Chapter

Gall Stones in Pediatric Population

Nida Mirza Shaikh

Abstract

Gall stones is a known entity in adults, but are considered uncommon in pediatric population, however in the recent years, mainly with wide spread use of ultrasonography, cholelithiasis in children is being frequently reported. Etiology of gall stones in children is not similar to adults. Pigment stones are the most frequently seen in children with hemolytic disease as the most common cause, however with the increase in obesity in children there is also rise in cholesterol stones. Many other causes like drugs, congenital hepatobiliary malformation and genetic causes are to be kept during evaluation of gall stones. Management of gall stones need a proper and timely work up for the causes of cholelithiasis is necessary in children. Surgical management with laparoscopic cholecystectomy is the treatment of choice in most of the cases however the timing of surgery should be optimized case to case basis.

Keywords: cholelithiasis in children, hemolytic anemia, pseudolithiasis

1. Introduction

Gall stones is a known entity in adults, but are considered uncommon in pediatric population with a prevalence of 0.13% to 0.2% [1] and no clear approach has been defined. However, in the recent years, mainly with wide spread use of ultrasonography, cholelithiasis in children is being frequently reported. Unlike adults the asymptomatic presentation is less likely in children (17–50%) [2, 3]. In children there is no difference in both genders pre pubertal, however there is female predominance after puberty. In some other cases, they are reported in association with clinical symptoms such as cholecystitis and cholangitis [4, 5]. Etiology of gall stones in children is not similar to adults. Many studies have shown haemolytic diseases are the most common causes of cholelithiasis in children [20–30%], followed by other cause like obesity, total parenteral nutrition, ileal disease or resection, congenital hepatobiliary diseases, use of ceftriaxone and idiopathic [6]. Other causes like metabolic syndrome, PFIC (progressive familial intrahepatic cholestasis), choledochal cyst, biliary cirrhosis, prematurity, necrotizing enterocolitis (NEC), Wilson disease, congenital heart diseases, cystic fibrosis, should also be considered.

2. Pathogenesis

Bile is mainly made up of water, bilirubin, cholesterol, bile pigments, and phospholipids. Imbalance in bile constituents [cholesterol, phospholipids, and bile salts] is the main cause of gallstone formation. Gallstone formation starts from the

sedimentation of cholesterol, bile pigments, and calcium salts which are insoluble [7]. By composition gallstones are divided into cholesterol gallstones or pigment stones. Unlike adults where mixed cholesterol gallstones are more common in adults, pigment stones are more common in children except adolescent girls.

2.1 Biliary sludge

Biliary sludge is mixture of mucin, calcium bilirubinate and cholesterol crystals, seen with prolonged fasting, sickle-cell disease, total parenteral nutrition, pregnancy and treatment with drugs like ceftriaxone, octreotide etc. [8]. Biliary sludge may resolve spontaneously or on removal of causative agent or may progress to gallstone development. Persistent sludge may give rise to complication like pancreatitis or cholangitis.

2.2 Cholesterol stones

Cholesterol supersaturation of bile with stasis predisposes to cholesterol gallstone formation, increased concentration of cholesterol also elevates the rate of crystallization leading to gallstone formation [9]. The cholesterol content is usually greater than 50%, with minimal calcium content, cholesterol stones are solitary, yellow-white, hard, crystalline, faceted, round, and smooth [10]. These stones are not radiopaque. Formation of cholesterol stones occurs due to hypersecretion of cholesterol, increased mucin production, and decreased gallbladder motility. Cholesterol stones are not commonly seen in children except adolescent girls. The risk factors for cholesterol stone formation in children include obesity, Hispanic ethnicity, family history, female sex (after puberty), and non-alcoholic fatty liver disease.

2.3 Pigment stones

Black pigment stones are formed due to supersaturation of bile with calcium bilirubinate [(to excess bilirubin) and are seen in haemolytic disorders and in association with total parenteral nutrition. These stones are commonly seen with hereditary haemolytic anaemias such as sickle cell disease, hereditary spherocytosis and thalassemia. Pigment stones are also seen with cirrhosis, total parenteral nutrition, ileal disease and ceftriaxone use. Black pigment stones are black to brown in color, hard, shiny, and crystalline, multiple, size of less than 5 mm, composed mainly of bile pigment polymer (40%) followed by calcium carbonate or phosphate, salts, cholesterol and mucin glycoprotein. Persons with Gilbert syndrome, are at increased risk for black pigment gallstones due to increased bilirubin production and a decrease in the bilirubin diphosphate-glucuronosyltransferase activity. Other etiologies for pigmented stones include medications such as ceftriaxone and octreotide. A decrease in the enterohepatic circulation of bile acids (seen with ileal disease or after ileal resection) is another predisposing factor for black stone formation. The mechanism responsible for gallstone formation in this setting is an interruption in the normal enterohepatic circulation of the endogenous bile salt pool [11].

Brown pigment stones are brown to orange in color, soft, greasy, multiple, and smooth composed mainly of calcium bilrubinate [60%] followed by, calcium palmitate, stearate soaps, cholesterol and mucin glycoprotein. Brown pigment stones are distinctly seen in the setting of a bacterial/parasitic infection and biliary stasis. These are also seen in bile duct anomaly and cirrhosis. These are more often seen in the bile ducts than in the gall bladder [12].

2.4 Hemolysis

Cholelithiasis is a well-known complication in pediatric patients with hemolytic anaemias like sickle cell disease, hereditary spherocytosis etc. The prevalence rate of gall stones in sickle cell disease ranges from 30 to 70% which increases progressively with age and is usually not seen before the age of five [13]. The prevalence of pigment gallstones in sickle cell disease is around 10% in children under 10 years of age, which increases to 40% in those aged 10–18 years, and 50% in adults [14–16]. The prevalence of gallstones in hereditary spherocytosis is 10–20% in children, while it raises to 40% in adult population [17, 18]. Incidence of gall stones in thalassemia is low as compared to sickle cell disease [19, 20]. Thalassaemic who also has Gilbert's syndrome genotype shows higher prevalence of gall stones [21, 22]. Whenever a child or adult with sickle cell disease experiences an episode of abdominal pain, cholelithiasis or biliary colic should be considered as differential diagnosis along with vaso-occlusive crisis. In sickle cell disease mutated red blood cells in the oxygenated form do not cause any problems, however in the deoxygenated form, they acquire sickle-like shape due to bond formation between replaced amino acid and globin molecules. This change in shape of red blood cells is reversible by reoxygenation however, changing shape again and again ruptures the cell membrane, which leads to hemolysis [23]. The bilirubin which is produced by hemolysis, further conjugated in the liver and excreted in the intestine as urobilinogen which is further absorbed and excreted multiple times through the enterohepatic circulation of bile.in hemolysis the abundance of urobilinogen in the bile leads to precipitation which may become calcified, which if continuous leads to gall stone formation [24].

2.5 Ceftriaxone-associated biliary pseudolithiasis

Ceftriaxone, is a third-generation cephalosporin, and is commonly used as broad-spectrum antibiotic in children. Gall stones or biliary sludge has been reported as a complication of ceftriaxone treatment since long [25]. The incidence of ceftriaxone induced pseudolithiasis is variable from 15–45%, depending on dose, duration and predisposing host factors [26–30]. Since biliary lithiasis is reversible and disappears on discontinuation of drug it has been termed pseudolithiasis [31]. Ceftriaxone is 40% excreted via bile, as an anion it concentrates in bile easily and readily forms an insoluble salt with calcium [calcium-ceftriaxone] that precipitates in gallbladder [32]. The predisposing risk factors for ceftriaxone induced biliary lithiasis are, high dose (>2 g or >200 mg/kg/day), long-term treatment, hypercalcemia, renal failure, and gallbladder stasis [33]. The mechanism of ceftriaxone induced lithiasis is explained in **Figure 1**. Most cases of ceftriaxone induced pseudolithiasis are asymptomatic and detected on sonography. If cholelithiasis is symptomatic, discontinuation of drug is to be done but in incidentally detected asymptomatic cases of there is no need to stop drug. Usually these sludge/stones appear after one week of therapy and disappear after two weeks of discontinuation of therapy, however the time duration may vary with patient [34, 35].

2.6 Genetics

Various lithogenic gene variants have been found linked to formation of gall stones. Genome-wide association study (GWAS) have found a hepatobiliary cholesterol transporter ABCG8 [p.D19H] as the most common genetic risk factor for gall stones [36]. Mutations in the ABCB4, ABCB11, CFTR [cystic fibrosis transmembrane conductance regulator] CYP7A1 gene causes gallstones by alteration in bile composition and secretion. Gall stone has been reported as initial symptom in early

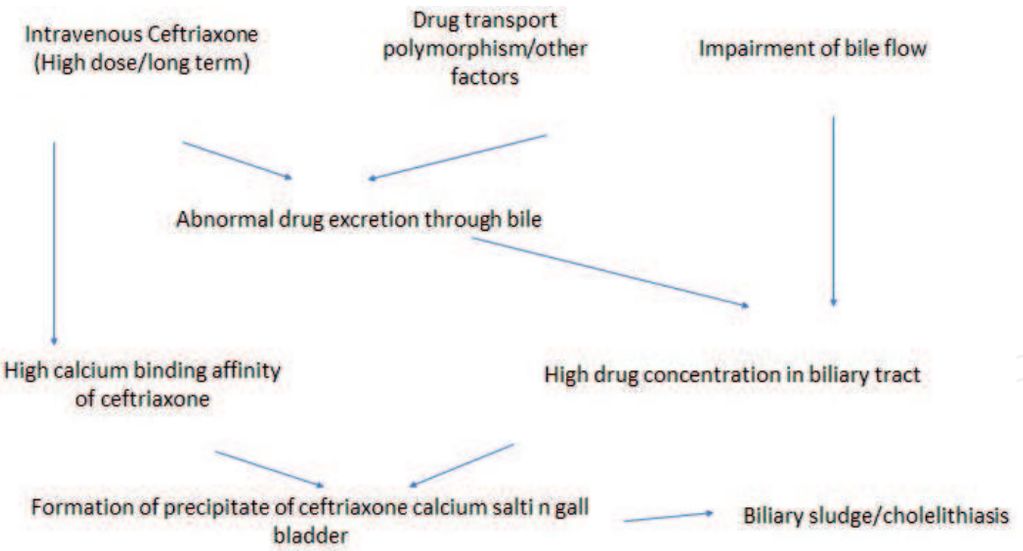

Figure 1.
Ceftriaxone induced pseudolithiasis.

childhood due to compound heterozygous mutation in ABCB4 gene (linked to progressive familial intrahepatic cholestasis type 3), these children are at risk of further developing decompensated chronic liver disease [37]. NPC1L1 [Niemann-Pick C1-Like 1] is responsible for intestinal and hepatobiliary cholesterol absorption. Functional studies showed that loss of function mutations of NPC1L1 are associated with decreased intestinal cholesterol absorption, changes in plasma low-density lipoprotein cholesterol levels decrease the reuptake of cholesterol from bile and thus promoting biliary cholesterol supersaturation. Gilbert promoter variant of the UDP glucuronosyl transferase gene [UGT1A1], appears to be an additional risk factor for gallstone risk. Studies have found that individuals predisposed to gall stone are characterized by an increased biliary output of cholesterol in the setting of relatively low intestinal cholesterol absorption, pointing to enhanced whole-body sterol clearance. An ethnic gradient in the ratios of phytosterols to cholesterol precursors (highest in Germans) is also apparent which correlates negatively with susceptibility to gallstones [38].

2.7 Obesity

In adults the association between obesity with cholelithiasis is well known. A higher incidence of cholelithiasis has also been noticed in obese children [39]. Obese children and those with a higher mean BMI (>21.5) are at higher risk of cholelithiasis and more symptomatic compared to children with a normal BMI [9]. It is recommended that children with biliary symptoms or cholelithiasis, as well as unclear ultrasonography of the bile ducts with a BMI of 23 or more should routinely undergo MRCP to rule out choledocholithiasis. There is mechanical hypothesis for more prevalence of choledocholithiasis in obese children which postulates that higher body fat content in the abdominal wall causes greater intra-abdominal pressure, resulting in external pressure on the wall of the gallbladder, this relatively higher pressure in the sub-hepatal region may results in a direct stimulus which further leads to dislodgment of the stone/sludge from the gallbladder into the extrahepatic biliary tree system, causing obstruction of the bile duct. The incidence of obesity in children rising in the some parts of world, the incidence of symptomatic cholelithiasis will also increase. Prevalence of cholelithiasis is significantly higher in patients with NAFLD (non-alcoholic fatty liver disease) [40].

2.8 Total parenteral nutrition and cholelithiasis

Total parenteral nutrition [TPN] impairs enterohepatic circulation and cholecystokinin induced gallbladder contraction resulting in biliary stasis, sludge and stones [41]. The risk of cholelithiasis increase with duration of TPN therapy, and if there is associated ileal resection or disease. Prolonged TPN therapy can lead to gallstones in 43% of children and it increases up to 64% in children with ileal resection or disease [42, 43]. Sludge formation occurs more rapidly in neonates with after a mean duration of 10 days of TPN infusion, as compared to adults where it takes more than 6 weeks.

3. Clinical features

Unlike adults, children are likely to be symptomatic, the prevalence of symptomatic children is from 50–70% [44]. The most common clinical presentation is right upper quadrant abdominal pain [usually after meals] which may be radiating to the right shoulder, nausea, vomiting and occasionally fever. Symptoms are more seen if cholelithiasis is associated with complications like cholestasis, cholecystitis, and cholangitis, in these settings additional symptoms like icterus and Murphy's sign can be seen. In infants, mostly cholelithiasis is asymptomatic and incidentally diagnosed on abdominal ultrasound.

3.1 Differential diagnosis of gall stones

The conditions mimicking the clinical features of cholelithiasis are gastroesophageal reflux disease, peptic ulcer disease, dyspepsia, acute acalculous cholecystitis, pancreatitis, hepatitis, irritable bowel syndrome, esophageal spasm, pneumonia, cardiac chest pain, and diabetic ketoacidosis and to be kept as differential diagnosis. A proper history and physical examination along with ultrasound imaging will help in making a final diagnosis.

4. Complications of gallstones

4.1 Acute calculous cholecystitis

Obstruction of the cystic duct by stones lead to inflammation of the gallbladder resulting in acute calculous cholecystitis. The obstruction causes gallbladder swelling followed by bile acid concentration, ischemia of gall bladder wall and occasionally, bacterial infection. Symptoms include pain similar to biliary colic with increased vomiting and fever. Patients usually have right upper quadrant tenderness on clinical examination and sometimes a palpable mass. Ultrasound can identify cholecystitis by presence of stone or sludge with gallbladder wall thickening and edema [double-wall sign], and pericholecystic fluid.

4.2 Common bile duct obstruction

The exact prevalence of choledocholithiasis in children is not known but they are uncommon in children. Common bile duct stones are mostly associated with gallstones except in few conditions like hemolysis where they can be primary. Presentation of choledocholithiasis include jaundice, acholic stools, and dark urine, sometimes presentation is with acute cholangitis, manifested by fever, jaundice, and

right upper quadrant pain. Choledocholithiasis should also be suspected in a patient with gallstones with raised conjugated bilirubin and/or a dilated common bile duct [as per age] on ultrasound.

4.3 Pancreatitis

Cholelithiasis is one of the leading cause of acute pancreatitis in adults, however the exact incidence of gallstone pancreatitis in children is not known. Patients with gallstone pancreatitis present with epigastric abdominal pain, nausea, and vomiting or jaundice. Sometimes gall stones are detected on evaluation of pancreatitis only. Ultrasound should be the first imaging modality followed by CT scan in doubtful cases. Biochemical investigation shows elevated serum amylase and lipase levels, and elevated conjugated serum bilirubin is often present.

5. Investigation

Ultrasound is the most accurate imaging study to evaluate for gall stones, can detect as small as 1.5 mm. On ultrasound gallstones appears as hyperechoic, single or multiple and characteristically cast an acoustic shadow in contrast biliary sludge appears echogenic on ultrasound, but does not cast an acoustic shadow. Both sensitivity and specificity of ultrasonography is 95% for gall stones, but it is low for stones in common bile duct [45]. Cholescintigraphy, with Tc 99 m labeled diisopropyl iminodiacetic acid [DISIDA], is the most accurate method of diagnosing acute cholecystitis, non-visualization of the gallbladder in an otherwise patent biliary system suggests acute cholecystitis. Magnetic resonance cholangiopancreatography (MRCP) is being used increasingly to investigate complicated gallstone disease and choledocholithiasis and for delineating pancreatic and biliary tract anatomy. Endoscopic retrograde cholangiopancreatography (ERCP) can be done for both diagnostic and therapeutic in common bile duct stones. Endoscopic ultrasound can be used for diagnosis in children with complicated biliary stone disease CT scan do not have much role in diagnosis of gall stones [46, 47]. There are no specific laboratory tests in diagnosing cholelithiasis, some blood tests are required for making etiological diagnosis and to rule out complications. These include Complete blood count, liver function tests, lipid profile [serum cholesterol (LDL, HDL, VLDL) and serum triglycerides], hemolytic profile [reticulocytes, osmotic fragility, quantitative glucose 6 phosphate dehydrogenase (G6PD) measurement, hemoglobin electrophoresis, direct coombs test], next generation sequencing (if genetic cause suspected) and sweat chloride test (if cystic fibrosis suspected) and serum amylase and lipase, if pancreatitis is suspected.

6. Management

Management of cholelithiasis is affected by several contributing factors, such as type of stone, anatomical status of gallstone, rate of symptoms in the child, underlying anatomical malformations, other underlying disease, inflammatory changes of the biliary system, and age of the child. Children with gallstones should be divided into two groups, symptomatic and asymptomatic. Symptomatic and complicated gallstones need cholecystectomy [48]. Gallstones which float in the gallbladder, having a diameter of less than 10 mm and are diagnosed incidentally in asymptomatic children, should be investigated for haemolytic diseases and underlying disorders and need to be treated after diagnosis. In infants mostly,

cholelithiasis resolves after several months of monitoring. However, cholelithiasis is not usually resolved spontaneously in older children. In a prospective study of children with nonpigmented gallstones it was found that, 50% remained or became asymptomatic, 32% experienced definite improvement in symptoms, and 18% had continued symptoms but none had any biliary complications [49]. The risk of subsequent hospital admission in children and adolescents with cholelithiasis increases by 5% for every 10 days [50]. Also, one fourth of children with gall stones, presents directly with complications [51]. Therapy with UDCA is recommended in asymptomatic patients with cholesterol stones [52]. However, the role of dissolution therapy in the management of gallstones in children remains to be defined, the use of UDCA therapy is restricted due to the long course of treatment, differential outcome, and the risk of side-effects such as diarrhea and liver dysfunction [53]. Gallstones when located in the common bile duct or around the pupillary sphincter, can cause cholangitis, obstruction of bile flow, and jaundice, stone removal should be done urgently tp relieve obstruction. In centres where pediatric ERCP is offered the endoscopic approach to relieve obstruction is safe and effective, if not laparoscopic exploration is also safe and effective alternative. In recent years, laparoscopic cholecystectomy (LC) has become the treatment of choice in the surgical management of children with cholelithiasis. Approach for mnagemement of gall stones in children given in **Figure 2**. LC is less invasive, has lower morbidity and mortality with shorter hospital stay in comparison to conventional open cholecystectomy [54]. Extracorporeal shock-wave lithotripsy is another therapeutic method, in selective cases like when the patient is asymptomatic or with the radiolucent gallstone.

In children receiving TPN especially longer duration should be assessed for gallstones. On discontinuation of TPN regimen and start of oral diet leads to establishment of bile flow which resolves bile sedimentation. TPN needs to be continued in cases where enteral feeding cant be done such as intestinal pseudo-obstruction or short bowel syndrome, in these patients therapeutic cholecystectomy should be done in presence of gallstones [55].

The approach to cholelithiasis in infancy is different as spontaneous resolution has been reported in a significant proportion of cases (cholelithiasis~50% and choledocholithiasis~30%). Spontaneous resolution within 6 months is more common

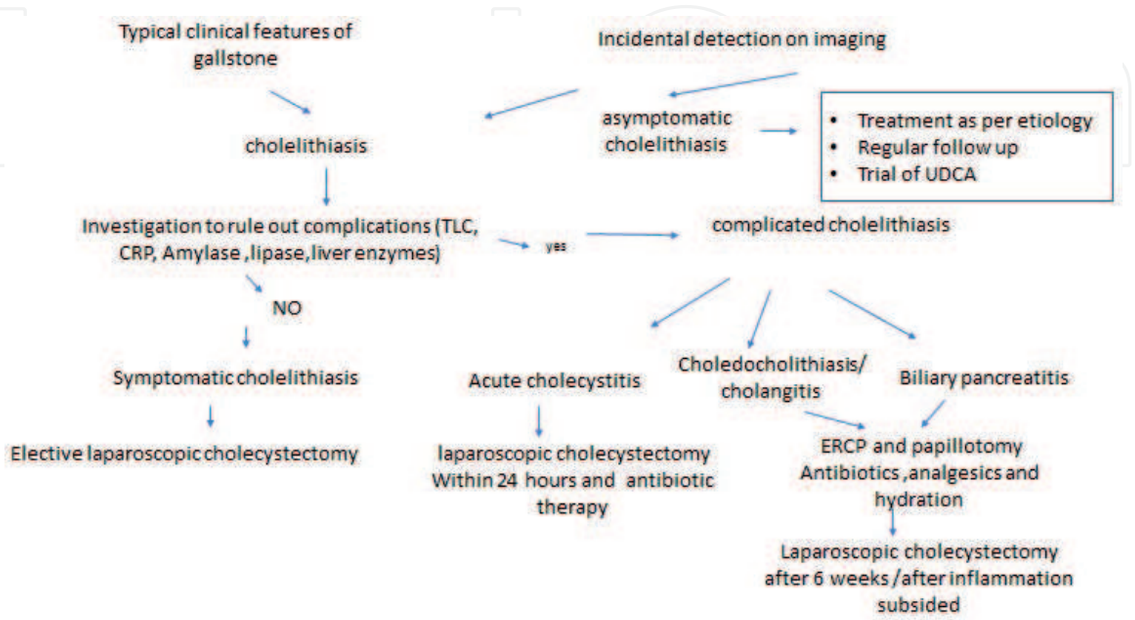

Figure 2.
Approach for management of gallstones in children.

with idiopathic and or asymptomatic gallstones than in patients with known predisposing factors. Cholecystectomy is indicated for symptomatic cholelithiasis, asymptomatic cholelithiasis persisting beyond 12 months and radiopaque calculi [56, 57].

6.1 Management of cholelithiasis in hemolytic disease

In children with hemolytic anaemias, screening for gall stones with Ultrasound is recommended from 5 years of age. Screening is also recommended before splenectomy as both splenectomy and cholecystectomy to be done in single setting in presence of gallstones [58, 59]. In sickle-cell disease, prophylactic cholecystectomy is recommended even for asymptomatic gallstones as it is difficult to differentiate an acute abdominal crisis from acute cholecystitis, and the morbidity and mortality of emergency cholecystectomy in acute crisis is much higher than in elective cholecystectomy [58]. To avoid sickling during the perioperative period hypotension, hypoxia, hypothermia, dehydration, and acidosis should be avoided and hemoglobin S should be kept below 30% and total hemoglobin should be at least of 11 g/dL [60, 61]. Many studies recommended LC in asymptomatic patients with hemolytic diseases to avoid the complications of urgent cholecystectomy and the chance of gallstone complications among the asymptomatic patients is upto 50% within 5 year of diagnosis [62]. Inflammation and infection of the gallbladder also increases the chance of a hemolytic crisis. Oral hydroxyurea reduces the frequency of cholelithiasis in some haemolytic diseases, such as thalassemia intermedia or major.

7. Prevention of gall stones

Gallstones are formed due to interaction of multiple factors like genetic, anatomical, systemic and metabolic abnormalities. However, there are some preventive factors especially for cholesterol gallstones which include regular diet, lifestyle, physical exercise, and intake of vitamin C. Lifestyle should include physical activity, ideal weight maintenance and weight reduction among overweight and obese children to prevent gall stones. It has been found that physical activity decreases the risk of symptomatic stones by about 30–70%. Regular exercise reduces insulin levels, insulin resistance, triglyceridemia, and fatty acid-dependent hypersecretion of gallbladder mucin. Also, physical activity has a prokinetic effect on the intestine and cholecystokinin-dependent gallbladder contraction. High fiber and regular eating pattern diets decrease hydrophobic bile acids, and reduces gallbladder stasis by increasing gallbladder emptying. Regular vitamin C supplementation or diet containing higher amount of vitamin C have a protective effect on gallstone formation. Situations associated with rapid loss of weight like very low-calorie diet or bariatric surgery, temporary oral UDCA may be recommended to prevent gall stone formation as the risk of cholelithiasis is much higher in these situations. There is also some role of fish oil polyunsaturated fatty acids on prevention of gall stones in obese patients. In sickle cell anemia hydroxyurea has been found to have some preventive role for pigment stones.

Conflict of interest

The author declare no conflict of interest.

IntechOpen

Author details

Nida Mirza Shaikh
Sri Aurbindo Institute of Medical Sciences, Indore, India

*Address all correspondence to: nydamirza.1@gmail.com

References

[1] Poddar U. Gallstone disease in children. Indian Pediatr. 2010 Nov;47(11):945-953. doi:10.1007/s13312-010-0159-2. PMID: 21149901.

[2] Wesdorp I, Bosman D, de Graaff A, Aronson D, van der Blij F, Taminiau J. Clinical presentations and predisposing factors of cholelithiasis and sludge in children. J Pediatr Gastroenterol Nutr. 2000;31(4):411-7.[PubMed: 11045839)

[3] 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(3):303-308. doi: 10.1097/MPG.0b013e3181b99c72 [PubMed: 20118803].

[4] Wyllie R, Hyams JS, Kay M. Pediatric Gastrointestinal and Liver Disease. 5th ed. Philadelphia, PA: Elsevier; 2016.

[5] Vegunta RK, Raso M, Pollock J, Misra S, Wallace LJ, Torres AJ, et al. Biliary dyskinesia: The most common indication for cholecystectomy in children. Surgery. 2005;138(4):726-731. doi: 10.1016/j.surg.2005.06.052 [PubMed: 16269302].

[6] Svensson J, Makin E. Gallstone disease in children. Semin Pediatr Surg. 2012 Aug;21(3):255-265. doi: 10.1053/j.sempedsurg.2012.05.008. PMID: 22800978

[7] Portincasa P, Moschetta A, Berardino M, Di-Ciaula A, Vacca M, Baldassarre G, et al. Impaired gallbladder motility and delayed orocecal transit contribute to pigment gallstone and biliary sludge formation in beta-thalassemia major adults. World J Gastroenterol. 2004;10(16):2383-90 [PubMed: 15285024].

[8] Hussaini SH, Pereira SP, Veysey MJ, Kennedy C, Jenkins P, Murphy GM, et al. Roles of gall bladder emptying and intestinal transit in the pathogenesis of octreotide induced gall bladder stones. Gut 1996;38: 775-783.

[9] Angelico M, Gandin C, Canuzzi P, Bertasi S, Cantafora A, De Santis A, et al. Gallstones in cystic fibrosis: a critical reappraisal. Hepatology. 1991;14(5):768-75 [PubMed: 1937382].

[10] Stringer MD, Taylor DR, Soloway RD. Gallstone composition: are children different?. J Pediatr. 2003;142(4):435-440 [PubMed: 12712064].

[11] Gallbladder, Gallstones, And diseases of the Gallbladder in children Deborah a. Goldman, MD* *Pediatric institute, Cleveland Clinic Foundation, Cleveland, OH.

[12] Schweizer P, Lenz MP, Kirschner HJ. Pathogenesis and symptomatology of cholelithiasis in childhood. Dig Surg 2000; 17: 459-467

[13] Al-Mulhim AS, Abdulatif MM, Ali AM. Laparoscopic cholecystectomy in children with sickle cell disease. Saudi J Gastroenterol. 2006;12(3):130.

[14] Webb DK, Darby JS, Dunn DT, Terry SI, Serjeant GR. Gallstones in Jamaican children with homozygous sickle-cell disease. Arch Dis Child 1989; 64: 693-696.

[15] Tripathy D, Dash BP, Mohapatra BN, Kar BC. Cholelithiasis in sickle cell disease in India. J Assoc Physicians India 1997; 45: 287-289.

[16] Do Santos Gumiero AP, Bellomo-Brandao MA, Costa-Pinto EAL. Gallstones in children with sickle cell disease followed up at a Brazilian hematology center. Arq Gastroenterol 2008; 45: 313-318.

[17] Manciu S, Matei E, Trandafir B. Hereditary Spherocytosis - Diagnosis, Surgical Treatment and Outcomes. A Literature Review. Chirurgia (Bucur). 2017 Mar-Apr;112(2):110-116. doi: 10.21614/chirurgia.112.2.110. PMID: 28463670.

[18] Croom RD 3rd, McMillan CW, Orringer EP, Sheldon GF. Hereditary spherocytosis. Recent experience and current concept of pathophysiology. Ann Surg 1986; 203: 34-39.

[19] Kar R, Rao S, Srinivas UM, Mishra P, Pati HP. Clinico-hematological profile of hereditary spherocytosis: Experience from a tertiary care center in North India. Hematology 2009; 14: 164-167.

[20] Kalayci AG, Albayrak D, Gunes M, Incesu L, Agac R. The incidence of gallbladder stones and gallbladder function in beta-thalassemic children. Acta Radiol 1999; 40: 440-443.

[21] Lotfi M, Keramati P, Assadsangabi R, Nabavizadeh SA, Karimi M. Ultrasonographic assessment of the prevalence of cholelithiasis and biliary sludge in beta-thalassemia patients in Iran. Med Sci Monit 2009; 15; CR398-CR402.

[22] Origa R, Galanello R, Perseu L, Tavazzi D, Cappellini MD, Terenzani L, et al. Cholelithiasis in thalassemia major. Eur J Hematol 2008; 82: 22-25.

[23] Banerjee, S.; Owen, C.; Chopra, S. Sickle cell hepatopathy. Hepatology 2001, 33, 1021-1028.

[24] Gardner, K.; Suddie, A.; Kane, P.; O'Grady, J.; Heaton, N.; Bomford, A.; Thein, S.L. How we treat sickle hepatopathy and liver transplantation in adults. Blood 2014, 123, 2302-2307.

[25] Schaad UB, Tschappeler H, Lentze MJ. Transient formation of precipitations in the gallbladder associated with ceftriaxone therapy. Pediatr Infect Dis 1986; 5: 708-710.

[26] Rosmorduc O, Hermelin B, Poupon R. MDR3 gene defect in adults with symptomatic intrahepatic and gallbladder cholesterol cholelithiasis. Gastroenterology 2001; 120: 1449-1467.

[27] Beretsky I, Lankin DH. Diagnosis of fetal cholelithiasis using real-time high resolution imaging employing digital detection. J Ultrasound Med 1983; 2: 381-383.

[28] Suma V, Marini A, Bucci N, Toffolutti T, Talenti E. Fetal gallstones: Sonographic and clinical observations. Ultrasound Obstet Gynecol 1998; 12: 439-441.

[29] Brown LD, Teele LR, Doubilet MP. Echogenic material in the fetal gallbladder: Sonographic and clinical observations. Radiology 1992; 182: 73-76.

[30] Abbitt LP, Mc Ilhenuy J. Prenatal detection of gallstones. J Clin Ultrasound 1990; 18: 202-204.

[31] Richards DM, Heel RC, Brogden RN, Speight TM, Avery GS. Ceftriaxone. A review of its antibacterial activity, pharmacological properties and therapeutic use. Drugs 1984; 27: 469-527.

[32] Shiffman ML, Keith FB, Moore EW. Pathogenesis of ceftriaxone-associated biliary sludge. In vitrostudies of calcium-ceftriaxone binding and solubility. Gastroenterology 1990; 99: 1772-1778.

[33] Lee SP, Lipsky BA, Teefey SA. Gallbladder sludge and antibiotics. Pediatr Infect Dis J 1990; 9: 422-423.

[34] Schaad UB, Wedgwood-Krucko J, Tschaeppeler H. Reversible ceftriaxone-associated biliary pseudolithiasis in children. Lancet 1988; 2: 1411-1413.

[35] Schaad UB, Suter S, Gianella-Borradori A, Pfenninger J,

Auckenthaler R, Bernath O, et al. A comparison of ceftriaxone and cefuroxome for the treatment of bacterial meningitis in children. N Engl J Med 1990; 322: 141-147.

[36] Buch Set al. A genome-wide association scan identifies the hepatic cholesterol transporter ABCG8 as a susceptibility factor for human gallstone disease. Nat Genet. 2007;39:995-999.

[37] Mirza N, Malhotra S, Sibal A. A novel compound heterozygous mutation in ABCB4 gene leading to Cholelithiasis, progressive familial intrahepatic cholestasis (type 3), and cirrhosis in a child. J Child Sci 2020;10:e134–e136.

[38] Rebholz C, Krawczyk M, Lammert F. Genetics of gallstone disease. Eur J Clin Invest. 2018 Jul;48(7):e12935. doi: 10.1111/eci.12935. Epub 2018 May 9. PMID: 29635711.

[39] Krawczyk M, Portincasa P, Lammert F. Predictive serum markers of gallstone disease: Gazing into a Crystall ball. J. Pediatr. Gastroenterol. Nutr. 2017;64:337-338

[40] Koebnick C, Smith N, Black MH, Porter AH., Richie BA, Hudson S, et al: Pediatric obesity and gallstone disease: Results from a cross-sectional study of over 510,000 youth. J Pediatr Gastroenterol Nutr., 2012: 5(3): 328.

[41] Jaruvongvanich V, Sanguankeo A, Upala S: Significant association between gallstone disease and nonalcoholic fatty liver disease: a systematic review and meta-analysis. Digestive diseases and sciences 61.8 (2016): 2389±2396. doi:10.1007/s10620-016-4125-2 PMID: 26993825

[42] Jawaheer G, Pierro A, Lloyd DA, Shaw NJ. Gallbladder contractility in neonates: Effects of parenteral and enteral feeding. Arch Dis Child Fetal Neonatal Ed 1995; 72: F200-F202.

[43] Roslyn JJ, Berquist WE, Pitt HA, Mann LL, Kangarloo H, DenBesten L, Ament ME. Increased risk of gallstones in children receiving total parenteral nutrition. Pediatrics 1983; 71: 784-789

[44] Enayet, A., Afifi, R.A., Mogahed, E.A. et al. Gallstones in Egyptian infants and children: Risk factors, complications and outcome: A single center experience. Egypt Liver Journal 10, 31 (2020). doi:10.1186/s43066-020-00037-9

[45] Millar AJW. Surgical disorders of the liver and bile ducts and portal hypertension. In: Kelly DA editors, Disease of the Liver and Biliary System in Children, 3rd Edition, Wiley-Blackwell Publication UK, 2008, pp. 433-474.

[46] Poddar U, Thapa BR, Bhasin DK, Prasad A, Nagi B, Singh K. Endoscopic retrograde cholangiopancreatography in the management of pancreatobiliary disorders in children. J Gastroenterol Hepatol 2001; 16: 927-931.

[47] Prasad H, Poddar U, Thapa BR, Bhasin DK, Singh K. Endoscopic management of post laparoscopic cholecystectomy bile leak in a child. Gastrointest Endosc 2000; 51: 506-507.

[48] Diez S, Müller H, Weiss C, Schellerer V, Besendörfer M. Cholelithiasis and cholecystitis in children and adolescents: Does this increasing diagnosis require a common guideline for pediatricians and pediatric surgeons?. BMC Gastroenterol. 2021;21(1):186. Published 2021 Apr 21. doi:10.1186/s12876-021-01772-y

[49] Bruch SW, Ein SH, Rocchi C, Kim PCW. The management of nonpigmented gallstones in children. J Pediatr Surg 2000; 35: 729-732.

[50] Sarrami M, Ridley W, Nightingale S, Wright T, Kumar R. Adolescent gallstones-need for early intervention in

symptomatic idiopathic gallstones. Pediatr Surg Int. 2019;35(5):569-574.

[51] Tannuri AC, Leal AJ, Velhote MC, Gonlcalves 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(11):2033-2038.

[52] Gutt C et al. Updated S3-guideline for prophylaxis, diagnosis and treatment of gallstones. German society for digestive and metabolic diseases (DGVS) and German Society for Surgery of the Alimentary Tract (DGAV)—AWMF Registry 021/008. Z Gastroenterol. 2018;56(8):912-66

[53] Gamba PG, Zancan L, Muraca M, Vilei MT, Talenti E, Guglielmi M. is there a place of medical treatment in children with gallstones? J Pediatr Surg 1997; 32: 476-478.

[54] Chan S, Currie J, Malik AI, Mahomed AA. Pediatric cholecystectomy: Shifting goalposts in the laparoscopic era. Surg Endosc 2008; 22: 1392-1395.

[55] Matos C, Avni EF, Van Gansbeke D, Pardou A, Struyven J. Total parenteral nutrition (TPN) and gallbladder diseases in neonates. Sonographic assessment. J Ultrasound Med. 1987;6(5):243-248 [PubMed: 3108519].

[56] Debray D, Pariente D, Gauthier F, Myara A, Bernard O. Cholelithiasis in infancy: A study of 40 cases. J Pediatr 1993; 122: 385-391.

[57] Holcomb GW Jr, Holcomb GW III. Cholelithiasis in infants, children and adolescents. Pediatric Rev 1990; 11: 268-274

[58] Marchetti M, Quaglini S, Barosi G. Prophylactic splenectomy and cholecystectomy in mild hereditary spherocytosis: Analyzing the decision in different clinical scenarios. J Intern Med 1998; 244: 217-226.

[59] Sandler A, Winkel G, Kimura K, Soper R. The role of prophylactic cholecystectomy during splenectomy in children with hereditary spherocytosis. J Pediatr Surg 1999; 34: 1077-1078.

[60] Al-Salem AH. Should cholecystectomy be performed concomitantly with splenectomy in children with sickle-cell disease? Pediatr Surg Int 2003; 19: 71-74.

[61] Muroni M, Loi V, Lionnet F, et al. Prophylactic laparoscopic cholecystectomy in adult sickle cell disease patients withcholelithiasis: A prospective cohort study. Int J Surg. 2015;22:62-66.

[62] Curro G, Meo A, Ippolito D, et al. Asymptomatic cholelithiasis in children with sickle cell disease: Early or delayed cholecystectomy? Ann Surg. 2007;245(1):126-129.