Management of Gallstones in the Pediatric Patient

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Ashanti L. Franklin, Faisal G. Qureshi, and Evan P. Nadler

Introduction

Infant and pediatric cholelithiasis, as well as other related gallbladder diseases, are becoming increasingly more common due to heightened awareness and the increased incidence of childhood obesity [1–5]. The prevalence of biliary sludge and gallstones in the pediatric population is estimated to be 1.46 % and 1.9 %, respectively, and the incidence is slightly higher in children undergoing abdominal sonogram for abdominal pain [4, 6]. Cholelithiasis in pediatric patients usually presents between the ages of 7 and 10, but this age range is changing as the childhood obesity epidemic continues [3, 4, 7, 8].

The majority of cases of childhood cholelithiasis are believed to be idiopathic. Only 20 % of gallstones are related to hematologic diseases including hereditary spherocytosis, sickle cell disease (SCD), and thalassemia [7, 9, 10]. Other risk factors for infantile and pediatric cholelithiasis and choledocholithiasis include total parenteral nutrition (TPN), ileal resection, inflammatory bowel disease, obesity, hereditary gallstones, cystic fibrosis, biliary tract anomalies, Gilbert's syndrome, and various medications (such as oral contraceptives, cyclosporine, or ceftriaxone) [4, 5, 7, 11–16].

In adults, cholelithiasis is often associated with obesity, and it is believed that the incidence of childhood obesity is associated with gallstones in children. According to the National Health and Nutrition Examination Survey, childhood and adolescent obesity increased to 17.1 % in 2003–2004 and is likely much higher today [17]. The incidence of severe obesity in children has tripled over the last 25 years [18]. Mehta and colleagues [19] reported on 404 children undergoing cholecystectomy, 16 % were overweight, 24 % were obese, and 15 % were severely obese. In a case control study there was a strong relation between the prevalence of obesity and increased

A.L. Franklin, M.D.
Children's National Health Systems, 111 Michigan Ave NW, Washington, DC 20002, USA

Department of Surgery, Howard University Hospital, 2041 Georgia Avenue NW, Washington, DC 20060, USA
e-mail: afranklin@cnmc.org; Ashanti.franklin@me.com

F.G. Qureshi, M.D.
The George Washington, University School of Medicine and Health Sciences, 111 Michigan Ave NW, Washington, DC 20002, USA

Department of Surgery, Children's National Medical Center, 111 Michigan Ave NW, Suite 4200, Washington, DC 20010, USA
e-mail: fqureshi@cnmc.org; Qureshimd@gmail.com

E.P. Nadler, M.D. (✉)
Children's National Medical Center, The George Washington University School of Medicine and Health Sciences, 111 Michigan Avenue, NW, Washington, DC 20010, USA

Department of Pediatric Surgery
Children's National Medical Center
111 Michigan Ave NW, Suite 4200, Washington, DC 20010, USA
e-mail: enadler@cnmc.org

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cholelithiasis-related hospitalizations in children [20]. In addition, Hispanic ethnicity and obesity strongly correlate with symptomatic gallbladder disease [19]. In this study, Hispanic children were also more likely to have obstructive gallbladder disease [19].

Gallstones can be classified as pigmented, cholesterol, or mixed-type stones. Pigment stones are typically associated with hemolytic disorders, but can be associated with inflammatory bowel disease, ileal resection, and Gilbert's syndrome [5]. Alternatively, cholesterol and mixed-type stones are commonly seen in obese children and adolescents [5, 19, 21].

Symptomatic gallstones in children present most commonly with right upper quadrant pain (75–85 %), followed by nausea or vomiting in 60 %. Jaundice is less frequently seen and epigastric tenderness is found in only one third of the patients. Jaundice is a more common clinical presentation in infants less than 1 year [1, 2, 7]. Gallstones can be asymptomatic in up to 17 % of children [4, 7]. Medical therapy is ineffective in children with symptomatic cholelithiasis and laparoscopic cholecystectomy is now the treatment of choice [7, 22, 23]. Complications of pediatric gallstone disease include choledocholithiasis, acute cholecystitis, chronic cholecystitis, cholangitis, and gallstone pancreatitis. In this chapter, we will predominantly focus on the diagnosis and management of acute cholecystitis in children; however, we will also touch upon acalculous cholecystitis, the management of gallstones with certain associated comorbid conditions that are unique to the pediatric population, and lastly the management of biliary dyskinesia in the pediatric population.

Acute Cholecystitis

Acute cholecystitis is relatively infrequent in the pediatric population in comparison to adults, but again this may be changing in light of the childhood obesity epidemic (Fig. 16.1). In children with symptomatic gallbladder disease, it is estimated that the prevalence of acute cholecystitis is 10 % with the vast majority of patients suffering solely from biliary colic [24]. Children commonly present with abdominal pain in the right upper quadrant (85–94 %) and less frequently in the epigastrium (34 %) [3, 24]. Accompanying symptoms include nausea and vomiting in up to 60 % of patients [5, 24]. Acute cholecystitis may also be associated with fever.

Laboratory investigations should include hepatic aminotransferases which are commonly elevated in the early course of biliary obstruction. In addition, serum bilirubin, alkaline phosphatase, and gamma-glutamyl transferase are elevated in patients with cholestatic disease. These patients may also have a normal or elevated white blood cell count (WBC). While children may have an atypical presentation of acute cholecystitis,

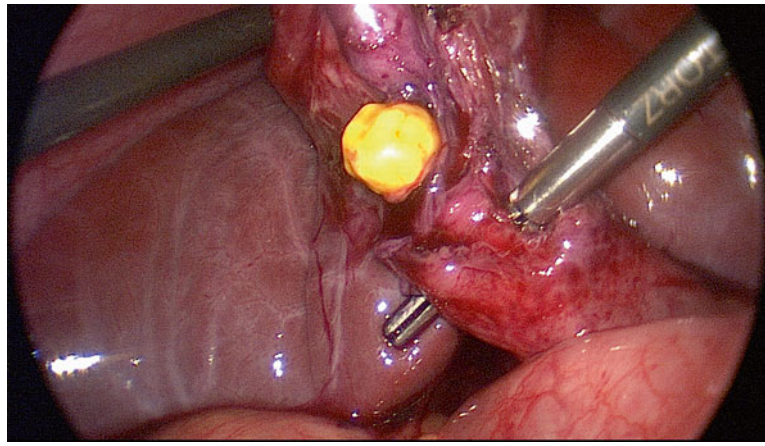

Fig. 16.1 Large gallbladder calculus in adolescent patient with severe acute cholecystitis. The patient had no risks for stone disease such as hemolytic disease or hypercholesterolemia. *Photo courtesy of Dr. Shaun Steigman*

right upper quadrant/epigastric pain along with a transabdominal ultrasound depicting gallstones or sludge, gallbladder wall thickening, an enlarged/distended gallbladder, pericholecystic fluid, and/or a sonographic Murphy's sign confirms or at least solidifies the diagnosis. Normal gallbladder wall thickness in children under 16 years of age is ≤3 mm [25]. The positive predictive value of ultrasound in pediatric cholecystitis is reported to be 67–87 % [26]. Tsai et al. [26] reported that 80 % of their pathological specimens after a cholecystectomy in children revealed chronic cholecystitis indicating that previous episodes of gallbladder inflammation occurred and thus children may have less severe episodes of cholecystitis when compared to adults.

The incidence of asymptomatic cholelithiasis in children is unclear. It is reported that up to 17 % of children are diagnosed with gallstones [4, 7]. Several authors have highlighted the incidence of acute cholecystitis as an initial presentation of gallstones. In one study, Bogue et al. [24] evaluated 194 asymptomatic children with cholelithiasis. Of these patients, nine suffered a complication of their gallstones including six patients with choledocholithiasis, two who suffered from gallstone pancreatitis, and one patient with acute cholecystitis. Six of these patients eventually underwent cholecystectomy, representing approximately a 3 % surgery rate. However, Tannuri et al. [27] found a slightly higher complication rate in their series where 56 of 223 (25.1 %) patients presented with a complication of cholelithiasis including 16 with acute cholecystitis. Overall, the progression to symptoms in children with incidentally diagnosed asymptomatic cholelithiasis is relatively low. Therefore it is advisable that asymptomatic gallstones in a pediatric patient without comorbidities be followed clinically, reserving an operation for only those patients who suffer from a complication or symptoms of their gallstones.

Laparoscopic Cholecystectomy

Laparoscopic cholecystectomy (LC) has become a mainstay in the management of cholecystitis in children, as it has in adults. Several authors have examined the safety, efficacy, and cost effectiveness of this procedure in the pediatric population. Holcomb and colleagues [28] were the first to report the safety and efficacy of LC for the management of acute cholecystitis in children. In this series, there were no complications during the follow-up period of 16 months (range 2–24 months). In addition, children undergoing elective LC had shorter length of stay, reduced analgesics, and decreased total hospital charges. Tannuri et al. [27] reported on 16 children with acute cholecystitis treated with LC. The authors reported conversion to open in two patients with acute cholecystitis and portal hypertension early in their series. This suggests that surgeon experience may reduce conversion rate, which has been found to be the case in adults. Similarly, this study also had no complications or bile duct injuries. LC is now the standard of care in managing gallstone disease in children.

The single port laparoscopic cholecystectomy has been reported in the literature for children with symptomatic gallstone disease. Ostlie et al. [29], in a prospective randomized trial, reported that the single port LC had a longer operating time and increased level of difficulty when compared to the traditional four port LC. There was no significant difference in hospital length of stay. Nonetheless single incision LC is considered to be a safe alternative to a standard LC in children with cholecystitis [30–32], although it is not the authors' preference. Its use is not widespread among pediatric surgeons.

The complication rate of LC is less than 5 %, with trocar site infections being the most common complication [3, 33, 34]. Children undergoing LC for acute cholecystitis and those with hemolytic disorders or other significant comorbid conditions have higher complication rates [8, 35]. The complication rate in those with SCD is 39 % in one series and the complications were mainly associated with the hemolytic disorder [36]. These patients had a higher incidence of respiratory compromise and readmission to the hospital for abdominal pain. Children undergoing LC with cardiac disease have a higher prevalence of multi-system organ failure [8, 37]. Bile duct

injury following LC in children is rare. In a large retrospective series, Kelley-Quon et al. [38] found a 0.36 % incidence of bile duct injury. Zeidan and colleagues [34] reported no bile duct injuries in 202 children undergoing LC. Thus, LC is safe and effective in children and there is no age-specific reason for children to be subjected to an open procedure.

Endoscopic Retrograde Cholangiopancreatography and Intraoperative Cholangiogram

Endoscopic retrograde cholangiopancreatography (ERCP) may be performed preoperatively or postoperatively if choledocholithiasis is present, depending on surgeon and endoscopist preferences. In children from ages 1 month to 18 years ERCP is a diagnostic and therapeutic tool with up to a 95 % success rate [39–42]. Post-ERCP pancreatitis occurs in up to 8 % of children and the incidence increases in children undergoing therapeutic ERCP. Hemorrhage and perforation are relatively rare and are observed in 0.3–2 % of children undergoing ERCP [40]. ERCP is considered to be safe and efficacious before, during, or after laparoscopic cholecystectomy with common bile duct (CBD) clearance attained in 95 % of the patients [7, 15, 43, 44]. Newman et al. [45] suggested that preoperative ERCP may be more efficacious if preoperative assessment demonstrates choledocholithiasis. An increased operative time by 86 % has been seen with concomitant ERCP and LC and therefore may impact operative costs, although this approach may be more desirable than two separate general anesthetics [23].

Intraoperative cholangiography (IOC) may be performed in children with CBD stones without the need for the additional general anesthesia required for ERCP. Holcomb et al. [23] performed IOC in 57 patients undergoing LC and had an 86 % success rate for completing the procedure, with an overall increase in operative time by 29 %. Kumar et al. [7] reported a 100 % success rate without any complication related to the IOC. In an effort to determine the role of IOCs in children with biliary stone disease, Waldhausen and colleagues [43] performed 63 IOCs in 100 children undergoing LC of which there were 55 positive studies, by their criteria. However, only 18 children were found to have CBD stones. IOC did not result in any complications, though it increased operative time by 35 % [43]. Based on their findings, Waldhausen et al. [43] recommended that routine IOC should be completed in children undergoing LC although whether this conclusion is supported by their data is debatable. Furthermore, they argued IOC could help avoid unnecessary ERCP and the obligatory second anesthetic. More recently there has been some controversy in the need for routine IOC at the time of LC since it often yields negative results and thus may not be necessary for the diagnosis of CBD stones in the vast majority of pediatric patients [27, 46]. In addition, the biliary tract can be delineated preoperatively in most children through ultrasonography [27]. Thus routine IOC at the time of LC is not routinely performed at our institution and many others around the country. Whether it is superior to merely obtaining the critical view for preventing injury to the CBD in children is unknown.

Acalculous Cholecystitis

Acute acalculous cholecystitis (AAC) in children is uncommon although the incidence is increasing. In children with cholecystitis, AAC accounts for up to 21.4 % of cases [47]. AAC is commonly associated with an infectious disease; however, it may be seen in previously healthy children as well. AAC has been associated with hepatitis, typhoid fever, sepsis, Epstein–Barr virus, cytomegalovirus, and pneumonia in children [48–53]. Children with AAC clinically present similar to acute calculous cholecystitis with RUQ and/or epigastric pain, fever, nausea, and vomiting. Occasionally, a palpable mass in the right upper quadrant is present. AAC may be associated with an elevated WBC and normal or slightly abnormal serum hepatic aminotransferase levels.

Abdominal ultrasound has a high specificity in diagnosing diseases of the biliary system, and gallbladder wall thickening in the absence of

gallstones is the most common ultrasonographic sign seen in children with AAC. Additionally, gallbladder distention, debris, and pericholecystic fluid may also be seen on sonogram. While computed tomography has a low sensitivity for cholelithiasis it can detect gallbladder perforation and visualization of the entire abdomen and pelvis, and thus is sometimes useful in the diagnosis of AAC.

Laparoscopic cholecystectomy is the treatment of choice for AAC in children. Alternatively, critically ill children may receive antibiotics, with or without a cholecystostomy, and an interval LC once their acute illness resolves. Karkera et al. [53] recommend an interval cholecystectomy in children with AAC, which is now becoming standard of care unless the child was otherwise healthy upon presentation with AAC.

Neonatal and Infantile Gallstones

Gallstones have been found in up to 0.5 % of newborns. Most patients are asymptomatic and the majority of infants have no recognized predisposing factor [54, 55]. However, associated risk factors include prematurity, Down's syndrome, polycythemia, hemolysis, biliary tract anomalies, phototherapy for jaundice, maternal morphine addiction, TPN, and nephrocalcinosis [12, 56–59]. Symptomatic infants have been treated successfully utilizing ERCP, open or laparoscopic cholecystectomy with or without ERCP, and CBD exploration [7, 34, 60, 61]; however, most patients can be treated with cholecystectomy alone if symptoms arise.

Up to 50 % of infants will have spontaneous resolution of gallstones [54, 56, 62, 63]. Several studies have recommended treating infants with choledocholithiasis conservatively with antibiotics and ursodeoxycholic acid [59, 64]. Although rare, there have been reported cases of acute cholecystitis in infants [65]. Fatal complications in infants including perforation, obstruction, and peritonitis have been reported [66]. Based on these findings, Jawad et al. [60] recommended observation of asymptomatic infants for 3–6 months. If there is failure of resolution or the presence of calcified stones, then LC is recommended by these authors [60]. Others suggest continuing to observe until symptoms present.

Hematologic Disorders and Biliary Stone Disease

Excess bilirubin due to hemolysis can coalesce in the gallbladder to form stones or sludge. The incidence of gallstones associated with hemolytic disorders has been reported as high as 41 %. However, most studies report an incidence closer to 20 % [3, 7, 8]. Hematological conditions associated with excessive hemolysis and the development of cholelithiasis or sludge are most commonly SCD or hereditary spherocytosis (HS) (≤43 %), and the thalassemia disorders (≤23 %) [10].

Laparoscopic cholecystectomy has been safely performed in children with hemolytic disorders and symptomatic gallstones. Children with SCD and gallbladder disease often receive preoperative packed red blood cell transfusions to achieve a hemoglobin level of 10 g/dL, or exchange transfusion to reduce the concentration of hemoglobin S to a level <50 % [35, 67, 68], to help prevent acute chest syndrome or a sickle cell crisis as a complication of general anesthesia. In addition, simultaneous elective laparoscopic cholecystectomy and splenectomy have been safely performed in children with SCD [69, 70].

Suell et al. [71] in a study of 83 children with SCD with ultrasonographic evidence of stones or sludge found that only 12 had clinical symptoms of cholecystitis. Of these, 54 patients underwent cholecystectomy, and 45/54 patients underwent packed red blood cell transfusion or exchange transfusion prior to the procedure. A total of 93 % of the patients who underwent cholecystectomy had chronic cholecystitis diagnosed in the pathologic specimen irrespective of their preoperative symptomatology. Surgical complications occurred in two patients: one patient suffered from an intra-abdominal hemorrhage requiring re-exploration, and the second patient developed

pancreatitis. Children with SCD who underwent elective cholecystectomy had a shorter hospital stay than those who underwent operation during an inpatient admission and also experienced fewer SCD crises. Based upon their findings, Suell et al. [71] suggested that elective LC should be considered at the time of initial gallstone diagnosis. Moreover, LC is the treatment of choice in children with SCD and acute cholecystitis [35].

The role of cholecystectomy in patients with HS and gallstones has not been as clearly delineated, but most authors recommend cholecystectomy in patients who are undergoing splenectomy, especially if they are symptomatic [10, 72, 73]. Marchetti et al. [74] determined that prophylactic splenectomy and cholecystectomy provide a gain in quality-adjusted life expectancy in patients with HS and asymptomatic cholelithiasis over the age of 6 years. Furthermore, this improvement may be enhanced by using the laparoscopic approach [75, 76]. There is no role for prophylactic cholecystectomy in patients with normal gallbladders undergoing splenectomy for HS [77].

Pigment stones form in children with beta-thalassemia due to bile stasis, causing an enlarged gallbladder and impaired emptying [78]. Patients with thalassemia or HS and co-inherited Gilbert's syndrome have a higher incidence of cholelithiasis, suggesting that children with concomitant disease should have early gallbladder ultrasonography and closer follow-up [79, 80]. As in patients with SCD, concomitant cholecystectomy with splenectomy has been successfully performed in patients with beta-thalassemia [81]. Feretis et al. [82] suggest that patients with beta-thalassemia undergo simultaneous splenectomy and prophylactic cholecystectomy; however, this recommendation has not been further studied.

Transplantation

Children after solid organ and bone marrow transplantation have a higher incidence of gallstones than non-transplant patients. This increase may be related to drug therapy (ceftriaxone, cyclosporine A, octreotide, and clofibrate), sepsis, parenteral nutrition, or surgical complications [83]. Hoffmeister et al. [84] followed 1,325 patients who underwent hematopoietic stem cell transplant in childhood and were followed for 40 years. There was an incidence of gallstones in 6.9 % after transplant. Of the 56 who underwent cholecystectomy, 20 had acute and/or chronic cholecystitis. Safford et al. reported the development of gallstones in 20/235 (8.5 %) children after bone marrow transplant [85]. Sakopoulos et al. [86] reported an overall rate of gallstone formation in children undergoing cardiac transplantation between 3.2 and 8 % in infants transplanted under the age of 3 months. Elective cholecystectomy is recommended for cardiac transplant patients with cholelithiasis regardless of symptomatology [87].

Biliary Dyskinesia

Biliary dyskinesia is characterized by biliary colic without evidence of cholelithiasis or acute cholecystitis. The diagnosis can be aided by demonstrating a gallbladder ejection fraction (EF) of <35 % on cholecystokinin hepatobiliary iminodiacetic acid scanning (CCK-HIDA) [5, 88, 89]. The incidence of biliary dyskinesia is increasing and reflects improved ability to diagnose the disease. The optimal management of biliary dyskinesia is unclear; however, laparoscopic cholecystectomy has more frequently become the treatment of choice. In fact, Lacher et al. [90] suggested that LC should be performed in all children with biliary dyskinesia and an EF <15 %. LC has up to a 95 % success rate in the treatment of biliary dyskinesia [91]. Histological examination often reveals an abnormal gallbladder with sludge and acute or chronic inflammation [92]. However other studies show a variable rate of resolution of symptoms in patients with biliary dyskinesia after LC: reports have suggested that anywhere from 44 to 96 % of children's symptoms resolved after LC for biliary dyskinesia [90, 93, 94]. Thus the true role of LC for biliary dyskinesia in children has yet to be definitively determined.

Summary

Childhood and adolescent obesity along with improved detection of gallstones has lead to an increased incidence of the diagnosis of acute cholecystitis in children. Laparoscopic cholecystectomy is safe, efficacious, and is the treatment of choice for acute and chronic cholecystitis, acalculous cholecystitis, and perhaps biliary dyskinesia. Similarly, laparoscopic cholecystectomy at the time of splenectomy can be performed in children with hematological disorders, with blood or exchange transfusion being highly recommended preoperatively. Cholecystectomy for biliary colic or acute cholecystitis is recommended in neonates and infants if symptoms do not resolve within 3–6 months or in previously asymptomatic infants when symptoms develop. ERCP for CBD stones or gallstone pancreatitis in infants and children has a high success rate and should be part of the treatment algorithm usually prior to laparoscopic cholecystectomy. In contrast, the utility of IOC as a routine practice in the pediatric population is unclear.

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