoscopic re-

Table 1. The response and dissolution rates of gallstones with UDCA therapy across multiple studies

Stone characteristics	Study details	Dissolution rate	Duration	Dosage	Reference
Stone size					
≤5 mm diameter	Pooled analysis (8 studies, 868 patients)	81% complete dissolution	Up to 2 years	8–10 mg/kg/day	16
≤20 mm diameter	Pooled analysis (8 studies, 868 patients)	Variable (size-dependent)	Up to 2 years	8–10 mg/kg/day	16
>20 mm diameter	Pooled analysis (8 studies, 868 patients)	Rarely dissolve	Up to 2 years	8–10 mg/kg/day	16
Stone composition					
Isodense (cholesterol-rich) on CT scan	Lee *et al*., 2015	87.1% response rate	Not specified	Not specified	18
Hyperdense/calcified on CT scan	Lee *et al*., 2015	6.2% response rate	Not specified	Not specified	18
Radiolucent stones	Meta-analysis (1993)	38% complete dissolution	>6 months	7 mg/kg/day	17
Predictive factors					
Partial dissolution at 6 months	Pooled analysis	>70% eventual complete dissolution	Ongoing therapy	8–10 mg/kg/day	16
No response at 12 months	Pooled analysis	Low likelihood of success	N/A	8–10 mg/kg/day	16
Post-bariatric surgery (treatment of formed stones)					
Post-LSG formed gallstones	Retrospective cohort (88 patients: 51 UDCA, 37 control; 2017–2023)	60% dissolution rate in UDCA group vs. control; stones < 5 mm had a higher success rate	Mean follow-up not specified	15 mg/kg/day	19

CT, computed tomography; LSG, laparoscopic sleeve gastrectomy; UDCA, ursodeoxycholic acid.

moval and aid in stone clearance in difficult cases. A randomized trial from Japan suggested that UDCA may lower the recurrence rate of CBD stones following endoscopic removal, with recurrence rates of 6.6% in the UDCA group compared to 18.6% in the untreated group, though statistical significance was not achieved due to the small sample size.[27] While the combination of UDCA, terpene, and endoscopic biliary stenting has been identified as an effective treatment for CBD stones,[24] two RCTs indicated that in-

Table 2. Clinical studies evaluating the efficacy and safety of UDCA combined with endoscopic treatment for choledocholithiasis/CBD stones

Study	Population	Intervention vs. Control	Baseline stone size	Change in stone size	Duct clearance	Complications
Hormati *et al*., 2020[23]	64 pts; multiple (>3) or large (>15 mm) CBD stones	ERCP + stent + UDCA vs. ERCP + stent	Not reported	4.09±1.87 mm vs. 3.22±1.31 mm (P = 0.034)	Not reported	No difference (pancreatitis, cholangitis, bleeding, perforation)
Lee *et al*., 2011[25]	51 elderly; difficult CBD stones	Multiple double-pigtail stents + UDCA + terpene vs. stents alone	A: 19.1/20.5 mm B: 21.3/22.6 mm	Both groups ↓ significantly; no difference (P = 0.685, P = 0.289)	73.7% vs. 86.4%	Cholangitis (A:1); stent migration (B:2); no serious AEs
Han *et al*., 2009[24]	Elderly; difficult CBD stones	Plastic stent + UDCA + terpene; no control	Not reported	Significant reduction (values not provided)	92.8%; avg 1.7 ERCP sessions	Well tolerated
Katsinelos *et al*., 2008[26]	41 difficult-to-extract stones	Plastic stent + UDCA vs. stent + placebo	Both: 1.61 cm	1.21 cm vs. 1.24 cm (P = 0.602)	76.9% vs. 75%	No major AEs; fragmentation similar (P = 0.558)

AEs, adverse events; CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; UDCA, ursodeoxycholic acid.

Table 3. Data from clinical studies evaluating the effect of UDCA and related agents on recurrence rates of CBD stones following endoscopic removal

Study	Study design	Intervention	Recurrence rate (Intervention)	Recurrence rate (Control)	Statistical significance
Yamamoto *et al*., 2016[27]	RCT	UDCA after endoscopic removal	6.6%	18.6% (no treatment)	Not significant (small sample)
Katsinelos *et al*., 2008[26]	RCT	Endoprosthesis + UDCA	No reduction in stone size	N/A	Not effective
Lee *et al*., 2011[25]	Prospective multicenter	Double-pigtail stents + choleretic agents	No benefit	N/A	Not effective
Song *et al*., 2016[28]	Retrospective	UDCA	Did not prevent recurrence	N/A	Not effective
Baek *et al*., 2009[29]	Retrospective	UDCA or terpenes	Did not prevent recurrence	N/A	Not effective
Sung *et al*., 2024[30]	Retrospective	UDCA alone	12.7%	41.5% (no medication)	Significant
Sung *et al*., 2024[30]	Retrospective	CDCA + Terpene	9.8%	41.5% (no medication)	Significant
Sung *et al*., 2024[30]	Retrospective	CDCA + UDCA + Terpene	5.2%	41.5% (no medication)	Significant

CDCA, chenodeoxycholic acid; RCT, randomized control trial; UDCA, ursodeoxycholic acid.

corporating UDCA into endoprosthetic treatment did not result in a reduction in CBD stone size.[25,26] Additionally, two other studies found that neither UDCA nor terpenes prevented the recurrence of CBD stones.[28,29] However, recent literature from Korea indicates that single-agent therapy with UDCA or combination therapy with CDCA and terpene significantly reduces CBD stone recurrence compared to no medication, with recurrence rates of 12.7% for single-agent and 9.8% for dual-agent therapy versus 41.5% for no medication. The combination of CDCA and UDCA with terpene was particularly effective, with a recurrence rate of 5.2%.[30] Table 3 summarizes the effect of UDCA and related agents on recurrence rates of CBD stones following endoscopic removal.[25-30]

Efficacy of UDCA in different patient populations

Pediatric – cholestasis

In pediatric patients, the primary indication for UDCA is cholestatic liver disease rather than gallstone dissolution. A recent systematic review and meta-analysis of 32 RCTs, including 2,153 children with cholestasis, found that UDCA improved clinical symptoms and biochemical markers of cholestasis, with a favorable safety profile.[31]

Pediatric – cholelithiasis

Evidence supporting the use of UDCA in pediatric cholelithiasis is limited, and its efficacy for gallstone dissolution in children is not well established. In an Italian multicenter study, only eight of 117 children treated with UDCA experienced stone dissolution, with recurrence in three cases. However, 65% of symptomatic children treated with UDCA became asymptomatic, indicating potential benefit for symptom relief rather than stone clearance.[32] Another Turkish study reported that UDCA did not consistently dissolve gallstones in children, except possibly in very young children, those with small (<5 mm), solitary, or ceftriaxone-associated stones, or biliary sludge, among 254 children with cholelithiasis.[33]

Given the limited availability of comprehensive data on the pediatric population, it is essential for future research to prioritize multicenter RCTs. This approach will more accurately determine the efficacy, safety, and optimal application of UDCA in pediatric cholelithiasis. Such studies should emphasize patient selection, stone characteristics, and long-term outcomes.

Pregnancy

UDCA is primarily used in the management of ICP, which is a rare condition usually seen during the third trimester and is associated with increased fetal complications, such as preterm birth and stillbirth. In a 2012 meta-analysis, UDCA demonstrated better efficacy in alleviating maternal pruritus and improving liver function tests in women with ICP.[34] However, in 2019, a randomized placebo-controlled trial, PITCHES, involving 605 women demonstrated that, while UDCA led to modest improvements in maternal pruritus and biochemical markers, there was no significant difference in adverse perinatal outcomes, such as perinatal death, preterm delivery, or neonatal unit admission, between those treated with UDCA (n = 305) and those receiving placebo (n = 300).[35] In clinical practice, these findings shift the primary rationale for UDCA use in pregnancy from presumed fetal benefit to maternal symptom relief and biochemical control.

Furthermore, there are no adequate and well-controlled studies of UDCA for gallstone disease in pregnant women, and the U.S. Food and Drug Administration does not recommend its use during pregnancy, especially in the early trimester or during lactation, due to insufficient evidence.[16] This highlights the need for careful counseling and shared decision-making when considering UDCA use in the first trimester or in pregnancies with borderline indications. Informed consent in these settings should explicitly address these evidentiary gaps and align treatment decisions with the patient's values and preferences. This also emphasizes the need for additional high-quality trials to guide evidence-based management of ICP.

Sickle cell disease

In patients with sickle cell disease, UDCA is not generally indi-

Table 4. The efficacy of UDCA therapy across different patient populations and clinical conditions

Population	Indication	Efficacy/Outcomes	Sample size	Study type	Reference
Pediatric (Cholestasis)	Cholestatic liver disease	Improved clinical symptoms and biochemical markers; favorable safety profile	2,153 children	Systematic review/ meta-analysis (32 RCTs)	31
Pediatric (Cholelithiasis)	Gallstone dissolution	8/117 (6.8%) stone dissolution; 3 recurrences; 65% of symptomatic children became asymptomatic	117 children	Italian multicenter study	32
Pediatric (Cholelithiasis)	Gallstone dissolution	No consistent dissolution except in very young children with small stones (<5 mm), solitary, ceftriaxone-associated stones, or biliary sludge	254 children	Turkish study	33
Pregnancy (ICP)	Intrahepatic cholestasis of pregnancy	Improved maternal pruritus and liver function tests	Meta-analysis	Meta-analysis	34
Pregnancy (ICP)	Intrahepatic cholestasis of pregnancy	No significant difference in adverse perinatal outcomes (perinatal death, preterm delivery, neonatal unit admission) vs. placebo	605 women (305 UDCA, 300 placebo)	RCT	35
Sickle cell disease	Gallstone management	Not effective (increased risk of pigment stones, for which UDCA is not effective)	N/A	Clinical guidance	36
Post-bariatric surgery	Gallstone prevention	Recommended 500–600 mg/day for 6 months after surgery	N/A	Clinical practice guidelines	37
Post-bariatric surgery (Prevention)	Gallstone formation prevention	UDCA significantly reduced the risk of gallstone formation (RR 0.27, 95% CI 0.18–0.41; $P < 0.001$) and symptomatic gallstone disease (RR 0.30, 95% CI 0.21–0.43; $P < 0.001$)	3,619 patients	Systematic review and meta-analysis (14 RCTs)	39
	Overall, gallstone incidence and symptomatic disease	Overall gallstone incidence (RR 0.13; $P < 0.0001$); symptomatic cholelithiasis (RR 5.70; $P < 0.00001$); cholecystectomy rates reduced (RR 3.05; $P = 0.002$)	2,767 patients	Updated meta-analysis (12 RCTs, 1993–2022)	38
Post-bariatric surgery (Treatment)	Gallstone dissolution in formed stones after LSG	60% dissolution rate in UDCA group vs. control; stones < 5 mm had higher success rate; symptoms (dyspepsia) decreased significantly	88 patients (51 UDCA, 37 control)	Retrospective cohort (2017–2023)	19
LPAC syndrome	Symptom relief, recurrence prevention	Alleviates symptoms and reduces recurrent stones (efficacy not yet confirmed by prospective studies)	N/A	Case reports/ clinical observation	40
PFIC type 3	Improve bile flow, reduce bile toxicity	Partial or complete improvement in liver tests and symptom resolution	N/A	Clinical observation	41

CI, confidence interval; ICP, intrahepatic cholestasis of pregnancy; LPAC, Low phospholipid-associated cholelithiasis; LSG, laparoscopic sleeve gastrectomy; PFIC, progressive familial intrahepatic cholestasis; RCT, randomized control trial; RR, relative risk; UDCA, ursodeoxycholic acid.

cated for gallstone management, as this population is at increased risk of pigment stones, for which UDCA is not effective.[36]

Post-bariatric surgery patients

The American Association of Clinical Endocrinologists, The Obesity Society, and the American Society for Metabolic and Bariatric Surgery recommend 500–600 mg/day UDCA for six months after bariatric surgery to prevent gallstone formation.[37] Recent meta-analyses have also shown that patients who received UDCA post-bariatric surgery had a lower incidence of gallstone formation and symptomatic gallstone disease.[38,39]

Low phospholipid-associated cholelithiasis syndrome

This is a rare genetic form of intrahepatic cholesterol lithiasis with a proposed defect in the ATP-binding cassette subfamily member 4 (ABCB4) gene. UDCA, administered at a daily dosage of 5–15 mg/kg, has been reported to alleviate symptoms and reduce the risk of recurrent stones in patients with gallstones. However, its efficacy has yet to be confirmed through prospective studies.[40]

Progressive familial intrahepatic cholestasis type 3

This is an autosomal recessive liver disorder associated with mutations in the ABCB4 gene. UDCA improves bile flow, reduces bile toxicity, and leads to partial or complete improvement in liver tests and symptom resolution.[41] Table 4 summarizes the efficacy of UDCA therapy across different patient populations and clinical conditions.[22,31-41]

Table 5. Recommended dosing regimens for UDCA across different patient cohorts

Indication	Patient population	Dosage	Frequency	Duration/Monitoring	Reference
Gallstone dissolution	Adults, pediatrics, geriatrics	8–10 mg/kg/day	2–3 divided doses	Up to 2 years; US every 6 months	16
Gallstone prevention (rapid weight loss)	Adults, high-risk (bariatric)	600 mg total (300 mg BID)	Twice daily	During the rapid weight loss period	37,39,44–46
Post-bariatric surgery prevention	Post-bariatric patients	500–600 mg/day	Daily	6 months after surgery	37
LPAC syndrome	Adults with ABCB4 defect	5–15 mg/kg/day	Daily	Long-term	40
PFIC type 3	Pediatric/adults with ABCB4 mutations	10–20 mg/kg/day	Daily	Long-term	41
Cholestasis (pediatric)	Children	10–20 mg/kg/day	Daily	Until resolution	31

BID, bis in die; LPAC, Low phospholipid-associated cholelithiasis; PFIC Progressive familial intrahepatic cholestasis; UDCA, ursodeoxycholic acid.

Dosage and administration for gallstone disease

UDCA is an orally administered drug that is predominantly absorbed through passive diffusion in the small intestine and, to a lesser extent, in the proximal colon.[42] Bile acids are required for the dissolution and absorption of UDCA; therefore, it is generally recommended to be taken with meals, which promotes bile secretion.[43] Similarly, UDCA absorption is decreased in patients with cholestasis; hence, they require a higher dose of UDCA. Co-administration with certain drugs, such as activated charcoal, aluminum-based antacids, high-dose calcium supplements, and bile acid sequestrants (cholestyramine and colestipol), can affect absorption, as these medications can bind to UDCA and limit its diffusion within the small intestine. These drugs are generally administered 2–6 h apart.[6] In pediatric and geriatric populations, dosing should be individualized, starting at the lower end of the dosing range, with careful monitoring for adverse effects. Table 5 outlines the recommended dosing regimens for UDCA across various clinical indications and patient populations.[16,31,37,39–41,44–46]

Safety and adverse effects of UDCA

Available evidence suggests that UDCA has an acceptable safety profile with minimal adverse effects. Diarrhea is the most frequently reported adverse effect seen in clinical studies.[16,47] It is likely related to the bacterial conversion of UDCA to CDCA in the colon, which acts as a secretory agent. Some less common adverse effects include right upper quadrant pain, rash, and pruritus, mainly reported in patients with cholestatic liver disease, such as PBC.[47] UDCA is considered safe for use even in patients with end-stage renal disease. UDCA is not recommended in the early trimester of pregnancy and during lactation due to limited evidence, as mentioned earlier. It is also relatively contraindicated in patients with obstructive jaundice due to complete biliary obstruction, as it can worsen hepatic injury due to excess accumulation of the drug. This has been reported in animal models. In one study, when UDCA was administered to mice with ligated bile ducts and those with biliary strictures, extensive biliary infarcts and hepatic necrosis were observed, resulting from the rupture of cholangioles.[48] Recently, a few case reports have shown benefit in using UDCA at low doses in patients with malignant biliary obstruction.[49]

There has been conflicting evidence on the long-term use of high-dose UDCA and the increased risk of colorectal cancer, especially in patients with PSC and ulcerative colitis (UC). Several mechanistic pathways have been proposed to explain these divergent findings. One hypothesis is that colonic bacteria can metabolize UDCA into lithocholic acid, a secondary bile acid capable of inducing DNA strand breaks and functioning as a potential co-mutagen.[50] This pathway provides a biologic rationale for the observed association between high-dose UDCA (28–30 mg/kg/day) and increased rates of colorectal neoplasia in a 2012 randomized trial of patients with PSC and UC.[51]

Conversely, earlier observational and retrospective studies suggested that UDCA might exert chemopreventive effects through multiple mechanisms. These include reducing the levels of hydrophobic, carcinogenic bile acids in the colon, stabilizing epithelial cell membranes, promoting apoptosis of dysplastic cells, and modulating inflammatory and oxidative stress pathways, such as farnesoid X receptor (FXR)/TGR5 and YAP-dependent signaling pathways implicated in carcinogenesis.[52,53] These mechanistic insights supported initial enthusiasm for UDCA as a potential chemoprotective agent. However, subsequent higher-quality clinical data have not consistently confirmed these benefits. A 2013 meta-analysis evaluating UDCA use in patients with PSC and UC found no statistically significant reduction in the risk of CRC or dysplasia in these patients.[54] Later, in 2016, a population-based study from Taiwan comprising predominantly chronic liver disease patients (78%) found that CRC risk was 41% lower among UDCA users than among nonusers.[55] Accordingly, the association between UDCA and CRC risk remains uncertain and requires additional studies to clarify its effect.

Clinical limitations of UDCA for gallstone dissolution

UDCA is primarily effective for the dissolution of radiolucent, cholesterol-rich gallstones measuring ≤20 mm, with the highest dissolution rates observed in stones ≤ 5 mm, achieving an efficacy of approximately 81%.[16,17] Its effectiveness diminishes significantly for stones > 20 mm, calcified or hyperdense stones (with response rates as low as 6.2%), pigment stones, and in patients exhibiting impaired gallbladder motility or multiple stones.[17,18,33,36] Another major limitation of this treatment is the recurrence of gallstones after successful dissolution, occurring in 30–50% of patients within two to five years.[16,17] The treatment necessitates long-term administration, often extending up to two years, accompanied by periodic ultrasonographic monitoring.[16] The dissolution process is slow due to limited oral bioavailability, frequently requiring several months of treatment. Table 6 summarizes the predictive factors for UDCA efficacy in gallstone dissolution.[11,16-18,22,33,36,56]

Table 6. Key predictive factors for UDCA efficacy in gallstone dissolution

Factor	Favorable for dissolution	Unfavorable for dissolution	Evidence source
Stone size	≤5 mm (81% complete dissolution); ≤10 mm (significantly better than >10 mm); ≤20 mm (variable, size-dependent)	>20 mm (rarely dissolve with UDCA alone)	Pooled analysis (868 patients)[16]; Meta-analysis[17]
Stone composition	Radiolucent, cholesterol-rich, isodense on CT (87.1% response rate)	Hyperdense (30.0% response), calcified stones (6.2% response rate)	Korean CT-based study[18]
Stone density on CT	Isodense stones: 85.7–88.2% response rate; Hypodense: 33.3% response rate	Hyperdense: 30.0%; Calcified: 6.2%	Korean CT-based study[18]
Biliary sludge	Overall response rate 87.5%; dissolution rate 85.42%	N/A	Korean CT-based study[18]
Gallbladder function	Gallbladder volume reduction > 60% after stimulating meal (indicates proper function)	Poor gallbladder motility	Single center RCT[11]
Early treatment response	Partial dissolution at 6 months (>70% chance of eventual complete dissolution)	No response at 12 months (low likelihood of success)	Pooled analysis[16]
Gut microbiome composition	Low abundance of Erysipelotrichi lineage; reduced overall abundance of Firmicutes phylum	High abundance of Firmicutes phylum (poor response); High Erysipelotrichi (unfavorable)	Prospective microbiome study (2024)[22]
Combination therapy	UDCA + n-3 PUFA: 90.5% response rate, 45.7% dissolution rate	UDCA monotherapy: 41.7% response rate, 9.9% dissolution rate	Korean RCT (2024)[56]
Number of stones	Solitary stones	Multiple stones	Turkish pediatric study[33]
Stone etiology	Cholesterol stones	Pigment stones (e.g., in sickle cell disease)	Clinical review[36]
Patient age (pediatric)	Very young children	Older children (except for specific circumstances)	Turkish pediatric study[33]
Associated conditions	Ceftriaxone-associated stones, biliary sludge	Calcified stones, complicated gallstones	Turkish pediatric study[33]; CT study[18]
Dosing adequacy	Adequate dose titration (≥7 mg/kg/day for >6 months)	Failure to titrate dose adequately; Low-dose UDCA (<7 mg/kg/day): 20.6% dissolution	Meta-analysis[17]

CT, computed tomography; PUFA, polyunsaturated fatty acids; RCT randomized control trial; UDCA. Ursodeoxycholic acid.

Comparison of UDCA with other medical and non-surgical treatments for gallstone disease

Combination regimens may enhance dissolution in certain patients. Small-scale studies suggest potential advantages of combining UDCA with CDCA, n-3 polyunsaturated fatty acids, or statins, particularly in patients with multiple stones.[23,24,26,27,57–59] Investigational approaches, such as herbal preparations, probiotics, and lipid-modifying agents like alirocumab, have been examined, but substantial clinical evidence is lacking.[57,60] Contact dissolution using organic solvents, such as methyl tert-butyl ether, is infrequently utilized due to safety concerns.[61] For patients with low phospholipid-associated cholelithiasis syndrome and ABCB4 variants, obeticholic acid may be considered a second-line agent when UDCA therapy proves ineffective.[40,62]

Extracorporeal shock wave lithotripsy (ESWL) is another non-surgical treatment option for gallstone disease, in which high-energy acoustic shock waves are precisely focused on the stones, causing mechanical stress and microfractures that gradually break the stones into smaller fragments.[63] It is appropriate for single, small, radiolucent stones and appears more effective when followed by UDCA. Similar to UDCA, ESWL has a low cure rate. Studies have shown that, within a carefully selected patient population, ESWL offers a cure rate of only 55%, and almost 30–50% of patients experience recurrent stone disease within the next four years.[3,64,65] Limited data are available from head-to-head RCTs comparing UDCA and ESWL monotherapy. ESWL has also been used in the management of CBD stones that could not be cleared with endoscopic sphincterotomy and ERCP. A single-center study involving 214 patients who underwent ESWL for choledocholithiasis reported an 89.7% success rate with ESWL and subsequent ERCP.[66] Similar results for ESWL and choledocholithiasis were reported in other studies.[67,68]

Surgical treatments for gallstone disease

Cholecystectomy is the preferred treatment for symptomatic gallstone disease, depending on the frequency and severity of symptoms, with a success rate greater than 95%.[3,22,32] Elective laparoscopic cholecystectomy is usually preferred and is the standard of care in uncomplicated disease. In patients with complications such as acute calculous cholecystitis, it is preferably performed early, within 72 h. Ten to forty percent of patients have persistent complaints after cholecystectomy, referred to as post-cholecystectomy syndrome. In an RCT, such patients were found to have microlithiasis, or crystals in the duodenal bile, which resolved with UDCA treatment over a few months.[69]

Routine cholecystectomy is not recommended for patients with asymptomatic gallstone disease, as there is limited data on the benefits of prophylactic surgery in these patients.[3] Exceptions include porcelain gallbladder, gallbladder polyps larger than 1 cm, and gallstones larger than 3 cm. Given the increased risk of malignancy, it is recommended that these patients undergo prophylactic cholecystectomy regardless of symptoms.[3,70] Following definitive surgical or endoscopic management, the recurrence rate of choledocholithiasis is estimated to be between 4% and 24%.[71] Currently, a two-stage treatment, including preoperative ERCP and laparoscopic cholecystectomy (ideally within 72 h), is recommended for the management of patients with simultaneous gallbladder and CBD stones.[3,70] In high-risk or cirrhotic patients with acute calculous cholecystitis, alternatives to surgery may include percutaneous cholecystostomy or endoscopic gallbladder drainage, which has gained popularity recently.[72–74]

Future directions

The gut–liver axis has become an important focus for research in recent times. Given that the biliary tract is connected to a complex microbial environment in the intestine, many researchers have explored the relationship between gut microbiomes and several biliary diseases. Wang *et al*.[75] performed a systematic review suggesting that patients with gallstones have a significantly different intestinal microbiome, characterized by an increase in pathogenic bacteria, which promotes inflammation, increases gut permeability, and elevates lithogenic bile acids. Moreover, several animal studies have demonstrated that these pathogenic bacteria possess complex mechanisms, such as activation of the FXR pathway, which converts primary bile acids into secondary bile acids, and cholesterol supersaturation in bile, which promotes gallstone formation.[75] Newer mouse model studies and studies in patients with gallstones receiving UDCA suggest that UDCA affects the gut microbiome, which may partially improve gut microbiome dysbiosis.[76,77] This interaction between UDCA and the gut microbiome will be essential for developing new treatment strategies. Combination therapy, such as UDCA plus an FXR agonist, is another novel approach that shows promise for cholelithiasis management, although robust clinical trials are needed. Current FXR agonist trials have demonstrated efficacy in cholestatic liver disease.[78]

Conclusions

UDCA remains the primary medical therapy for managing symptomatic cholelithiasis in select patient populations and those who are poor surgical candidates or who decline cholecystectomy. It has a good safety profile and is effective at gradually reducing stone burden; however, its therapeutic efficacy in managing gallstone disease is limited by high recurrence rates. As research advances, novel bile acid modulators and combination strategies may expand the role of medical therapy in the management of cholelithiasis.

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Conflict of interest

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