

Gallstone Disease in Children

UJJAL PODDAR

Correspondence to: Dr Ujjal Poddar, Department of Pediatric Gastroenterology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Raebareli Road, Lucknow 226 014, Uttar Pradesh, India. ujjalpoddar@hotmail.com

Context: Little is known about the epidemiology of cholelithiasis in children. Cholelithiasis and choledocholithiasis were considered to be uncommon in infants and children but have been increasingly diagnosed in recent years due to widespread use of ultrasonography. However, there is not much of information from India and no consensus among Indian pediatricians and pediatric surgeons regarding management of gallstones in children. Hence, the purpose of this review is to increase awareness about the management of gallstones in children. **Methods:** Extensive electronic (PubMed) literature search was made for this purpose and literature (original articles, clinical trials, case series, review articles) related to gallstones in children were reviewed. **Conclusions:** The etiologies of cholelithiasis are hemolytic (20%-30%), other known etiology (40%-50%) such as total parenteral nutrition, ileal disease, congenital biliary diseases, and idiopathic (30-40 %). Spontaneous resolution of gallstones is frequent in infants and hence a period of observation is recommended even for choledocholithiasis. Children with gallstones can present with typical biliary symptoms (50%), nonspecific symptoms (25%), be asymptomatic (20%) or complicated (5%-10%). Cholecystectomy is useful in children with typical biliary symptoms but is not recommended in those with non-specific symptoms. Prophylactic cholecystectomy is recommended in children with hemolytic disorders.

Key words: *Choledocholithiasis, Cholelithiasis, Outcome.*

Cholelithiasis or gallstones are quite common in adults. The prevalence of gallstones among adult population in the West is 10% to 20% (1,2) and this figure in India is 3% to 6%(3,4). Interestingly the prevalence of gallstones is seven times more frequent in north India than in south India(5) and the composition of gallstones is also different in different parts India. In north and eastern India, gallstones are predominantly cholesterol stones and mixed stones; on the other hand, in south India, pigment stones are predominant(6,7). The natural history of gallstones in adults has shown that the majority (more than 80%) are incidentally detected asymptomatic gallstones(8) and the majority of them (>80%) remains asymptomatic on long term follow up; even if they develop complications (like pancreatitis, cholecystitis, choledocholithiasis), they are usually preceded by biliary colic(1,9). Hence, in adults, prophylactic cholecystectomy is not recom-

mended for asymptomatic gallstones. However, the picture is not so clear in children.

Gallstones were considered to be uncommon in infants and children but have been increasingly diagnosed in the recent years, mainly due to wide spread use of ultrasonography. There is not much information about cholelithiasis in children from India and there is no consensus among Indian pediatricians and pediatric surgeons regarding the management of gallstones in children. Hence, the purpose of this review is to increase awareness about the management of gallstones in children.

METHODS

A detailed electronic (PubMed) literature search was made for this purpose and English language literature (original articles, clinical trials, case series, case report, letter, meta-analysis, practice guideline, randomized controlled trial) related to gallstones in

children (key words used: gallstones, children, ceftriaxone, fetal gallstones) were reviewed. The period of search was from 1965 to December 2009. During this period a total of 372 articles were published of which relevant 61 articles were included in this review.

EPIDEMIOLOGY

Little is known about the epidemiology of cholelithiasis in children. Cholelithiasis and choledocholithiasis have been increasingly diagnosed in recent years in children. This phenomenon may be attributed to better medical imaging (especially ultrasonography) and its usage in investigating children with unexplained abdominal pain and/or a genuine increase in the incidence of cholelithiasis due to increasing use of total parenteral nutrition, frusemide and phototherapy in the infants(10). The exact prevalence of gallstones in children is not known. Studies from Europe have shown an overall prevalence of gallstone disease of 0.13% to 0.2% in children(11,12). In Japan, the prevalence of gallstone disease is reported to be less than 0.13% of children(13). The only report from India by Ganesh, *et al.* has shown a prevalence of 0.3% in a hospital based observation among 13,675 children(14). However, the prevalence of gallstones among obese children and adolescents was shown to be quite high (2% of 493 children) in a recent study(15). Studies on cholelithiasis in children have shown a bimodal distribution, with a small peak in infancy and a steadily rising incidence from early adolescence onwards(11,16). Boys and girls are equally affected in early childhood, but as in adults, a clear female preponderance emerges during adolescence.

A unique subset is chronic hemolytic disease. In this condition, cholelithiasis is usually not seen before the age of five and thereafter, the incidence increases progressively with age. In sickle-cell disease, the prevalence of pigment gallstones was reported to be 10% to 15% in children under 10 years of age, it increased to 40% in those aged 10-18 years, and 50% in adults(17-19). The prevalence of gallstones in hereditary spherocytosis was 10% to 20% and in adult series it was 40%(20,21). In thalassemia, the reported figure is low (10% to 15%)(22,23). With longer survival of thalassemia

patients, higher prevalence of gallstones (50%) has been reported(24). The highest prevalence of gallstones have been reported in thalassemics with Gilbert's syndrome genotype(24,25). However, in a study on 64 patients with median age of 10 (range, 5 to 20) years with thalassemia major from Chandigarh, none had gallstones(26).

PATHOGENESIS

Gallstones are either cholesterol gallstones (pure and mixed) or pigment stones (black or brown). Cholesterol supersaturation of bile with stasis predisposes to cholesterol gallstone formation. Mixed cholesterol gallstones are the commonest stones in adults and in adolescent girls. However, pigment stones are more common in children. Black pigment stones are formed due to supersaturation of bile with calcium bilirubinate and are seen in hemolytic disorders and in association with total parenteral nutrition. Brown pigment stones are associated with infection and biliary stasis and form more often in the bile ducts than in the gallbladder(16).

Biliary sludge is composed of mucin, calcium bilirubinate and cholesterol crystals. It is commonly associated with prolonged fasting, total parenteral nutrition, pregnancy, sickle-cell disease, treatment with ceftriaxone or octreotide(27). The natural history of biliary sludge is variable; it may resolve spontaneously or may progress to gallstone development. Persistent sludge may give rise to biliary complications (such as obstruction or infection).

Etiologically cholelithiasis (**Table I**)(11,16) in children can be divided into three groups; hemolytic, other known etiology, and idiopathic. Almost 20% to 30% of all gallstones in children are due to hemolytic diseases such as sickle-cell disease, hereditary spherocytosis and thalassemia. In around 40% to 50% of cases, gallstones are due to another known etiology such as total parenteral nutrition, prolonged fasting, ileal disease or ileal resection, frusemide therapy, congenital biliary diseases such as choledochal cyst, chronic liver disease and progressive familial intrahepatic cholestasis (PFIC). Around 30% to 40% of cases are idiopathic. As in adults, gallstones in adolescent girls are more often idiopathic(16).

TABLE I ETIOLOGY OF GALLSTONES IN CHILDREN(11,16)

Type of gallstones	Proportion of all gallstones in children	Etiology
Hemolytic	20%-30%	Sickle-cell disease, hereditary spherocytosis, thalassemia major
Non-hemolytic	40%-50%	TPN, prolonged fasting, ileal disease (like Crohn's disease) or resection, prematurity, frusemide therapy, cardiopulmonary bypass, congenital biliary malformations, PFIC, chronic liver disease, cystic fibrosis, OCP, teenage pregnancy
Idiopathic	30-40%	No predisposing factor

TPN: total parenteral nutrition, PFIC: progressive familial intrahepatic cholestasis, OCP: oral contraceptive pills

Total parenteral nutrition and cholelithiasis

Total parenteral nutrition (TPN) impairs enterohepatic circulation and cholecystokinin induced gallbladder contraction resulting in biliary stasis, sludge and stones(28). The longer the duration of TPN therapy, the higher the risk of developing cholelithiasis(29). The risk of developing gallstones in children on prolonged TPN therapy is increased if there is concomitant ileal resection or disease. In a study of 21 children on prolonged TPN (more than 3 months), Roslyn, *et al.* have shown that 43% of children developed gallstones but this figure was 64% in children with ileal resection or disease(29). Sludge develops more rapidly in neonates than in adults after a mean time of TPN infusion in neonates of 10 days, as compared with more than 6 weeks in adults. In a prospective study of 41 neonates, Matos, *et al.* have shown that gallbladder sludge appeared in 18 (44%) of those infants who had received TPN infusion for a mean period of 10 days(30). In 12 infants, the sludge cleared within one week of resuming enteral feeding but two of the remaining infants went on to develop asymptomatic gallstones. Spontaneous resolution occurred in one of these two infants by 6 months while the calculi persisted in the other baby.

Ceftriaxone-associated biliary pseudolithiasis

Ceftriaxone, a third-generation cephalosporin, is a popular drug among pediatricians as it has a broad spectrum of antimicrobial activity and good CSF penetration. Biliary sludge or biliary lithiasis has been reported as a potential complication of ceftriaxone treatment since 1986(31). Since ceftriaxone induced biliary lithiasis is reversible and disappears on discontinuation of therapy it is called 'pseudolithiasis'. In a patient with normal renal function, 60% of the drug is excreted unchanged into the urine and 40% is excreted into the bile(32). Ceftriaxone is an anion, can concentrate in bile 20 to 150 times more than in serum and readily forms an insoluble salt with calcium (calcium-ceftriaxone) that precipitates in gallbladder(33). The risk factors for ceftriaxone pseudolithiasis are hypercalcemia, renal failure (leads to increase biliary concentration), high dose (>2g or >200mg/kg/day), long-term treatment and gallbladder stasis(34).

The incidence of ceftriaxone induced pseudolithiasis is 15% to 46% in various prospective studies(38-42). Usually pseudoliths appear after 6 (range, 3 to 22) days of therapy and disappear after 15 (range, 2-63) days of discontinuation of therapy(35,36). Most cases of ceftriaxone induced pseudolithiasis are asymptomatic and detected on sonography but rarely (0-19% of cases)(36), they can produce symptoms like pain abdomen, nausea, vomiting and biliary obstruction. In symptomatic cases, discontinuation of drug is recommended. However, cessation of drug therapy is unnecessary in incidentally detected asymptomatic cases of ceftriaxone induce pseudolithiasis.

Low phospholipid associated cholelithiasis (LPAC)

Gallstones in the adolescent age group with a strong family history of gallstones under the age of 40 years, intrahepatic cholestasis of pregnancy or a cholestatic reaction to oral contraception should raise the suspicion of a rare condition called low phospholipid associated cholelithiasis (LPAC)(37). The underlying cause is a mutation in MDR3, a gene which encodes the ABCB4 transporter. This protein is responsible for the translocation of phosphatidylcholine across the canalicular membrane of hepato-

cytes which then solubilises cholesterol in bile. In the absence of phosphatidylcholine, bile becomes supersaturated with cholesterol and predisposes to gallstone formation. This condition is more frequent in females than in males (3:1). Apart from a family history of cholesterol gallstones amongst first degree relatives, intrahepatic hyperechoic foci (cholesterol crystal deposits in intrahepatic bile ducts) are a characteristic sign of the LPAC syndrome. The typical biliary symptoms experienced by these patients are probably due to cholesterol crystal deposits and bile duct inflammation as symptoms recur in more than half of the cases after cholecystectomy. Ursodeoxycholic acid (UDCA) appears to relieve biliary symptoms long before the dissolution of intrahepatic stones(38).

CLINICAL PRESENTATION

Table II summarizes the clinical presentations at different age of presentation.

Fetal Cholelithiasis

The prenatal diagnosis of fetal gallstones has been reported since 1983(39) but is a rare finding and little is known about the natural history and clinical significance. The most cases of fetal cholelithiasis reported in the literature are detected in the third trimester of pregnancy with no apparent sex predilection and all were identified as incidental findings. The echogenic material detected in fetal gallbladder is usually sludge as in most reported cases there was lack of acoustic shadowing. The prognosis

of fetal gallstones is very good as complete spontaneous resolution has been documented in the majority of cases between 1 and 12 months after birth and those that persist are rarely symptomatic(40). There are several hypotheses put forward to explain the formation of fetal gallstones but none are conclusive. Brown, *et al.* have suggested that increased level of estrogen might predispose to the formation of stones by increasing the secretion of cholesterol and reducing the synthesis of bile acids(41). Other possible predisposing factors are: use of narcotics in pregnant women, hemolytic anemia, blood group incompatibility, structural abnormalities like choledochal cyst, pregnancy induced cholestasis, etc.(42,43).

Cholelithiasis in infancy

Cholelithiasis is uncommon in infants but increasing numbers are reported in recent years mainly due to increasing use of ultrasonography (US). Gallstones in infancy are usually asymptomatic but occasionally can present with cholestatic jaundice, transient acholic stools, sepsis and abdominal pain. In symptomatic infants, gallstones are more often associated with stones in the common bile duct (CBD) than stones in the gallbladder alone(44,45). In a series of 13 cases of cholelithiasis in infants, St-Vil, *et al.* have reported that 11 were asymptomatic and detected by US done for unrelated problems(44). In another series of 40 cases of cholelithiasis in infancy, Debray, *et al.* have shown that 6 had isolated gallstones and were asymptomatic whereas 34 had bile duct obstruction and were symptomatic(45).

TABLE II CLINICAL PRESENTATIONS OF GALLSTONES IN CHILDREN(46,47)

Age group	Proportion of all gallstones in children	Clinical presentations
Infants (< 2yrs)	10%	1. Symptomatic: Cholestatic jaundice, transient acholic stools, abdominal pain, and sepsis. 2. Asymptomatic: incidental detection.
Children (2-14 yrs)	40%	1. Typical biliary symptoms (40%-50%): right upper quadrant or epigastric pain with or without nausea, vomiting and fat intolerance. 2. Non-specific abdominal pain (20%-30%). 3. Acute abdomen (5%-10%): due to acute cholecystitis, pancreatitis or cholangitis. 4. Asymptomatic (20%).
Adolescents(14-18 yrs)	50%	Same as in children but right upper quadrant pain and fatty food intolerance are more common in adolescents than in children.

Cholelithiasis in children

Children with gallstones can present with acute abdominal pain due to cholecystitis, cholangitis or pancreatitis. However, an acute presentation is uncommon (5% to 10% of cases only). Most commonly, children with cholelithiasis present with typical right upper quadrant pain (50%) or non-specific abdominal symptoms (25%) including poorly localized abdominal pain and nausea. Around 20% of cases are asymptomatic (incidentally detected stones)(11,46,47). Gallstones in children are more often (60%) symptomatic than in adults (20%)(46). The type of symptoms depend on the age of presentation, older children (6 years or more) often localize pain in the right upper quadrant whereas younger children (5 years or less) tend to present with nonspecific symptoms(11). Fatty food intolerance, a typical symptom of gallstone disease in adults, tends to be reported by older children(47).

Cholelithiasis in adolescents

In this age group, the symptoms are similar to those reported in adults. Fatty food intolerance, biliary colic and acute or chronic cholecystitis are usual presenting features of symptomatic patients(47).

Diagnosis

The universally used and the most accurate diagnostic test in detecting the presence of gallstones is ultrasonography. Gallstones are usually mobile, single or multiple and characteristically cast an acoustic shadow. Biliary sludge though appearing echogenic on ultrasound, does not cast an acoustic shadow. A stone, as small as 1.5 mm, can be detected by ultrasonography. The sensitivity and specificity of ultrasonography exceeds 95% for gallbladder cholelithiasis, but this figure is only 50%-75% for choledocholithiasis. In children 20% to 50% gallstones are radiopaque(48).

Cholescintigraphy, with technetium 99^m labeled diisopropyl iminodiacetic acid (DISIDA), is the most accurate method of diagnosing acute cholecystitis. Nonvisualization 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. Endoscopic retrograde cholangiopancreatography (ERCP) offers the additional advantage of therapeutic intervention in common bile duct stones(49,50).

MANAGEMENT

Management of gallstones depends on the symptoms and the age of the patient. Symptomatic gallstones need cholecystectomy and same is true for complicated gallstones but there is no consensus about the management of asymptomatic gallstones in children. In a prospective study of children with non-pigmented gallstones, Bruch SW, *et al.* followed 41 children with non-specific or no symptoms for 21 months(51). Of these, 50% remained or became asymptomatic, 32% experienced definite improvement in symptoms, 18% had continued symptoms but none had any biliary complications. Wesdorp, *et al.*(11) have substantiated this observation in their study of 82 children with cholelithiasis who were followed up for a mean period of 4.6 years. The suggested treatment algorithm for gallstones in children is given in **Fig.1**. Children with gallstones should be divided into two groups. Those with typical symptoms (right upper quadrant or epigastric pain, nausea, vomiting and fatty food intolerance) should have their gallbladders removed. Asymptomatic children or children with nonspecific symptoms can undergo safe follow up. These children will require observation into adulthood to determine their lifetime risk of developing symptoms.

In recent years, laparoscopic cholecystectomy has become the treatment of choice in the surgical management of children with cholelithiasis. It has the advantage of being less invasive with lower morbidity and mortality and shorter hospital stay over conventional open cholecystectomy(52).

The role of dissolution therapy in the management of gallstones in children remains to be defined. The only study of UDCA therapy for gallstones in children by Gamba, *et al.* have shown disappointing results(53). Of 15 children with radiolucent stones (<10 mm) and a functional gallbladder treated for one year, stones disappeared completely in only two cases but returned later in both.

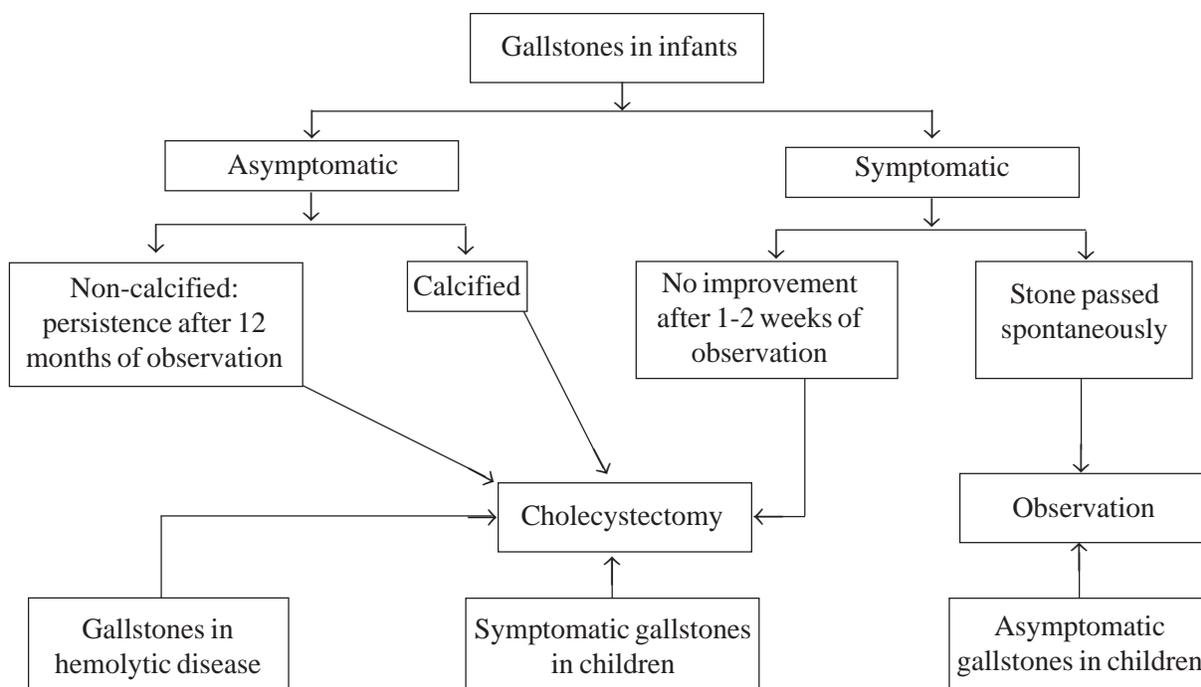


FIG. 1. Management algorithm for gallstones in children.

Extracorporeal shock-wave lithotripsy for gallstones in children has been successful in a single case report(54). The approach to cholelithiasis in infancy is different as spontaneous resolution has been reported in a significant proportion of cases (cholelithiasis almost 50% and choledocholithiasis 30%)(44,45,55). Spontaneous resolution within 6 months is more common with idiopathic gallstones than in patients with known predisposing factors. Asymptomatic infants with idiopathic cholelithiasis be observed for spontaneous resolution. Even for choledocholithiasis, an observation period of 1-2 weeks is recommended before active therapy as there is a chance of spontaneous resolution. Cholecystectomy is indicated for symptomatic cholelithiasis, asymptomatic cholelithiasis persisting beyond 12 months and radiopaque calculi(44,45).

Management of cholelithiasis in hemolytic disease

In this group of children, screening with US is recommended at around 5 years of age. Screening is also recommended before splenectomy as both splenectomy and cholecystectomy can be combined in presence of gallstones and it confers a survival

benefit over splenectomy alone in hereditary spherocytosis(56). However, there is no advantage of doing cholecystectomy with splenectomy if there are no gallstones as these patients are not at an increased risk of cholelithiasis after splenectomy(57). 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 this setting is much higher than in elective cholecystectomy(58). To avoid sickling during the perioperative period it is recommended that hemoglobin S be decreased to at least 30% and total hemoglobin be increased to at least 11 g/dL. During the surgery and recovery period, hypotension, dehydration, hypoxia, hypothermia and acidosis should be prevented(47).

Choledocholithiasis

Most often common bile duct (CBD) stones are associated with gallstones except in hemolytic conditions where these may be the primary stones. Overall CBD stones are uncommon in children (only

KEY MESSAGES

- Gallstone disease is uncommon in children but more cases are being diagnosed due to increasing use of ultrasonography.
- Gallstones in infants most often resolve spontaneously.
- Gallstones in a setting of hemolytic disease develop after 5 years of age and require prophylactic cholecystectomy.
- Asymptomatic gallstones or gallstones with atypical symptoms may be observed as the natural history is benign.

10% of all gallstones)(16,59), but infants have a higher incidence(45). Clinical presentation of CBD stones comprises jaundice, cholangitis, and gallstone pancreatitis. A CBD stone should also be suspected in a patient with gallstones with hyperbilirubinemia (total bilirubin >1.3 mg/dL) and/or a dilated CBD on US (>6 mm). The most appropriate method of investigation and management of CBD stones seems to be laparoscopic cholecystectomy (LC) with intraoperative cholangiogram (IOC) followed by ERCP(60). In a study of 48 cases of suspected CBD stones, Mah, *et al.* have compared preoperative ERCP followed by LC with LC+IOC followed by ERCP(61). The diagnostic yield of ERCP in detecting CBD stone was just 23% with the former approach compared with 100% with the latter approach.

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