

Original Article



OPEN ACCESS

Received: Mar 10, 2020

Accepted: May 1, 2020

Correspondence to

Jae Hong Park

Department of Pediatrics, Pusan National University Yangsan Hospital, 20 Geumo-ro, Mulgeum-eup, Yangsan 50612, Korea.
E-mail: jhongpark@pusan.ac.kr

Copyright © 2020 by The Korean Society of Pediatric Gastroenterology, Hepatology and Nutrition

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs

Yeoun Joo Lee <https://orcid.org/0000-0001-8012-5433>
Yeh Seul Park <https://orcid.org/0000-0002-6335-8726>
Jae Hong Park <https://orcid.org/0000-0002-5274-7064>

Conflict of Interest

The authors have no financial conflicts of interest.

Cholecystectomy is Feasible in Children with Small-Sized or Large Numbers of Gallstones and in Those with Persistent Symptoms Despite Medical Treatment

Yeoun Joo Lee , Yeh Seul Park , and Jae Hong Park

Department of Pediatrics, Pusan National University School of Medicine, Yangsan, Korea

ABSTRACT

Purpose: We investigated the clinical features and factors affecting the choice of treatment modality and the course of pediatric gallstone (GS) disease.

Methods: We retrospectively analyzed the medical records of 65 patients diagnosed with GS using imaging studies between January 2009 and December 2017 were included.

Results: This study included 65 patients (33 boys and 32 girls; mean age, 8.5±5.3 years; range, 0.2–18 years) who primarily presented with abdominal pain (34%), jaundice (18%), and vomiting (8%). Idiopathic GS occurred in 36 patients (55.4%). The risk factors for GS included antibiotic use, obesity, hemolytic disease, and chemotherapy in 8 (12.3%), 7 (10.8%), 6 (9.2%), and 4 patients (6.2%), respectively. We observed multiple stones (including sandy stones) in 31 patients (47.7%), a single stone in 17 (26.2%), and several stones in 17 (26.2%). GS with a diameter of <5 mm occurred in 45 patients (69.2%). Comorbidities included hepatitis, choledocholithiasis, cholecystitis, and acute pancreatitis in 20 (30.8%), 11 (16.9%), 11 (16.9%), and 4 patients (6.2%), respectively. Ursodeoxycholic acid (UDCA) was administered to 54 patients (83.1%), leading to stone dissolution in 22 patients (33.8%) within 6 months. Cholecystectomy was performed in 18 patients (27.7%) (mean age, 11.9±5.1 years). Most patients treated surgically had multiple stones (83%) and stones measuring <5 mm in size (89%), and 66.7% of patients had cholesterol stones.

Conclusion: Cholecystectomy is feasible in patients with small-sized or large numbers of GS and those with persistent abdominal pain and/or jaundice. UDCA administration with close follow-up is recommended in patients with uncomplicated GS.

Keywords: Cholelithiasis; Child; Treatment

INTRODUCTION

Gallstones (GS) are relatively rare in children. However, widespread ultrasonographic screening in suspected cases with better detection of asymptomatic GS has led to an increasing incidence of this condition. The prevalence of GS varies across countries and ethnicities. The estimation of true prevalence is difficult because a few patients are asymptomatic. The prevalence rates of pediatric GS disease in Italy and Japan were 0.13 to 0.2% [1] and 0.13% [2], respectively. A Dutch study reported a prevalence rate of 1.9% [3].

Susceptibility to GS is determined by complex interactions between environmental and genetic factors. Comorbidities including hemolytic disorders, prolonged total parenteral nutrition, or cystic fibrosis predispose to pediatric GS disease [3,4]. Recent studies report that the increasing incidence of pediatric GS parallels the increase in cases of childhood obesity [5]. Notably, cholesterol GS are associated with obesity, type 2 diabetes, dyslipidemia, and hyperinsulinemia [6]. A previous study reported a GS prevalence rate of 2% in 493 children and adolescents diagnosed with obesity [7].

The number of patients with GS requiring cholecystectomy is increasing along with changing indications for surgery [5,8-10]. Patient selection is important to identify those amenable to medical therapy. However, few studies have reported the natural history of pediatric GS disease. No prospective randomized controlled trials have compared medical and surgical treatments, and no clear guidelines have defined indications for medical versus surgical treatments in children with GS. Few reports have described the medications effective in these cases and the duration of their use. Surgical indications and the optimal timing of surgery remain unclear.

Therefore, we investigated the clinical features and factors affecting the choice of treatment modality in pediatric GS disease.

MATERIALS AND METHODS

We retrospectively analyzed the medical records of 65 patients (<18 years) diagnosed with GS based on imaging studies who received treatment at Pusan National University Children's Hospital between January 2009 and December 2017. Patients with gallbladder sludge were excluded. This study was approved by the Institutional Review Board of Pusan National University Yangsan Hospital (No. 05-2019-151).

The following patient characteristics were evaluated: demographics, presenting symptoms, risk factors for GS, comorbidities, history of antibiotic use, stone characteristics based on imaging studies, therapeutic approaches employed, and outcomes. Patients were categorized into two groups based on stone size (<5 vs. ≥5 mm) and three groups based on stone number (single vs. several [≤5] vs. multiple [>5]). Ursodeoxycholic acid (UDCA, 8–10 mg/kg/day) was administered to patients without specific indications for cholecystectomy. Follow-up assessment was performed every 3 months with clinical and ultrasonographic examinations. Stone dissolution was defined as the absence of GS on follow-up abdominal ultrasonography.

The primary indications for cholecystectomy included symptomatic cholelithiasis, complicated obstructive disease, and abdominal pain in the right upper quadrant that persisted despite receiving medical treatment for >1 week. Complicated obstructive disease was defined as definitively diagnosed with GS pancreatitis, jaundice, choledocholithiasis, or common bile duct dilatation observed on imaging studies. We compared the clinical features and outcomes in patients undergoing cholecystectomy.

The *t*-test was used to compare differences in continuous variables between groups, and the chi-square or Fisher's exact test was used to compare categorical variables. The *p*-values <0.05 were considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics ver. 21.0 software (IBM Co., Armonk, NY, USA).

Table 1. Age and sex wise distribution of patients (n=65)

Variable	Boys	Girls	Total
Age (yr)			
<1	2 (3.1)	2 (3.1)	4 (6.2)
2–5	11 (16.9)	6 (9.2)	17 (26.2)
6–12	13 (20.0)	13 (20.0)	26 (40.0)
>13	7 (10.8)	11 (16.9)	18 (27.7)
Mean age (yr)		8.5±5.3 (0.2–18.0)	
Total	33 (50.8)	32 (49.2)	65 (100.0)

Values are presented as number (%) or mean±standard deviation (range).

RESULTS

This study included 65 patients (33 boys, 32 girls), and the mean age of patients was 8.5±5.3 years (range, 0.2–18.0 years). The age distribution of patients with GS was as follows: 6–12 years (26 patients [40.0%]), >13 years (18 [27.7%]), 2–5 years (17 [26.2%]), and <1 year (4 [6.2%]) (**Table 1**).

Patients' presenting symptoms included abdominal pain (n=27, 41.5%), jaundice (n=14, 21.5%), vomiting (n=6, 9.2%), and irritability (n=1, 1.5%). Notably, 32 patients (49.2%) were diagnosed incidentally without GS-induced symptoms.

The risk factors for GS included antibiotic use (12.3%), obesity (10.8%), hemolytic disease (9.2%), chemotherapy (6.2%), and biliary tract disease (3.1%). No risk factor for GS was identified in 36 patients (55.4%).

Comorbidities included the diagnosis of a single disorder or a combination of the following disorders: hepatitis (n=20, 30.8%), choledocholithiasis (n=11, 16.9%), cholecystitis (n=11, 16.9%), and GS pancreatitis (n=4, 6.2%).

We observed multiple stones in 31 patients (47.7%), a single stone in 17 (26.2%), and several GS in 17 patients (26.2%). GS measured <5 mm in 45 patients (69.2%) and were visualized on plain abdominal radiography in 7 patients (11%) (**Table 2**).

UDCA was administered to 54 patients (83.1%). Stone dissolution following UDCA administration occurred in 24 patients (44.4%), of which 22 (40.7%) showed stone dissolution within 6 months. Recurrent stones were observed in 7 patients (10.8%), and 18 patients (27.7%) underwent cholecystectomy (**Table 3**).

Table 2. Characteristics of gallbladder stones

Characteristics	Number (n=65)
No. of stones	
Single	17 (26.2)
Several	17 (26.2)
Multiple	31 (47.7)
Size of stones (mm)	
<5	45 (69.2)
≥5	20 (30.8)
Visible on the plain X-ray	7 (10.8)

Values are presented as number (%).

Table 3. Treatment and outcomes of gallbladder stones

Treatment and outcome	Number (n=65)
Ursodeoxycholic acid	54 (83.1)
Dissolution of stone	24 (36.9)
<1 mo	2 (3.1)
1-6 mo	20 (30.8)
6 mo	2 (3.1)
Relapse	7 (10.8)
Cholecystectomy	18 (27.7)

Values are presented as number (%).

Table 4. Comparison of clinical features with or without cholecystectomy

Characteristics	Cholecystectomy (+) (n=18)	Cholecystectomy (-) (n=47)	p-value
Boys:girls	8:10	25:22	
Mean age (yr)	11.9±5.1	7.2±4.9	0.002*
Presenting symptom			
Abdominal pain	16 (88.9)	12 (25.5)	0.000†
Jaundice	8 (44.4)	6 (12.8)	0.005†
Asymptomatic	0 (0.0)	32 (68.1)	0.000‡
No. of stone			
Single	0 (0.0)	17 (36.2)	
Several	3 (16.7)	14 (29.8)	
Multiple	15 (83.3)	16 (34.0)	0.001†
Size of stone			0.039‡
<5 mm	16 (88.9)	29 (61.7)	
≥5 mm	2 (11.1)	18 (38.3)	
Accompanying diseases			
Hepatitis	11 (61.1)	9 (19.1)	
Choledocholithiasis	6 (33.3)	5 (10.6)	
Cholecystitis	9 (50.0)	2 (4.3)	
Gallstone pancreatitis	3 (16.7)	1 (2.1)	

Values are presented as number only, mean±standard deviation, or number (%).

*t-test, †Chi-square test, ‡Fisher's exact test.

The mean ages of patients who received surgical and nonsurgical treatments were 11.9±5.1 and 7.2±4.9 years, respectively. Among the patients treated surgically, 66.7% had cholesterol stones. Most patients who underwent surgery had multiple stones (83%) and stones measuring <5 mm in size (89%). The univariate analysis showed a significant association between the risk of cholecystectomy and older age ($p=0.002$), abdominal pain ($p<0.001$), jaundice ($p=0.005$), multiple stones ($p=0.001$), and small-sized stones ($p=0.039$). No significant intergroup differences were observed in the prevalence of hepatitis ($p=0.065$), choledocholithiasis ($p=0.396$), cholecystitis ($p=0.258$), and GS pancreatitis ($p=0.745$) (Table 4).

DISCUSSION

In this study, we observed that cholecystectomy is more commonly performed in older patients, patients with small-sized and large numbers of GS, and those with accompanying symptoms such as abdominal pain and/or jaundice. UDCA administration with close follow-up is recommended in patients with uncomplicated stones.

Previous studies regarding the prevalence of GS have reported a bimodal distribution with a small peak in infancy that increases throughout adolescence showing a marked female preponderance [5,11,12]. Boys and girls are equally affected during early childhood; however, a clear female preponderance observed during adolescence is similar to that observed in

adulthood [3,5,11,13]. Mehta et al. [5] reported an increase in the mean age of diagnosis of GS disease. The previously reported mean age for pediatric GS disease ranged from 8.4 to 10.0 years [9,14]; however, Mehta et al. [5] reported a significantly higher mean age of 13.0 years (67% of the patients were aged 13-18 years). In our study, the mean age of patients was 8.5 years, and no sex difference was observed with respect to age. An age-related increase in incidence was not observed.

Pediatric GS disease is attributable to conditions that predispose children to various types of GS [15]. Cholelithiasis in infancy is typically associated with prematurity, total parenteral nutrition, abdominal surgery, or sepsis. Hemolytic disease is the most common associated comorbidity in adolescents. Recent data suggest that nonhemolytic risk factors, including pregnancy, oral contraceptive use, and obesity, are increasingly being recognized as contributors to GS [5]. The prevalence of GS in Korea resembles trends observed in Western countries owing to the westernization of lifestyle and an improved socioeconomic status [16,17]. In our study, 55.4% of patients showed no risk factor for GS, consistent with the results of previous studies [5,13]. The risk factors for GS included antibiotic use (12.3%), obesity (10.8%), hemolytic disease (9.2%), chemotherapy (6.2%), and biliary tract disease (3.1%).

GS in adults are asymptomatic in >80% of patients [18]; however, only 17 to 50% of children with GS are asymptomatic [11,13,19]. In our study, 49.2% of children were asymptomatic. Tannuri et al. [20] reported that 25% of patients presented with complications including pancreatitis, choledocholithiasis, or acute calculous cholecystitis as the first sign of cholelithiasis. In the present study, comorbidities included the diagnosis of a single disorder or a combination of the following disorders: hepatitis (30.8%), choledocholithiasis (16.9%), cholecystitis (16.9%), and GS pancreatitis (6.2%). The most common presenting symptom in symptomatic patients was abdominal pain (41.5%).

Ultrasonography is the most efficient and convenient diagnostic tool for GS. Plain abdominal radiography and computed tomography can detect only calcified stones. In our study, plain abdominal radiography revealed stones in 11% of patients. Such stones are usually calcified cholesterol stones or contain calcium bilirubinate and are not amenable to dissolution [21].

The treatment of GS depends upon the patient's symptoms, types of GS, and their location. Currently, medical therapy is based on the clinical stage: asymptomatic, symptomatic, and complicated disease [22]. Asymptomatic GS rarely warrant treatment owing to their benign natural course and a low risk of progression to symptomatic disease.

UDCA is the drug of choice for the medical management of GS. It decreases biliary cholesterol saturation by 40 to 60% by inhibiting the intestinal absorption and biliary secretion of cholesterol, as indicated by a reduced cholesterol fraction of biliary lipids [23]. Few reports in the literature have described the role of UDCA in children. Della Corte et al. [19] reported UDCA-induced symptom resolution in 65% of children (n=117), with stone dissolution in only 8 children and recurrence in 3 children upon treatment completion.

The criteria for UDCA treatment include cholesterol-rich, non-calcified GS with a diameter of <20 mm and a patent cystic duct. Reportedly, the UDCA-induced dissolution rate was 30 to 60%; however, the initial diameter of GS is the most important determinant of the dissolution rate [24,25]. Differentiation of cholesterol stones based on imaging studies is challenging. Cholesterol GS constitute approximately 75% of the GS identified in patients in the United States

and westernized countries. The remaining are pigment stones containing <30% cholesterol by weight [6]. Of the patients treated surgically in this study, 66.7% had cholesterol stones.

A clinical study reported complete disappearance of small stones (<5 mm) following 6-month UDCA treatment in approximately 90% of patients [26]. UDCA administration should be continued for 3 months following complete stone dissolution to ensure disintegration of microscopic stones that may not be detected ultrasonographically. Minimal or no change in GS diameter within 6–12 months of UDCA treatment indicates a poor prognostic sign for dissolution [24].

In our study, 83.1% of patients received UDCA. Stone dissolution occurred in 44.4% of patients, of which 40.7% showed dissolution within 6 months. Among patients who were refractory to UDCA treatment for 6 months, only 3.1% showed stone dissolution within a year after treatment. Our results concur with those of previous studies, which suggest that at least 6-month UDCA administration is necessary in children with GS.

A high recurrence rate is a limitation of UDCA therapy for GS dissolution. Several studies have reported the 5- and 12-year recurrence rates of 30 to 50% and 50 to 70%, respectively, after successful treatment, particularly in patients with multiple GS [24–26]. In this study, the recurrence rate was 10.8%. However, a study performed in patients with symptomatic GS who underwent long-term follow-up of 18 years reported that compared with no treatment, UDCA therapy reduced the incidence of biliary pain and acute cholecystitis [27]. Another study reported that nearly 75% of patients required cholecystectomy despite the administration of UDCA or placebo for 100 days [28], suggesting that UDCA may be ineffective in patients with complicated GS disease.

An increased incidence of GS was associated with a corresponding increase in the cholecystectomy prevalence [5,10,29]. Cholecystectomy is the current gold standard to treat symptomatic or complicated GS [22]. In our study, 27.7% of patients underwent cholecystectomy, and all procedures were performed early during the disease course. The indications for cholecystectomy included symptomatic cholelithiasis, complicated obstructive disease, and abdominal pain in the right upper quadrant that persisted despite receiving medical treatment for >1 week. UDCA administration was ineffective in these patients, and owing to the patient's poor condition, medical treatment could not be continued until a therapeutic effect was obvious.

Choledocholithiasis is observed in 10%–20% of patients undergoing surgery for GS [30]. A consensus development conference statement recommends that the common bile duct must be evaluated in all cases of symptomatic GS, and even asymptomatic GS require treatment when accompanied by choledocholithiasis [31]. Compared with solitary or multiple large stones, small-sized and numerous GS increase the risk of migration within the biliary tree [32,33]; therefore, multiple small GS predispose to synchronous asymptomatic choledocholithiasis [34]. In our study, most patients treated surgically had multiple stones (83%) and small-sized stones with a diameter of <5 mm (89%).

The retrospective design and small sample size are the limitations of this study. Further large-scale studies are warranted to gain a better understanding of the clinical course and factors affecting the choice of treatment modality in children with GS. In conclusion, asymptomatic or incidental GS can be treated nonsurgically. UDCA administration with

close follow-up is recommended even in symptomatic patients with uncomplicated stones. Cholecystectomy is feasible in patients with small-sized or large numbers of GS, and those with persistent abdominal pain and/or jaundice.

ACKNOWLEDGEMENTS

This work was supported by a 2-year research grant of Pusan National University.

REFERENCES

1. Palasciano G, Portincasa P, Vinciguerra V, Velardi A, Tardi S, Baldassarre G, et al. Gallstone prevalence and gallbladder volume in children and adolescents: an epidemiological ultrasonographic survey and relationship to body mass index. *Am J Gastroenterol* 1989;84:1378-82.
[PUBMED](#)
2. Nomura H, Kashiwagi S, Hayashi J, Kajiyama W, Ikematsu H, Noguchi A, et al. Prevalence of gallstone disease in a general population of Okinawa, Japan. *Am J Epidemiol* 1988;128:598-605.
[PUBMED](#) | [CROSSREF](#)
3. Wesdorp I, Bosman D, de Graaff A, Aronson D, van der Blij F, Taminiu J. Clinical presentations and predisposing factors of cholelithiasis and sludge in children. *J Pediatr Gastroenterol Nutr* 2000;31:411-7.
[PUBMED](#) | [CROSSREF](#)
4. Herzog D, Bouchard G. High rate of complicated idiopathic gallstone disease in pediatric patients of a North American tertiary care center. *World J Gastroenterol* 2008;14:1544-8.
[PUBMED](#) | [CROSSREF](#)
5. Mehta S, Lopez ME, Chumpitazi BP, Mazziotti MV, Brandt ML, Fishman DS. Clinical characteristics and risk factors for symptomatic pediatric gallbladder disease. *Pediatrics* 2012;129:e82-8.
[PUBMED](#) | [CROSSREF](#)
6. Di Ciaula A, Wang DQ, Wang HH, Bonfrate L, Portincasa P. Targets for current pharmacologic therapy in cholesterol gallstone disease. *Gastroenterol Clin North Am* 2010;39:245-64, viii-ix.
[PUBMED](#) | [CROSSREF](#)
7. Kaechele V, Wabitsch M, Thiere D, Kessler AL, Haenle MM, Mayer H, et al. Prevalence of gallbladder stone disease in obese children and adolescents: influence of the degree of obesity, sex, and pubertal development. *J Pediatr Gastroenterol Nutr* 2006;42:66-70.
[PUBMED](#) | [CROSSREF](#)
8. Waldhausen JH, Benjamin DR. Cholecystectomy is becoming an increasingly common operation in children. *Am J Surg* 1999;177:364-7.
[PUBMED](#) | [CROSSREF](#)
9. Miltenburg DM, Schaffer R 3rd, Breslin T, Brandt ML. Changing indications for pediatric cholecystectomy. *Pediatrics* 2000;105:1250-3.
[PUBMED](#) | [CROSSREF](#)
10. Balaguer EJ, Price MR, Burd RS. National trends in the utilization of cholecystectomy in children. *J Surg Res* 2006;134:68-73.
[PUBMED](#) | [CROSSREF](#)
11. Bogue CO, Murphy AJ, Gerstle JT, Moineddin R, Daneman A. Risk factors, complications, and outcomes of gallstones in children: a single-center review. *J Pediatr Gastroenterol Nutr* 2010;50:303-8.
[PUBMED](#) | [CROSSREF](#)
12. Stringer MD. Gallbladder disease and cholelithiasis. In: Howard ER, Stringer MD, Colombani PM, eds. *Surgery of the liver, bile ducts and pancreas in children*. 2nd ed. London: Arnold Publishers, 2002:189-208.
13. Serdaroglu F, Koca YS, Saltik F, Koca T, Dereci S, Akcam M, et al. Gallstones in childhood: etiology, clinical features, and prognosis. *Eur J Gastroenterol Hepatol* 2016;28:1468-72.
[PUBMED](#) | [CROSSREF](#)
14. Friesen CA, Roberts CC. Cholelithiasis. Clinical characteristics in children. Case analysis and literature review. *Clin Pediatr (Phila)* 1989;28:294-8.
[PUBMED](#) | [CROSSREF](#)

15. Svensson J, Makin E. Gallstone disease in children. *Semin Pediatr Surg* 2012;21:255-65.
[PUBMED](#) | [CROSSREF](#)
16. Chang YR, Jang JY, Kwon W, Park JW, Kang MJ, Ryu JK, et al. Changes in demographic features of gallstone disease: 30 years of surgically treated patients. *Gut Liver* 2013;7:719-24.
[PUBMED](#) | [CROSSREF](#)
17. Jeong SU, Lee SK. Obesity and gallbladder diseases. *Korean J Gastroenterol* 2012;59:27-34.
[PUBMED](#) | [CROSSREF](#)
18. Gracie WA, Ransohoff DF. The natural history of silent gallstones: the innocent gallstone is not a myth. *N Engl J Med* 1982;307:798-800.
[PUBMED](#) | [CROSSREF](#)
19. Della Corte C, Falchetti D, Nebbia G, Calacoci M, Pastore M, Francavilla R, et al. Management of cholelithiasis in Italian children: a national multicenter study. *World J Gastroenterol* 2008;14:1383-8.
[PUBMED](#) | [CROSSREF](#)
20. Tannuri AC, Leal AJ, Velhote MC, Gonçalves ME, Tannuri U. Management of gallstone disease in children: a new protocol based on the experience of a single center. *J Pediatr Surg* 2012;47:2033-8.
[PUBMED](#) | [CROSSREF](#)
21. Venneman NG, Buskens E, Besselink MG, Stads S, Go PM, Bosscha K, et al. Small gallstones are associated with increased risk of acute pancreatitis: potential benefits of prophylactic cholecystectomy? *Am J Gastroenterol* 2005;100:2540-50.
[PUBMED](#) | [CROSSREF](#)
22. Guarino MP, Cocca S, Altomare A, Emerenziani S, Cicala M. Ursodeoxycholic acid therapy in gallbladder disease, a story not yet completed. *World J Gastroenterol* 2013;19:5029-34.
[PUBMED](#) | [CROSSREF](#)
23. Roma MG, Toledo FD, Boaglio AC, Basiglio CL, Crocenzi FA, Sánchez Pozzi EJ. Ursodeoxycholic acid in cholestasis: linking action mechanisms to therapeutic applications. *Clin Sci (Lond)* 2011;121:523-44.
[PUBMED](#) | [CROSSREF](#)
24. Lazaridis KN, Gores GJ, Lindor KD. Ursodeoxycholic acid 'mechanisms of action and clinical use in hepatobiliary disorders'. *J Hepatol* 2001;35:134-46.
[PUBMED](#) | [CROSSREF](#)
25. Villanova N, Bazzoli F, Taroni F, Frabboni R, Mazzella G, Festi D, et al. Gallstone recurrence after successful oral bile acid treatment. A 12-year follow-up study and evaluation of long-term postdissolution treatment. *Gastroenterology* 1989;97:726-31.
[PUBMED](#) | [CROSSREF](#)
26. Portincasa P, Ciaula AD, Bonfrate L, Wang DQ. Therapy of gallstone disease: what it was, what it is, what it will be. *World J Gastrointest Pharmacol Ther* 2012;3:7-20.
[PUBMED](#) | [CROSSREF](#)
27. Tomida S, Abei M, Yamaguchi T, Matsuzaki Y, Shoda J, Tanaka N, et al. Long-term ursodeoxycholic acid therapy is associated with reduced risk of biliary pain and acute cholecystitis in patients with gallbladder stones: a cohort analysis. *Hepatology* 1999;30:6-13.
[PUBMED](#) | [CROSSREF](#)
28. Venneman NG, Besselink MG, Keulemans YC, Vanberge-Henegouwen GP, Boermeester MA, Broeders IA, et al. Ursodeoxycholic acid exerts no beneficial effect in patients with symptomatic gallstones awaiting cholecystectomy. *Hepatology* 2006;43:1276-83.
[PUBMED](#) | [CROSSREF](#)
29. Khoo AK, Cartwright R, Berry S, Davenport M. Cholecystectomy in English children: evidence of an epidemic (1997-2012). *J Pediatr Surg* 2014;49:284-8, discussion 288.
[PUBMED](#) | [CROSSREF](#)
30. National Institutes of Health consensus development conference statement on gallstones and laparoscopic cholecystectomy. *Am J Surg* 1993;165:390-8.
[PUBMED](#) | [CROSSREF](#)
31. Scientific Committee of the European Association for Endoscopic Surgery (E.A.E.S.). Diagnosis and treatment of common bile duct stones (CBDS). Results of a consensus development conference. *Surg Endosc* 1998;12:856-64.
[PUBMED](#) | [CROSSREF](#)
32. Huguier M, Bornet P, Charpak Y, Houry S, Chastang C. Selective contraindications based on multivariate analysis for operative cholangiography in biliary lithiasis. *Surg Gynecol Obstet* 1991;172:470-4.
[PUBMED](#)

33. Taylor TV, Armstrong CP, Rimmer S, Lucas SB, Jeacock J, Gunn AA. Prediction of choledocholithiasis using a pocket microcomputer. *Br J Surg* 1988;75:138-40.
[PUBMED](#) | [CROSSREF](#)
34. Costi R, Sarli L, Caruso G, Iusco D, Gobbi S, Violi V, et al. Preoperative ultrasonographic assessment of the number and size of gallbladder stones: is it a useful predictor of asymptomatic choledochal lithiasis? *J Ultrasound Med* 2002;21:971-6.
[PUBMED](#) | [CROSSREF](#)