Gallbladder, Gallstones, and Diseases of the Gallbladder in Children

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PRACTICE GAP

Pediatric providers should have a heightened awareness of gallbladder diseases in children, which have increased in incidence during the past few decades.

OBJECTIVES After completing this review, readers should be able to:

1. Understand gallbladder issues in children.
2. Understand what pediatric population is at increased risk for cholelithiasis.
3. Be able to recognize the signs and symptoms associated with gallstone disease in children.
4. Know what treatments are available and when to refer for surgery.
5. Understand the concepts associated with other diseases of the gallbladder.

ABSTRACT

There is an increased incidence of gallstones in the pediatric population, most likely due to the rise of childhood obesity. There needs to be increased awareness of gallstones in this population and of other risk factors associated with gallstone formation in children.

Diseases of the gallbladder have been known to occur since antiquity, with models of the gallbladder and biliary tree dating back thousands of years. In fact, gallstones have been found in mummies from ancient Egypt. Some historians have even postulated that Alexander the Great died of an acute episode of cholecystitis. Although this organ has been described for centuries in historical medical accounts, it has only been in the past 100 years that the function and diseases of the gallbladder have been better recognized. The incidence of these disorders is relatively uncommon in children compared with adults. However, during the past several decades there has been increased recognition of diseases of the gallbladder, including gallstones, in the pediatric population. This may stem from the abrupt rise in childhood obesity, which carries an increased risk of gallstone formation.

AUTHOR DISCLOSURE Dr. Goldman has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.
Therefore, there needs to be awareness among pediatric providers about gallbladder disease and an understanding of the current medical recommendations. This review focuses on the gallbladder, its development and function, recognition of the variety of gallstones and their etiologies, along with the clinical presentation of gallbladder disease. In addition, medical evaluation, treatment, and indications for surgical intervention are discussed.

The gallbladder diverticulum is present at approximately 5 weeks’ gestation during embryologic development and arises from a region of the ventral foregut proximal to the liver. The anatomical regions of the gallbladder include the fundus, body, infundibulum, and neck. Its arterial blood supply is via the cystic artery, which originates from the right hepatic artery, and innervation is via both sympathetic and parasympathetic fibers. It is the parasympathetic innervation via the vagus nerve that contributes to the regulation of gallbladder motility. The gallbladder’s function is to store and concentrate bile. By an active sodium transport mechanism, bile can be concentrated 5- to 20-fold in the gallbladder lumen. Cholecystokinin, a hormone released by cells in the duodenum, is a potent stimulator of gallbladder contraction and causes the gallbladder to empty its contents via the common bile duct into the duodenum. The content in the gallbladder is bile, which is composed mainly of water along with bile acids (chenodeoxycholic acid and cholic acid), bilirubin, cholesterol, fatty acids, and lecithin, along with various electrolytes, such as sodium, potassium, calcium, chloride, and bicarbonate. (1)

Congenital anomalies of the gallbladder, such as double gallbladder, bilobed gallbladder, and gallbladder diverticulum, may be a potential risk factor for bile stasis, inflammation, and stone formation. In addition, agenesis of the gallbladder does occur with an incidence of 1 to 65 per 100,000, with a female predominance of 3:1. This gallbladder agenesis phenotype can be seen in patients with biliary atresia, cystic fibrosis, and congenital heart disease. Infants with this anomaly can be asymptomatic. However, approximately 50% have symptoms of cholestasis. (1)

There are proposed genetic mechanisms that increase the risk of gallstone formation. Genetic factors that affect susceptibility to gallstone formation have been strongly supported by family studies, especially in high-prevalence populations, such as American Indians, which indicates the presence of potential lithogenic genes. Although no specific genes have been identified to date, there exist some candidates, such as the human LITH genes, including lith1 (ABDB11) and lith2 (ABCC2). These gene loci cause an overexpression and promote biliary sterol secretion while decreasing the absorption of dietary cholesterol, thereby leading to stone formation. Another population at risk for gallstone formation is patients with cystic fibrosis, which predisposes to pigment stone formation with an incidence of up to 30% compared with age-matched controls. Patients with progressive familial intrahepatic cholestasis type 2, which is caused by a defect in the bile salt export protein, are also predisposed to gallstone formation. The genetically caused hemolytic anemias, such as hereditary spherocytosis, sickle cell disease, and erythrocyte enzyme deficiencies, also predispose patients to pigment stone formation secondary to resultant hemolysis and increase in bilirubin production. (2)

Gallstone formation, also known as cholelithiasis, occurs secondary to mechanisms that can alter the proportion of the bile constituents and change gallbladder motility. Gallstones are varied in their composition and include the following:

1. Cholesterol stones, in developed countries, account for approximately 70% of gallstones. The cholesterol content is usually greater than 50%, with minimal calcium content. The prevalence of cholesterol stones increases with age, with its incidence rising dramatically with early menarche. The risk factors for cholesterol stone formation in children include obesity, Hispanic ethnicity, family history, parity, and female sex. The metabolic syndrome, which is linked to nonalcoholic fatty liver disease, is also associated with cholesterol gallstone formation. It is presumed that in obesity there is excessive hepatic cholesterol secretion, which leads to an increased risk of gallstone formation. These stones are radiolucent and, therefore, are not discernable on an abdominal radiograph. Formation of cholesterol stones is postulated to occur from hypersecretion of cholesterol, increased mucin production, and decreased gallbladder motility. These factors in combination lead to the creation of cholesterol crystals, which act as a nidus for stone formation. The stones are hard and layered, with a yellow to white color.

2. Black or pigmented stones require excessive bilirubin in the bile for their formation. These stones are commonly seen with hereditary hemolytic anemia such as sickle cell disease and hereditary spherocytosis. Even in very young children with sickle cell anemia, approximately 45% of children can have gallbladder stones and/or sludge present in the gallbladder. In contrast, although children with hereditary spherocytosis, have an increased incidence of gallstones, they are encountered less frequently than in children with sickle cell disease. Gilbert syndrome has an increased incidence of black pigment gallstones. Patients with Gilbert syndrome, which is a benign form of unconjugated hyperbilirubinemia often noticed during times of stress, infection, or dehydration, are at increased risk for black stone formation due to the mechanism of
increased bilirubin production and a decrease in the bilirubin diphosphate-glucuronyltransferase activity. Other etiologies for pigmented stones include medications such as ceftriaxone. Interestingly, after discontinuation of the medication, these gallstones often resolve spontaneously. Another predisposing factor for black stone formation is a decrease in the enterohepatic circulation of bile acids, such as is seen with ileal disease or after ileal resection. The mechanism responsible for gallstone formation in this setting is an interruption in the normal enterohepatic circulation of the endogenous bile salt pool.

3. Brown stones are orange to brown in color and are distinctly seen in the setting of a bacterial or parasitic infection. Brown stones contain a large amount of fatty acids and calcium bilirubinate. Recurrence of these stones in the common bile duct is possible even years after cholecystectomy.

4. Calcium carbonate stones are primarily composed of calcium carbonate, and the mechanism of stone formation is unknown. Postulated mechanisms for their formation include cystic duct obstruction and increased mucin formation. (3) Gallstones in children may present in early infancy and have a peak incidence during adolescence. They are known to occur in utero and can be identified on prenatal ultrasound. The significance of prenatal gallstones is not clear. Predisposing maternal risk factors for prenatal gallstone formation include type 1 diabetes mellitus, sepsis, and medication exposure, such as ceftriaxone, furosemide, and prostaglandin E2. Fetal factors that increase the risk of gallstone development include Rh/ABO incompatibility, Trisomy 21, oligohydramnios, intrauterine growth retardation, and translocation 10:11. In general, the prognosis for prenatally diagnosed stones is excellent, and most gallstones will resolve spontaneously in the first year of life without any medical intervention. (4)

Cholelithiasis during early infancy represents approximately 10% of gallstones in the pediatric population. Various clinical scenarios during this period include very ill premature infants who are often fasting and exposed to various agents that can predispose to gallstone formation, including total parenteral nutrition; medications such as diuretics, narcotics, and antibiotics; and blood products. In infants who have had an ileal resection secondary to necrotizing enterocolitis, the normal enterohepatic circulation of serum bile acids is disrupted and predisposes these infants to potential stone formation. In general, unless the infant is symptomatic with jaundice and fever, no intervention is necessary, and the stones do resolve with time without any intervention. (5) In a review by Klar et al, (6) 19 children younger than 2 years who were diagnosed as having gallstones were followed up for up to 13 years. Most of the children were asymptomatic, with spontaneous resolution of the stones in 50%. Conservative management in the infant and toddler was strongly advised, and surgical intervention was not warranted unless the young child was symptomatic.

With respect to finding cholelithiasis in the older child, the pathogenesis is often multifactorial and usually associated with an increase in cholesterol and very low-density lipoprotein secretion in the gallbladder coupled with gallbladder dysmotility. The presentation in this age group can be quite varied. (7) Although the presenting symptom in infants and toddlers is usually jaundice, older children often are asymptomatic or have vague abdominal complaints. Gallstones can be found incidentally on ultrasound imaging, sometimes in the setting of evaluation of chronic periumbilical abdominal pain. In general, the classic presentation of right upper quadrant pain and vomiting is lacking. It is rare to find intolerance to greasy foods, which is commonly reported in adults. The finding of multiple stones or a single large gallstone in the gallbladder can cause potential complications such as obstruction of the cystic duct with resulting cholecystitis, passage into the common bile duct causing cholestocholithiasis with a rise in bilirubin and liver enzyme levels, and obstruction of the pancreatic duct with resulting pancreatitis.

If a child presents with these potential scenarios, further medical and surgical decisions are warranted. Currently, there are no clear-cut guidelines regarding the management of gallstones in an asymptomatic child with normal bio-chemical liver test results, and no defined strategies for surgical management exist. Alternative medical treatments, such as the use of ursodeoxycholic acid and cholesterol-lowering agents, may prevent further stone formation; however, these measures have been ineffective in gallstone dissolution and currently are not recommended. (8)(9)

Although the likelihood of spontaneous resolution is low in children beyond infancy, one must consider potential surgical complications, especially in the setting of asymptomatic stones. In a review article, Rothstein and Harmon (10) concluded that for symptomatic children, a laparoscopic surgical approach is preferred and that in patients with hemolytic anemias who are at high risk for stone formation, an elective cholecystectomy for asymptomatic gallstones is recommended. In patients who are symptomatic with gallstones, the surgery can be performed electively. Surgical management includes both open and laparoscopic techniques, the latter of which has gained popularity in recent decades and is the preferred means of surgical approach in both adults and children with similar surgical outcomes. Laparoscopy is associated with a shorter length of stay. Although the risks associated with cholecystectomy are minimal, potential complications do exist, such as injury to the bile duct, especially in the young child.
Cholecystectomy is strongly advised in patients with known hemolytic anemias who have evidence of gallstones, symptomatic patients with recurrent right upper quadrant abdominal pain, and in patients with a history of gallstone pancreatitis. If there are known stones in the common bile duct, it is preferred that the patients undergo a preoperative endoscopic retrograde cholangiopancreatography (ERCP) for clearance of the stones in the common bile duct, which is then followed by laparoscopic cholecystectomy. When there is concern about common bile duct stones in young patients and an ERCP is not accessible or feasible, then an intraoperative cholangiogram with possible laparoscopic surgical exploration may need to be performed to clear the stones at the time of cholecystectomy.

Acute cholecystitis, an inflammatory condition of the gallbladder, is thought to occur when a stone becomes impacted in the cystic duct, causing inflammatory changes of the gallbladder. The classic triad of epigastric or right upper quadrant pain with nausea, vomiting, and fever can be present. Laboratory studies are notable for an elevated white blood cell count and elevated bilirubin, liver enzyme, and alkaline phosphatase levels. Lipase/amylase levels can be mildly elevated, even in the absence of pancreatitis. The diagnosis of acute cholecystitis can be confirmed by physical findings, abnormal laboratory tests, and confirmatory imaging. Ultrasonography findings include the presence of gallstones, a thickened gallbladder wall, and gallbladder dilation. If the diagnosis is in doubt, hepatobiliary scintigraphy can be performed, which can confirm the diagnosis by lack of visualization of the gallbladder when a radioisotope marker is used. Treatment of acute cholecystitis consists of bowel rest, administration of intravenous fluids, and, in some situations, administration of intravenous antibiotics, especially if the patient is febrile or there are concerns about biliary obstruction. Once the inflammation has improved, cholecystectomy is recommended as the treatment of choice. Interestingly, children can present with chronic cholecystitis, and the pathologic findings at surgery are remarkable for long-term changes in the gallbladder and the surrounding tissue that are suggestive of recurrent inflammatory episodes of the gallbladder.

When there is concern for acute choledocholithiasis with serum elevations of bilirubin or lipase levels, one should consider that a stone is lodged in the common bile duct. Clinically, the child presents with jaundice, fever, and abdominal pain. Laboratory investigations may show elevated white blood cell counts and elevated liver enzyme levels. If fever is present, broad spectrum antibiotic coverage is warranted. The diagnosis can be confirmed by cross-sectional imaging with ultrasonography, which can provide information about the level of obstruction in the biliary tract and also identify a stone. Ultrasonography also provides information about measurements of the common bile duct, which in adults is generally less than 5 mm in diameter. If ultrasonography fails to identify a stone, magnetic resonance cholangiopancreatography may be helpful to provide further anatomical details of the pancreatic and hepatobiliary system. In a confirmed case of a stone that is lodged in the common bile duct causing obstruction, the patient may require ERCP for stone removal, which is then followed by cholecystectomy. Alternatively, if ERCP is not available, then an intraoperative cholangiogram can be performed at the time of the cholecystectomy to identify stones in the common bile duct and enable removal at the time of surgery.

Acute hydrops of the gallbladder should be mentioned because it does occur in children and is defined as an acute, noncalculation, sterile, and noninflammatory distention of the gallbladder. It is seen in association with systemic illness, such as scarlet fever, Kawasaki syndrome, Epstein-Barr virus infection, and Henoch-Schönlein purpura. The signs and symptoms include acute abdominal pain with nausea and vomiting. Fever and jaundice may also be apparent. On physical examination, there may be right upper quadrant tenderness, and the gallbladder may be palpable. Imaging with ultrasonography may aid in the diagnosis by demonstrating a distended gallbladder without calculi. Management is often conservative, with supportive care. A cholecystostomy is rarely performed. However, a cholecystostomy may be indicated if the gallbladder appears to be gangrenous on imaging, displaying features such as luminal distension, pericholecystic abscess or fluid, and/or the presence of gas in the gallbladder wall or lumen. In general, the prognosis of acute hydrops is excellent. It is postulated that acute hydrops is from local enlargement of the lymph nodes along with vasculitis that causes gallbladder ischemia.

Acalculous cholecystitis is an acute inflammation of the gallbladder without the presence of stones. It is rare in children but has been associated with infections and severe systemic inflammatory disease states. The associated risk factors include infection, trauma, and systemic vasculitis. The pathogenesis is multifactorial, with bile stasis leading to local ischemia and inflammation. Signs and symptoms may include right upper quadrant or epigastric pain, nausea, vomiting, and jaundice. Treatment is often conservative with broad spectrum intravenous antibiotics and intravenous fluids. Rarely is a cholecystectomy indicated. However, a cholecystectomy may need to be considered if a critically ill child’s condition becomes increasingly worse. The distinction between acalculous cholecystitis and acute hydrops is often difficult and often the distinction is made based on the histologic findings. In general, acalculous cholecystitis occurs in the gravely ill patient and hydrops in a less critical setting.
Biliary dyskinesia is classified as a functional gallbladder disorder, which in adults is characterized by decreased gallbladder activity and contractility in the absence of any obstruction. Biliary dyskinesia presents with right upper quadrant or epigastric discomfort, which is attributed to increased pressure in the gallbladder lumen caused by uncoordinated gallbladder contractions in the absence of gallstones or biliary sludge. Diagnosis can be supported by a gallbladder emptying scan, which uses a radioactive bile tracer to quantitate gallbladder evacuation combined with the use of cholecystokin and nuclear imaging to measure the so-called gallbladder ejection fraction. A gallbladder ejection fraction of less than 35% is suggestive of biliary dyskinesia.

(13) There are distinct Rome IV diagnostic criteria published in the adult literature regarding diagnostic criteria, including location of the pain in the epigastrium or right upper quadrant with all of the following features:
1. The pain builds up to a steady level and lasts at least 30 minutes.
2. The pain occurs at various intervals, and the severity can interrupt activities, including sleep.
3. There is no relation to bowel habits, and the pain is not relieved by antacid medication or postural changes.
4. The discomfort can also be accompanied by nausea and vomiting.

Although these specific criteria do not exist for children, the diagnosis can be considered in children with chronic right upper quadrant pain in the absence of gallstones and findings of a low gallbladder ejection fraction on cholecystokin cholecintigraphy. (14) There has been a growing indication for cholecystectomy in children and adolescents with features suggestive of biliary dyskinesia, accounting for 25% to 58% of gallbladder surgeries in children. However, controversy remains regarding outcomes in these children, who often remain symptomatic after surgery, and further studies are needed to validate this condition in children given the lack of consensus for which ejection fraction warrants surgical intervention and the lack of positive predictive value in testing.

Summary

- There should be an increased awareness of the presence of gallstones in children among practitioners in pediatrics. The recent rise in the diagnosis of gallstones in children most likely correlates with the increased incidence of childhood obesity.

- Based on strong evidence, the common etiologies for gallstone development in children include obesity along with hemolytic anemia, medication, and infection. Cholesterol stones are the most common subtype seen in children.

- Based on strong evidence, the presence of gallstones in children can be asymptomatic. However, gallstones can also present with classic right upper quadrant pain or epigastric pain and vomiting. Other signs and symptoms can be nonspecific.

- Based on consensus, ultrasonography is a good screening tool if the presence of gallstones in a child is suspected.

- Based on consensus, the management of a child with asymptomatic gallstones is a conservative wait-and-see approach. However, if the child is symptomatic, a surgical laparoscopic approach is preferred.

- Based on consensus and opinion, other diseases of the gallbladder include acute hydrops and acalculous cholecystitis. “Functional” disorder of the gallbladder, known as “biliary dyskinesia,” remains a controversial issue in both the adult and pediatric populations.
1. A 10-year-old obese Hispanic girl is brought to the clinic by her parents for a health supervision visit. She reports having intermittent diffuse abdominal pain most often localized to the right upper quadrant region. She has no associated vomiting, diarrhea, or fever. Her mother and aunt have a history of gallbladder disease and gallstones. You discuss with the parents that you are concerned that the child has gallstones. The mother asks you what type of gallstones her daughter might have. This patient is at risk for which of the following types of gallstones?
   A. Bilirubin.
   B. Calcium bilirubinate.
   C. Calcium carbonate.
   D. Cholesterol.
   E. Fatty acid.

2. Physical examination of the patient in the vignette in question 1 shows an obese Hispanic girl in no acute distress. Her abdomen is soft, with generalized discomfort on deep palpation, particularly in the right upper quadrant region. You suspect gallstones and initiate an evaluation. Which of the following is the most appropriate next step in management?
   A. Abdominal radiography.
   B. Comprehensive metabolic panel.
   C. Genetic testing.
   D. Magnetic resonance imaging of the abdomen.
   E. Upper endoscopy.

3. A female infant who was born prematurely at 30 weeks’ gestation is brought to the clinic for her 4-month health supervision visit. She was discharged from the NICU at 10 weeks of age, and she comes today for her first outpatient health supervision visit. Review of her records from the NICU shows that she was diagnosed as having gallstones by abdominal ultrasonography. She is feeding well, with no vomiting or diarrhea. She is noted to have good growth and development. Her mother has type 1 diabetes. Which of the following is the best next step in the management of this patient?
   A. Daily blood glucose monitoring.
   B. Genetic testing.
   C. Monthly liver ultrasonography.
   D. Reassurance that the stones will likely resolve without intervention.
   E. Referral to a pediatric surgeon.

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4. A 13-year-old boy is brought to the clinic by his parents with right upper quadrant abdominal pain, multiple episodes of emesis, and fever for the past several days. Laboratory studies show elevations in the white blood cell count and serum bilirubin, liver enzyme, and alkaline phosphatase levels. Your first impression is acute cholecystitis. Which of the following mechanisms is the most likely cause of this condition?

A. Congenital absence of the gallbladder.
B. Extremely elevated cholesterol levels.
C. Recent preceding viral infection.
D. Significant preceding abdominal trauma.
E. A stone that becomes impacted in the cystic duct.

5. A 14-year-old girl presents to the emergency department with worsening jaundice, fever, and abdominal pain for the past several days. Laboratory investigations show elevated white blood cell count and liver enzyme levels. She is started on broad spectrum antibiotics. Which of the following is the most appropriate next step in diagnosis?

A. Abdominal radiography.
B. Abdominal ultrasonography.
C. Computed tomography of the abdomen.
D. Hepatobiliary scintigraphy.
E. Magnetic resonance cholangiopancreatography.
F. Upper endoscopy.
# Gallbladder, Gallstones, and Diseases of the Gallbladder in Children

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