

REVIEW

The Specific features of pediatric cholelithiasis. A Literature review.

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ABSTRACT

Cholelithiasis is the occurrence of one or several gallstones in the gallbladder. It can be complicated by choledocholithiasis, acute or chronic cholecystitis, cholangitis, biliary pancreatitis, biliary ileus, etc. The causes of this disorder in the pediatric population can be hemolytic (hereditary spherocytosis, thalassemia, or sickle cell anemia) or non-hemolytic - other hereditary disorders such as cystic fibrosis, Wilson's disease or ileum disorders, total parenteral nutrition, use of certain medication, choledochal cysts, organ transplantation and, in adolescence, those similar to adult patients (obesity). Most gallstones found in children are cholesterol or pigmented gallstones. There are many diagnostic imaging methods for objectifying gallstones and their complications (such as choledocholithiasis that requires ERCP). There are also some differential diagnoses that should be taken into consideration before treatment (biliary dyskinesia, Oddi sphincter dysfunction, neonatal jaundice, cholestasis, pediatric cholecystitis, pediatric pancreatitis and pancreatic pseudocysts, as well as pediatric pyelonephritis). The first line of treatment of cholelithiasis is diet, saline infusions and medication, and if cholelithiasis is symptomatic and/or complicated, then cholecystectomy is recommended. The surgical approach may be an open procedure or laparoscopy. Some studies show that injuries of the bile ducts are more common in laparoscopic treatment of pediatric cholelithiasis, but nevertheless it has been shown that with an experienced team and good preparation it is the gold standard in the treatment of pediatric cholelithiasis.

We present a comprehensive review of the literature on the clinical presentation, pathophysiology, diagnostic evaluation, and management of cholelithiasis in the pediatric population. Laparoscopic cholecystectomy is safe and effective in children, and shows the same advantages reported in adults.

Keywords: cholelithiasis, cholecystitis, choledocholithiasis, gallstones, laparoscopic treatment of cholelithiasis, pediatric cholelithiasis, adolescence, hemolytic.

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Introduction

Cholelithiasis is the existence of one or several gallstones in the gallbladder or bile ducts. Cholecystitis refers to an inflammation of the gallbladder. Acute cholecystitis predominantly occurs as a complication of gallstone disease, and typically develops in patients with a history of symptomatic gallstones. Less often, acute cholecystitis may develop without gallstones (non-calculous cholecystitis)¹.

This disease is much more common in the adult population, but due to obesity in adolescence and the survival of neonates with short bowel syndrome (due to necrotizing colitis), the need for total parenteral nutrition, or some hereditary conditions, such as spherocytosis, gallstones can also be found in the pediatric population²⁻⁵.

Epidemiology

The prevalence and incidence of pediatric patients with cholelithiasis depend on several factors, such as: age, sex, concomitant morbidity, ethnical background, and genetic factors⁴. The prevalence of cholelithiasis within the pediatric population has been rising since 1960, although it was first mentioned by Gibson in 1737. In children, the global prevalence is 1.9%, with two peaks: children younger than 2 years and early adolescence⁴⁻⁶.

Infants younger than 6 months account for 10% of all cases, children from 6 months to 10 years account for 21% of all cases, and adolescents from 11 to 21 years account for 69% of all cases of pediatric cholelithiasis (it is most often seen in the second decade of life, and the distribution before puberty is the same between the sexes, whereas after puberty it is seen dominantly in females with a ratio of 4:1, as it is in adults)^{7,8}. Four percent of all cholecystectomies are performed on patients younger than 20 years⁷.

Morbidity and mortality in cholelithiasis are connected with complications such as cholecystitis and ascending cholangitis. The main morbidity within uncomplicated cholelithiasis is chronic abdominal pain that can be disabling⁸. The incidence of cholesterol

cholelithiasis is greater in Northern Europe, the USA and in Native Americans, and pigmented gallstones are more often seen in Asians⁹.

Pathogenesis

The pathogenesis of cholelithiasis is similar in adult and pediatric populations. There are two main types of gallstones: cholesterol and pigmented gallstones^{9,10}. The factors that enable the formation of gallstones are: the abnormal composition of the bile, bile stasis, and infection of the bile ducts¹⁰. An imbalance between the main bile ingredients, an increase in cholesterol or bilirubin, or a decrease in the substances that enable crystallization, lead to the abnormal composition of the bile and the formation of gallstones.

The ratios of the ingredients of the bile, bile salts, lecithin, and cholesterol, are very important – normally bile salts comprise for 77%, lecithin 18% and cholesterol around 5%. In this situation all of these components are bile soluble, but water resorption still occurs where there is a significant concentration of bile. Significant changes in this ratio lead to the formation of cholesterol gallstones¹¹. In normal circumstances, cholesterol merges with bile salts and phospholipids (lecithin) in the bile and becomes hydro soluble. The precondition for the creation of cholesterol gallstones is bile oversaturated with cholesterol (lithogenic bile – lithogenic index shows the percentage of saturation of the bile with cholesterol and depends on the secretion of the bile acids and cholesterol over a 24-hour period). Due to obesity, frequent stimulus by food/insulin increases the activity of HMG-CoA reductase, which increases the creation of cholesterol (Figure 1)¹². This means that the bile does not have sufficient capacity to dissolve it, so super saturation gives cholesterol the opportunity to precipitate and form solid crystals of monohydrate-cholesterol. Due to the hyper-secretion of the mucus mentioned above these crystals are entrapped in that mucus, which aggregates as gallstones^{9,10}. Increased concentrations of cholesterol in bile may be caused by the decreased secretion of bile salts and lecithin¹².

The pathogenesis of pigmented gallstones is also complicated. There are two types: black and brown, and both consist of calcium bilirubinate that reacts with glycoproteins in the formation of gallstones⁷. Black stones are formed by three mechanisms: an increase in unconjugated bilirubin and levels of free Ca^{2+} , and a decrease in the levels of the factors that enable the solubility of the bilirubin and calcium in the bile. Increased levels of calcium in bile occur due to an increase in ionized calcium in the plasma or a reduction in the substances that bind calcium (bile salts micelles and lecithin - cholesterol vesicles). This occurs in unbalanced enterohepatic circulation due to ileal resection or total parenteral nutrition⁷. The bilirubin secreted in the bile by hepatocytes is mostly conjugated bilirubin, and as such is hydro soluble, although there is small amount of unconjugated bilirubin (this bilirubin, as fatty acids, phosphates, carbonates and other anions, has the tendency to create a non-soluble precipitate that contains calcium that enters the bile passively together with other electrolytes). In states of chronic hemolysis, extensive decomposition of the hemes occurs, which leads to a high concentration of unconjugated bilirubin, whereby crystals of calcium bilirubinate are formed and gallstones created. Due to oxidation, the precipitation of the bilirubin becomes black. Black pigment gallstones occur in sterile bile in the gallbladder, and due to the calcium carbonate and phosphates, more than half of them are radio opalescent. Brown gallstones can occur de novo in infected gallbladders and extrahepatic bile ducts¹⁰. Bacterial lysosomal beta glucuronidase (E Coli) hydrolyses bilirubin diglucuronide into free bilirubin and glucuronic acid. Afterwards freed bilirubin binds calcium, and calcium bilirubinate is made as the core of a gallstone¹². Gallstones can be made due to the activity of bacterial phospholipases in the bilious lecithin where fat acids that bind to calcium are set free¹⁰.

The etiology of cholelithiasis

The causes of cholelithiasis within the pediatric population are mostly connected to preexisting conditions which can be categorized as: hemolytic, nonhemolytic

and idiopathic^{13,14}. In the past, hemolysis was the most common, but diet and increasing obesity in children are now factors that more frequently cause pediatric gallstones. Also, the increase in the use of total parenteral nutrition in infants and toddlers is also a growing cause of nonhemolytic cholelithiasis within the pediatric population^{14,15}.

As a result, it is common for hemolytic ailments (hereditary spherocytosis, sickle cell anemia, thalassemia major^{7,14-16}) to cause 20-30% of the total cases, the non-hemolytic form 40-50%, and idiopathic 30-40% of cases of cholelithiasis within the pediatric population¹⁴.

The non-hemolytic causes are mostly: total parenteral nutrition, diseases of the ileum such as Crohn's disease, ileal resection, necrotizing enterocolitis, hepatobiliary diseases, systemic infections, use of some medicines (Ceftriaxone, Chlofibrate, octeotride, oral contraceptives), cystic fibrosis, pregnancy, congenital diseases of the bilious system (choledochal cysts, progressive family intrahepatic cholestasis)¹⁴, and also in children who have undergone heart transplantation and used medicines such as cyclosporine, children that were on ECMO as newborns¹⁵ and children with artificial heart valves where consequential development of black pigment gallstones occurs⁷ (Figure 1).

In puberty, the most common gallstones are those with black pigment (50% in the pediatric population), while during adolescence cholesterol gallstones occur more often. Calcium carbonate gallstones are more frequent within the pediatric population (in comparison with adults) at 25%. Calcium carbonate and black pigment gallstones are very frequent in children younger than 10 years. Cholesterol gallstones account for 22% of all gallstones. Brown pigment gallstones that occur in bile stasis and bilious infection can be found in 3% of all cases^{7,8,15}.

Fetal cholelithiasis is mostly discovered in the third trimester as an accidental finding. There are many hypotheses about the causes of this condition,

such as increased levels of estrogen, use of certain medicines during pregnancy, hemolytic anemia, incompatibility of blood types, structural abnormalities (choledochal cysts), and cholestasis caused by pregnancy. The prognosis is good because in most cases spontaneous resolution occurs within the first 12 months, or the cases remain asymptomatic. Material found in fetal gallbladders during ultrasound checkups is mostly bilious sludge¹⁴.

In small children, the causes of cholelithiasis can be: prolonged total parenteral nutrition, diseases of the ileum, prematurity, dehydration, diuretics, liver immaturity, and cephalosporin used in therapy³.

Infection as the cause for cholelithiasis in the pediatric population is most common in children younger than 5 years; hemolytic disease is most common in the population from 6 to 12 years of age, and rare in younger children, whereas obesity, ileum diseases and positive family history, use of oral contraceptives, cystic fibrosis and pregnancy are the most common causes in adolescence^{6,15}.

Hemolytic causes of pediatric cholelithiasis

20-40% of children with cholelithiasis have some kind of hemolytic disease: hereditary spherocytosis, sickle cell anemia and thalassemia are the most common and are considered to be the greatest risk factor for the development of symptomatic cholelithiasis in the pediatric population^{3,8,16}. Hereditary spherocytosis is the most common autosomal dominant disease and in 25% of cases it is autosomal recessive. It is a disorder of the red blood cell membrane, where they are round in shape and have decreased plasticity, so they become vulnerable to sequestration and destruction in the spleen⁹. The incidence is 43% to 63% and it is more common in girls¹⁵. When children have mild hereditary spherocytosis, cholelithiasis can be the first sign of red blood cell destruction, where pigmented gallstones are formed due to the increased formation of unconjugated bilirubin because of the vulnerability and hemolysis of spheroid red blood cells. The incidence increases over the years, so periodic ultrasound examinations are recommended¹⁷.

Sickle cell anemia, where the structure of hemoglobin is abnormal, leads to the formation of gallstones through the same mechanism as hereditary spherocytosis, and the incidence of cholelithiasis within this population is almost double that in other populations. Pigment gallstones can be seen in 50% of children with sickle cell anemia up to the age of 22 years^{8,15}. As the child gets older, the incidence of cholelithiasis increases from 10% to 55%¹⁶. It is considered that the prevalence of cholelithiasis in children under the age of 10 with sickle cell anemia is 10%, and it increases up to 40% at 10-18 years of age, and up to 50% in adults (14). One study found that patients with sickle cell anemia and cholelithiasis had a similar rate of bilirubin formation, bilirubin clearance and serum values of non-conjugated bilirubin as patients with sickle cell anemia without cholelithiasis. So, it is a common hypothesis that unconjugated hyperbilirubinemia is not enough by itself to induce the formation of pigment gallstones. In the same study it was found that patients who developed cholelithiasis had been on long-term fasts and had an increased gallbladder volume after meals. The assumption is that bilious stasis occurs due to incomplete discharge, which leads to the creation of sludge, and afterwards gallstones. In one study with 35 patients with sickle cell anemia and gall sand, 23 patients (65.7%) had cholelithiasis. So elective cholecystectomy is advised when gall sludge is found with or without the presence of gallstones¹⁵. The prevalence of cholelithiasis in thalassemia is low – 10-15%. However, with patients that live longer it increases to 50%¹⁴. The incidence of cholelithiasis in thalassemia major was lower than was found in previous studies, mostly due to the hyper transfusion regime where marrowbone is blocked when it comes to the creation of vulnerable cells that are easily destroyed and hemolyzed¹⁵.

Non-hemolytic causes

Obesity. It is thought that the increase in obesity is one of the main reasons for the increase in cholelithiasis in the pediatric population. Obesity, as well as sudden weight loss, lead to increased bilious secretion of bilirubin. Obese people show increased activity of

hydroxyl-3-metilglutaril (HMG)-coa reductase, and consequently have increased secretion of bilirubin in the gallbladder. With the early start of obesity, the early appearance of lithogenic bile also begins, especially in cases of extreme obesity within the pediatric population^{8,19}. Almost 50% of all cases of cholelithiasis in the pediatric population are connected to obesity. Adolescent cholecystitis is most common in obese children during sudden calorie restrictions and weight loss²⁰.

Medication. Octeotride, Ceftriaxone, Cyclosporine, Furosemide and Chlofibrate are drugs that may be related to the appearance of gallstones²¹. Ceftriaxone cholelithiasis is reversible and will end after the therapy is no longer given, so it is known as pseudolithiasis. In patients with normal renal function, 60% of Ceftriaxone is excreted through their urine in unchanged form, while 40% is secreted to the bile. It is an anion and can become concentrated in bile 20 to 150 times more than in serum, and therefore can form insoluble salts with calcium that are deposited in the gallbladder⁴. Ceftriaxone causes reversible cholelithiasis through several mechanisms: 1. It squeezes out bilirubin connected to unconjugated bilirubin in the blood; 2. it binds with calcium in the gallbladder and bile ducts, and initiates the creation of gallstones, especially in children younger than 10 years of age that are taking Ceftriaxone and exceeding the daily dose^{21,22}. Risk factors for Ceftriaxone induced pseudolithiasis are: hypercalcemia, renal failure, high dosage of the medicine (>2gr or > 200mg/kg/day), long treatment, fasting induced bile stasis, dehydration, and age above 2 years⁷. Reversible pseudolithiasis can be seen in 17%-40% of these children after at least 4 days of therapy, while some data show that it usually begins after 6 days of treatment and ceases 15 days after finishing the therapy^{4,14}.

Most cases are non-symptomatic and can only be seen on ultrasound, but rarely (in 0-19% of cases) there may be symptoms such as abdominal pain, vomiting, nausea, and bilious obstruction. Discontinuation of therapy is advised in symptomatic cases but is not necessary in asymptomatic cases¹⁴. It has been proved

that children with cholelithiasis that developed due to Ceftriaxone therapy have spontaneous resolution more often than in cholelithiasis caused by other reasons⁴. Cyclosporine used in children who have undergone marrowbone or parenchymatous organ transplantation can be lithogenic in high doses, even when it is hepatotoxic. Furosemide is one of the concomitant factors of prematurity, sepsis and small intestine ailments. Octeotride has a wide spectrum of agency and is used to treat bleeding in the upper part of the gastrointestinal system, secretory diarrhea, acromegaly and gastroentero-pancreatic endocrine tumors. Cholelithiasis developed in 50% of patients who were on long term therapy with Octeotride, due to stasis of the gallbladder caused by this medicine or its impact on bile absorption⁷. Chlofibrate inhibits the activity of Acyl-CoA cholesterol acyltransferases (ACAT) which decreases conversion of the cholesterol in cholesterol esters with a consequent increase in bile saturation with cholesterol, and the creation of gallstones⁷.

Total parenteral nutrition. The most common condition related to non-hemolytic cholelithiasis, especially in neonates and toddlers, is total parenteral nutrition. The mechanism of development of cholelithiasis can be related to the change in composition of the bile, initiated by amino acid infusions, and many believe that the intake of fat increases the harmful effects of this kind of amino acid intake¹⁵. Gallstones may also be formed in this situation because of the increase in the level of free calcium in the bile, which leads to a decrease in the material that binds calcium, such as bile salt micelle and lecithin - cholesterol vesicles⁷. Creation of gallstones in premature neonates on total parenteral nutrition has four phases: decreased bile flow due to the immaturity of the hepatobiliary system, bilious stasis, and the creation of bile sludge and formation of gallstones. Neonates and toddlers who are premature have immature transport of bile acids, bile secretion and bile flow stimulation⁷. If, alongside this preexisting condition, they also have total parenteral nutrition because oral feeding has been halted, the enterohepatic circulation is disturbed, and bilious stasis occurs due to the disturbance in

gallbladder contraction (in normal circumstances this happens due to hormonal stimulation from the gastrointestinal tract through cholecystokinin). Other factors (that are necessary for the development of gallstones since only a few of the many children on total parenteral nutrition develop gallstones) include lower gestation weight – 50% of premature neonates that had gestation weight lower than 1000 g develop cholelithiasis⁷. The gallstones that are formed due to total parenteral nutrition are mostly pigmented and they originate in the gallbladder. They have a high concentration of calcium phosphate, or calcium carbonate and bilirubin and cholesterol, and can be considered specific – gallstones induced by total parenteral nutrition⁷. Prolonged total parenteral nutrition involves an even higher risk of cholelithiasis. The risk is even higher with a concomitant ileum condition. There is a common opinion that 43% of children on long term parenteral nutrition will develop cholelithiasis¹⁵. In the study by Roslyn et al., where the connection between total parenteral nutrition and cholelithiasis was studied, it was shown that 43% of children who were on total parenteral nutrition developed cholelithiasis, in comparison to 64% of children with an ileal condition or ileal resection^{15,23}.

Ileum conditions. In children with IBD, cholelithiasis is described in 2.3% of patients²⁴. In Crohn's disease, due to inflammation of the terminal ileum, or post-operatively after ileum resection, the enterohepatic circulation is disturbed and malabsorption of bile salts occurs, which changes the normal bile composition. When there is a preexisting condition of the ileum, black pigmented gallstones are formed through the same mechanisms as in total parenteral nutrition – an increase in free calcium in the bile due to a decrease in the matter that binds it⁷.

Cystic fibrosis. Over the years cholelithiasis and abnormalities of the gallbladder increase when there is a precondition such as cystic fibrosis. Expression of the gene for regulation of transmembrane conduction (the CFTR gene), that is mutated in cystic fibrosis in the hepatobiliary system, is present on the level of the epithelium of the gallbladder and bile ducts. CFTR

protein is part of the regulation of the composition of water and electrolytes in the bile, and has an impact on the transport of sodium and chloride ions, and so on bile alkalization. Due to the abnormal CFTR proteins, the bile is viscose and thick, and it causes bilious stasis and increases the risk for cholelithiasis⁵. Stenosis of the duct of choledochus is found in 94% of patients with cystic fibrosis with a liver condition. This stenosis results in an enlarged gallbladder. Cholelithiasis in cystic fibrosis can also be caused by excessive loss of bile salts due to malabsorption. The bile composition becomes abnormal, with high levels of cholesterol because of the decrease in the quantity of bile salts, where the bile becomes lithogenic. Bile acid malabsorption responds well to pancreatic hormone treatment. There are those who believe that cholelithiasis cannot develop without pancreas insufficiency⁷.

Choledochal cysts. This is a congenital anomaly of the bilious ducts, and 80% of these cases are diagnosed in the first 10 years of life. 30-70% have an anomaly of the site of emergence of the ductus choledochus and the pancreatic duct outside of the duodenum. One complication of choledochal cysts can be cholelithiasis, due to long term subclinical ductal inflammation and bilious stasis. Children with choledochal cysts are usually recognized by the presence of a palpable mass and jaundice, whereas adults more often have symptomatic cholelithiasis and acute cholecystitis^{26,27}.

Hereditary illnesses. Hereditary disturbances of bilious transport, such as the lack of the pump for secretion of bile salts – mutation of the ABCB11 gene and MDR3 deficiency (multidrug resistance 3) and mutation of the ABCB4 gene, can be responsible for infantile cholelithiasis⁷. The ABCB11 gene gives instructions for the synthesis of proteins that comprise the bile salt export pump situated in the liver. Conditions connected to these mutations are: benign intrahepatic cholestasis, progressive familial intrahepatic cholestasis, and intrahepatic cholestasis of pregnancy²⁸. Mutations of the ABCB4 gene are increasingly being discovered in children and adults with recurrent cholestasis and cholesterol cholelithiasis⁸. With the descending regulation of the APOBEC

RNA specific enzyme apoprotein b, there is decreased expression of 7-alpha-hydroxylase that decreases the conversion of cholesterol into bile acids and causes cholesterol hyper saturation, which predisposes to the creation of gallstones. Excessive expression of sterol protein carrier 2 (SCP2) and increased levels of the protein that binds retinol (RBP4) is proved in most patients with cholesterol cholelithiasis. Other genes with a strong connection to gallstone formation are ABCG5, ABCG8, CYP7A1 and CCK1R. Polymorphisms of liver uridine diphosphate (UDP), glucuronosyltransferases (UGT1A1) are described in patients with hemolytic diseases with a predisposition for the development of cholelithiasis⁷.

Wilson's disease is a rare hereditary autosomal recessive condition of copper metabolism where copper accumulates excessively in the liver, brain, and other

tissues. Liver cirrhosis and recurrent hemolysis episodes (two common complications of this condition) are an ideal base for the development of gallstones²⁹. In Wilson's disease, Combs negative intravenous hemolysis occurs as the consequence of the oxidative damage of red blood cells by free radicals that are released into the blood due to the excessive accumulation of copper in the liver^{30,31}.

Organ transplantation. Heart transplantation in toddlers younger than 3 months leads to a higher risk for cholelithiasis than in those with kidney or liver transplantations. Children that have undergone bone marrow transplants also have a strong probability of development of cholelithiasis⁷. Idiopathic cholelithiasis is more common in adolescent females than other age groups¹⁴.

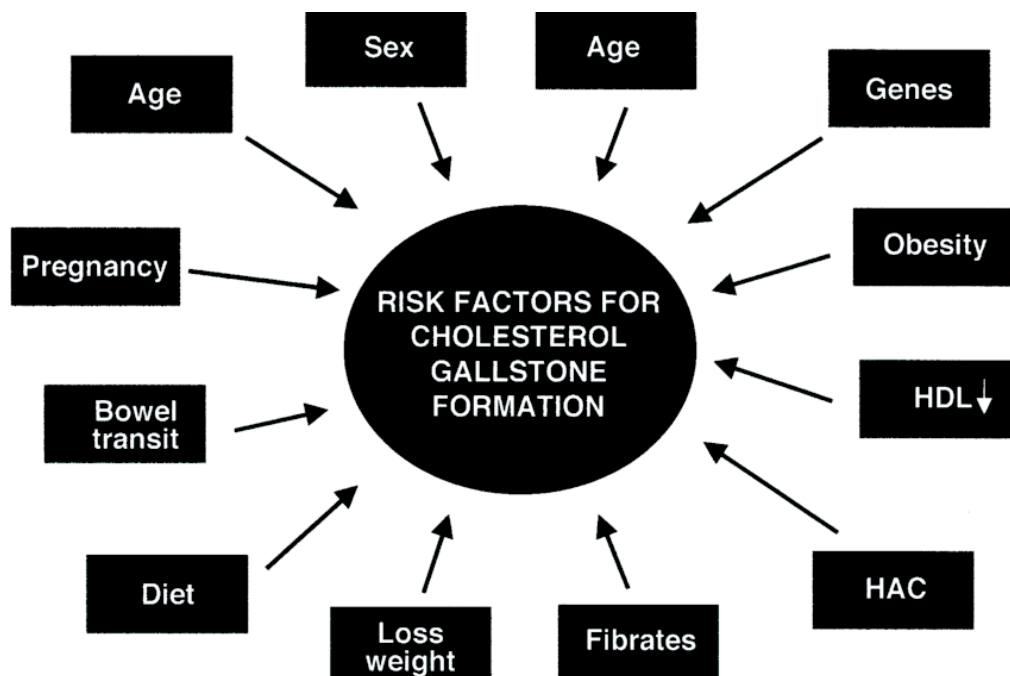


Figure 1. Risk factors for cholelithiasis – cholesterol gallstone formation.

Clinical presentation

Cholelithiasis in childhood can be either with or without symptoms. Whereas 80% of adults have no symptoms, 40% of afflicted children have symptoms when the diagnosis is made. Pediatric patients can have various clinical presentations – from typical bilious colic with nausea and vomiting, to nonspecific intermittent pain that can either be diffuse or localized in the epigastria, or acute abdominal pain with high fever in children that have usually developed complications of cholelithiasis⁶. Symptoms depend on the age of the patient. Children older than 6 years usually have pain under the right rib cage, whereas children younger than 5 years have nonspecific abdominal symptoms¹⁴. Pediatric cholelithiasis in children younger than 2 years usually presents without any symptoms. Symptomatic cholelithiasis at this age implies well-developed choledocholithiasis because these patients have irritability, jaundice, acholic stools, sepsis, and abdominal pain as basic symptoms^{14,21}. Infants and children younger than 5 years usually have nonspecific symptoms due to the lack of possibility of describing their discomfort⁶. Children aged 2-14 years most often have common bilious colic (50%) or nonspecific abdominal symptoms (25%), nonspecific pain, and nausea. Acute abdominal pain due to cholecystitis, cholangitis and pancreatitis is rare in this age group (5-10%) and 20% of cases are asymptomatic¹⁴. Adolescents (14-18 years) have typical bilious colic like adults. Intolerance of fatty food that is a typical symptom in adults, is only present in adolescents¹⁴.

Bilious colic is an episode of moderate to strong pain under the right rib cage or in the epigastria that irradiates into the interscapular area, right scapula or right shoulder (Collins' sign). It develops suddenly, within 30-90 minutes after ingestion of food, and can last for several hours. It is often combined with nausea and/or vomiting^{8,32}. An episode that lasts longer than 5 hours should give rise to the suspicion of acute cholecystitis³³. The provoking factor for bilious colic is ingestion of a fatty meal after long-term fasting, or ingestion of a normal meal. It is more common during the night³³. Pain is caused by contractions of

the gallbladder against the intraluminal obstruction caused by gallstones in the neck of the cystic duct³⁴. These are isometric contractions of the smooth muscles of the obstructed gallbladder under the impact of CCK (cholecystokinin) after a meal³⁵. Pain occurs when the stimulus for gallbladder contraction caused by secretion of CCK stops after the end of a fatty meal or with the spontaneous movement of a gallstone that is stuck. It is visceral pain and often each subsequent attack is more painful than the previous one³⁴.

Some patients may have an atypical clinical presentation where the pain is localized in the back or upper left or lower right part of the abdomen. Flatulence and burping may be part of this pain attack³⁶. Bilious colic, without infection and inflammation, does not show any clinical signs during physical examination³⁵.

Complications of cholelithiasis

Complications of acute cholelithiasis can be acute or chronic cholecystitis, choledocholithiasis with or without cholangitis, bilious pancreatitis, cholecystocholedochal, cholecystoduodenal or cholecystoenteric fistula, where biliary ileus or gallbladder carcinoma may develop³⁶. The most common complication at pediatric age is bilious pancreatitis (8-27%), although some authors mention cholecystitis and choledocholithiasis (8.89%-18%) as the most common complications^{7,4}.

Diagnosis

Diagnostic procedures in the pediatric population are similar to those used in adult patients. Diagnosis includes: laboratory findings (complete and differential blood count, ALT (alanine transaminase), AST (aspartate aminotransferase), ALP (alkaline phosphatase), total bilirubin, direct and indirect bilirubin, GGT, amylases and lipases and urine evaluation⁸.

Radiographic methods used are X rays, ultrasound, which is a sensitive, cheap, and reliable diagnostic method, and bilious scintigraphy, CT, MRI, fluoroscopic cholangiography, ERCP (endoscopic retrograde

cholangiopancreatography) where there is a suspicion of obstruction, choledocholithiasis, biopsy of suspicious lesions, obstructive jaundice, cholangitis and bilious pancreatitis^{36,37}. MRCP and EUS also exist.

Differential diagnosis of pediatric cholelithiasis

Biliary dyskinesia This disease is increasing in pediatric populations and can be treated successfully with laparoscopic cholecystectomy¹⁶. Pediatric biliary dyskinesia is diagnosed by three criteria: chronic or recurrent pain (or discomfort) in the epigastria or under the right rib cage, the nonexistence of gallstones and abnormal ejection fraction, or the gallbladder seen on cholescintigraphy with CCK stimulation³⁸.

Oddi sphincter dysfunction This disorder presents with pain in the right abdominal quadrant, recurrent pancreatitis, and normal liver function tests. It can be caused by a structural abnormality of the sphincter due to trauma caused by the passage of a gallstone, pancreatitis, or congenital anomalies, where there is inflammation and consequential fibrosis with the increase in sphincter pressure. Dysfunction can also be a functional disorder with unclear etiology. Diagnosis is made when there is biliary pain, and a choledochal duct diameter >12mm that increases with the use of cholecystokinin³⁵.

Neonatal jaundice This is usually a transient physiological phenomenon as the result of increased lysis of red blood cells and decreased excretory capacity of the liver due to decreased concentrations of ligandin and the reduced activity of glucuronyl transferase. Although jaundice is not a symptom of cholelithiasis, newborns and infants show irritability, jaundice, acholic stools, sepsis and abdominal pain as the first symptoms, because in this population symptomatic cholelithiasis implies developed choledocholithiasis. Jaundice is more frequent within the pediatric population than in adults even without obstruction of the choledochal duct^{14,21}.

Cholestasis This is defined as the reduced flow of bile due to damaged liver function or obstruction of the bile flow through the intrahepatic or extrahepatic bile ducts. The clinical definition of this disorder is any case where matter that normally excretes through the bile is retained. Pediatric biliary atresia is the most commonly treated surgical cause of cholestasis in newborns. It is characterized by obliteration or discontinuity of the extrahepatic biliary system that results in obstruction of bile flow^{39,40}.

Pediatric cholecystitis This causes much worse pain than uncomplicated cholelithiasis. The patient has fever and anorexia, nausea and may vomit. The pain increases upon pressure on this area (which is not usual in biliary colic) due to peritonitis with a positive Murphy sign – suddenly stopping breathing during palpation of the area under the right rib cage^{34,35,41}.

Pediatric pancreatitis and pseudocysts of the pancreas Children with acute pancreatitis have epigastric pain (87%), vomiting (64%), abdominal tenderness (77%) and abdominal distension (18%). Sometimes pancreatitis is complicated by cavities filled with pancreatic enzymes – pseudocysts⁴².

Pediatric pyelonephritis The presentation depends on the age of the child. There may be pain in the abdomen or loins, with fever, anorexia, vomiting and hematuria. Adolescent females with this disease may have pain in the upper abdominal quadrant, which may be misunderstood as cholelithiasis and/or cholecystitis⁴³.

Treatment

Medication

Drug therapy implies adequate hydration and pain treatment. In uncomplicated cholelithiasis, a low-fat diet is recommended, while in cholecystitis choledocholithiasis/cholangitis oral intake is stopped and a nasogastric tube is placed, with rehydration and pain management (NSAIL) as well as antibiotics.

The two oral drugs used in the lysis of cholesterol gallstones are Chenodiol (chenodeoxycholic acid) and Ursodiol (ursodeoxycholic acid). They are both selective hydroxymethylglutaryl-coa reductase (HMG COA) inhibitors which lead to suppression of the synthesis of cholesterol in the liver. Ursodiol also blocks intestinal absorption of cholesterol. The side effects of these drugs are diarrhea and hepatotoxicity. A combination of these two drugs is more efficient and decreases the side effects by up to 50%. The disadvantages of this combination are long term treatment, recurrence after discontinuation of treatment, a low success rate and high treatment costs⁷. Pigmented gallstones do not react to Ursodiol therapy³³. In one study where children were administered 25 mg/kg/day of ursodeoxycholic acid for an average time period of 13 months, resolution of clinical discomfort was shown in up to 83.7% of the patients, but complete dissolution of the gallstones occurred in only 7.2% of cases, and cholelithiasis developed again in 50% of the children. None of them had any side effects¹. The FDA has not approved ursodeoxycholic acid in pediatric patients, so this treatment is not recommended in symptomatic cholelithiasis and is indicated only for those who cannot be treated surgically⁹. Also, patients with cholesterol cholelithiasis that develop recurrent choledocholithiasis after cholecystectomy should be treated long term with ursodeoxycholic acid³³.

Extracorporeal lithotripsy

Extracorporeal shock wave lithotripsy (ESWL) creates waves of high amplitude focused on the gallstone, and in most patients, it causes stone fragmentation to a size that enables their spontaneous intestinal elimination^{7,44}. This method can only be used in radiotransparent stones, which limits the application of this method in the pediatric population⁷. In view of the fact that the fragments may still cause biliary colic and cholecystitis, additional oral therapy may be required²¹. The best results are achieved in patients with a solitary gallstone 0.5 to 2 cm in size³⁵. All techniques that involve leaving gallstones in the gallbladder have a recurrence rate of 10% within one year, and a five-year rate of recurrence is up to

50%²¹. The two main complications of lithotripsy are cholecystitis and pancreatitis (1-2%)³¹.

Preoperative medication management

For rehydration, 5% dextrose in 0.2% saline or 5% dextrose in 0.45% saline with 20 mEq of potassium in one liter is used. Children that are threatened by vaso occlusion (sickle cell anemia) are administered hydration at a 1.5 times higher rate²¹.

Antibiotics are administered in acute cholecystitis, choledocholithiasis and biliary pancreatitis with pancreatic necrosis⁴⁵. Prophylactic antibiotic therapy is administered before ERCP or PTCH, and before elective cholecystectomy, because it significantly reduces rates of postoperative infection³⁰. Antibiotics are administered for the most common microorganisms causing infection (*E. coli*, *Klebsiella* species, and *Streptococcus* species). The most efficient antibiotics are: ureidopenicillins (Piperacillin, Mezlocillin), ampicillin sulbactam, fluorochinolones, (Ciprofloxacin, Moxifloxacin) and the third generation of cephalosporins. Intravenous therapy is indicated in patients with severe acute cholecystitis. If there is any suspicion of gangrenous or emphysematous cholecystitis, antibiotics that "cover" anaerobic bacteria are administered (Metronidazole). Carbapenems (Imipenem/Meropenem) act against bacteria that cause ascendant cholangitis and are used in the most severe infections when other antibiotics do not work³³.

Miperidine or NSAID are usually used for pain management, and morphine should be avoided due to the possibility of sphincter of Oddi spasms³³.

Surgical intervention

History

Georg Kelling was the first to describe the basic principles of endoscopy of the abdomen. Kelling performed the procedure on a dog. Almost exactly one hundred years ago, Jacobaeus performed the first endoscopy on humans. Major advances in endoscopy were achieved

from the 1960s to the 1980s, accompanied by a transition from diagnostic to surgical laparoscopy. These developments are inseparably linked with the names of Raoul Palmer in Paris and Kurt Semm in Kiel.

Heinz Kalk developed a superior laparoscope with improved lenses, and the first forward-viewing scope in 1929, earning him the title “the Father of Modern Laparoscopy.”

The first laparoscopic appendectomy was performed by Semm on 13th September 1980 at the Department of Obstetrics and Gynecology of the University of Kiel. It was extremely unusual and an international sensation at the time.

The first surgeon to perform a laparoscopic cholecystectomy met with a similar fate. The German surgeon Erich Muhe used his “galloscope,” a 3-cm, direct-vision laparoscope of his own design, to remove a gallbladder.

The first case of laparoscopy in pediatric surgery was reported by Stephen Gans in 1971, in his landmark publication, “Advances in Endoscopy of Infants and Children,” as a peritoneoscopy. Initially, application of laparoscopy in children was for diagnostic purposes.

Open cholecystectomy was the gold standard until the early 1990’s when it was replaced by laparoscopic cholecystectomy that became the new gold standard for this disease. Carl Langebuch performed the first successful cholecystectomy in 1882, and Phillip Moret, the French gynecologist, performed the first laparoscopic cholecystectomy in 1987^{36,46}.

Cholecystectomy

Cholecystectomy in cholelithiasis

Elective cholecystectomy is the best treatment for symptomatic cholelithiasis. Laparoscopic access is considered to be best for most patients. When important structures cannot be seen clearly, conversion to an open procedure is usually advised³⁶. Only 2.5% of laparoscopic procedures are completed with

conversion to an open procedure⁴⁵. When it comes to urgent laparoscopic procedures performed in complicated cholelithiasis, the incidence of conversion is 10-30%³⁶. There is a difference from adults, where prophylactic cholecystectomy is not advised (because only 1% of patients develop complications before the first symptoms), as children should undergo surgery immediately after diagnosis of cholelithiasis because complications in this population are more frequent (25.1%) and the first presentation of the disease may be due to complications^{35,47}.

Cholecystectomy is indicated in symptomatic cholelithiasis, asymptomatic cholelithiasis with radiotransparent gallstones that have existed for longer than 1 year, and when radio opalescent gallstones are present¹⁴. Asymptomatic children, or those with a nonspecific presentation, should be observed and the long-term risk for symptom development evaluated¹⁴.

In children younger than 2 years the approach is different due to the high percentage of spontaneous resolution (cholelithiasis 50%, choledocholithiasis 30% of cases). In toddlers, whether it is a case of cholelithiasis due to TPP or for other reasons, observation is recommended because gallstones at this age are often dissolved after the maturation of the hepatobiliary system, and recurrence is rare²¹. Even in choledocholithiasis, observation for 1-2 weeks before surgery is recommended due to the possibility of spontaneous resolution¹⁴. Spontaneous resolution within 6 months is more common in idiopathic cholelithiasis than other causes¹⁴.

Cholecystectomy in hemolytic cholelithiasis

With these children in mind, ultrasound screening for cholelithiasis is recommended when the child is 5 years old. It is also performed just before splenectomy due to the possibility of combined splenectomy and cholecystectomy¹⁴. In hereditary spherocytosis and asymptomatic cholelithiasis, cholecystectomy with splenectomy can be performed. If these patients do not have cholelithiasis, there is no need for cholecystectomy since the risk for cholelithiasis after splenectomy is low⁶. In patients with sickle cell

anemia, elective cholecystectomy is recommended right after the diagnosis, nevertheless there may still be symptoms because in this population complications of cholelithiasis even after cholecystectomy are much more often^{45,48,14,16}. Acute thoracic syndrome can occur in 20% of patients with sickle cell anemia who have had abdominal surgery, and the laparoscopic approach does not reduce the incidence of this complication. Diligent preoperative preparation can reduce the incidence of this syndrome¹⁵. Prior to surgery the patients should be administered a transfusion to reach a hemoglobin level of 10 g/dl (6.21 mmol/l) and to decrease levels of S hemoglobin up to 30%, to reduce the likelihood of vaso occlusive crisis (to which these patients are prone, as well as to pneumonia, sepsis and pulmonary infarctions due to secondary hypoxia, dehydration and acidosis as a response to anesthesia). These patients need adequate hydration, analgesia and oxygen therapy^{45,14}.

Cholecystectomy in complicated cholelithiasis

Cholecystectomy is the treatment of choice for acute cholecystitis. Although many surgeons previously preferred to postpone cholecystectomy for 6 weeks after the initial episode of acute cholecystitis, recent studies show that even in the first week of the disease, surgical treatment can be performed by laparoscopy with the same or even improved morbidity, mortality and hospital stay duration, and a similar rate of conversion into an open procedure. In acute cholecystitis, a better success rate is found if cholecystectomy is performed within 3 days from the beginning of symptoms⁴⁵. If the inflammatory process has spread to the porta hepatis so that the anatomy of that region is unclear, conversion to an open procedure is recommended.

Patients do not need ERCP without evidence of choledocholithiasis because this procedure can lead to the development of pancreatitis. When patients have choledocholithiasis, ERCP should be performed for examination and gallstone removal from the choledochal duct. When ERCP is not feasible, MRCP can be done to confirm choledocholithiasis⁴⁵. Preoperatively, patients can be divided into three groups in relation to

the risk for choledocholithiasis: 1) High risk patients (risk >50%) are those with jaundice or cholangitis, a dilated main bile duct or gallstones visualized in the main bile duct on preoperative ultrasound. 2) Patients with moderate risk are those with a history of jaundice or pancreatitis, moderately elevated alkali phosphatase or bilirubin preoperatively, or multiple small gallstones on ultrasound visualized. (10-50%) 3) Patients with large gallstones, without a history of jaundice or pancreatitis, and with normal hepatic function are low risk patients (<5%). In patients with high risk for choledocholithiasis, preoperative ERCP is recommended, whereas in patients with a moderate risk, MRCP or EUS is recommended (and if choledocholithiasis is found then ERCP should be performed). Intraoperative cholangiography is also used for detection of choledocholithiasis. When gallstones are found intraoperatively, laparoscopic exploration through the cystic duct, laparoscopic choledochotomy, with exploration of the main bile duct, open exploration of the main bile duct or postoperative ERCP with endoscopic sphincterotomy can be performed. If a small gallstone is seen (2 mm), it can be moved to the duodenum by irrigation through the main bile duct using a cholangiography catheter and with relaxation of the sphincter of Oddi (intravenous administration of glucagon 1-2 mg). If this is not feasible, the stone usually passes into the duodenum postoperatively⁴⁹.

When acute biliary pancreatitis occurs, ERCP is indicated, with sphincterotomy and stone extraction and this will end the pancreatitis episode. After dealing with pancreatitis, cholecystectomy is performed. If there is a mild form of pancreatitis present with gallstones, cholecystectomy, and intraoperative cholangiography or preoperative ERCP are performed³⁵.

There are many guidelines for the diagnosis and treatment of pediatric cholelithiasis. Very applicable guidelines were published in BMC Gastroenterology in 2021 by Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Pediatric Surgery, Department of Surgery, University Hospital Erlangen, Erlangen, Germany (Figure 2)³⁶.

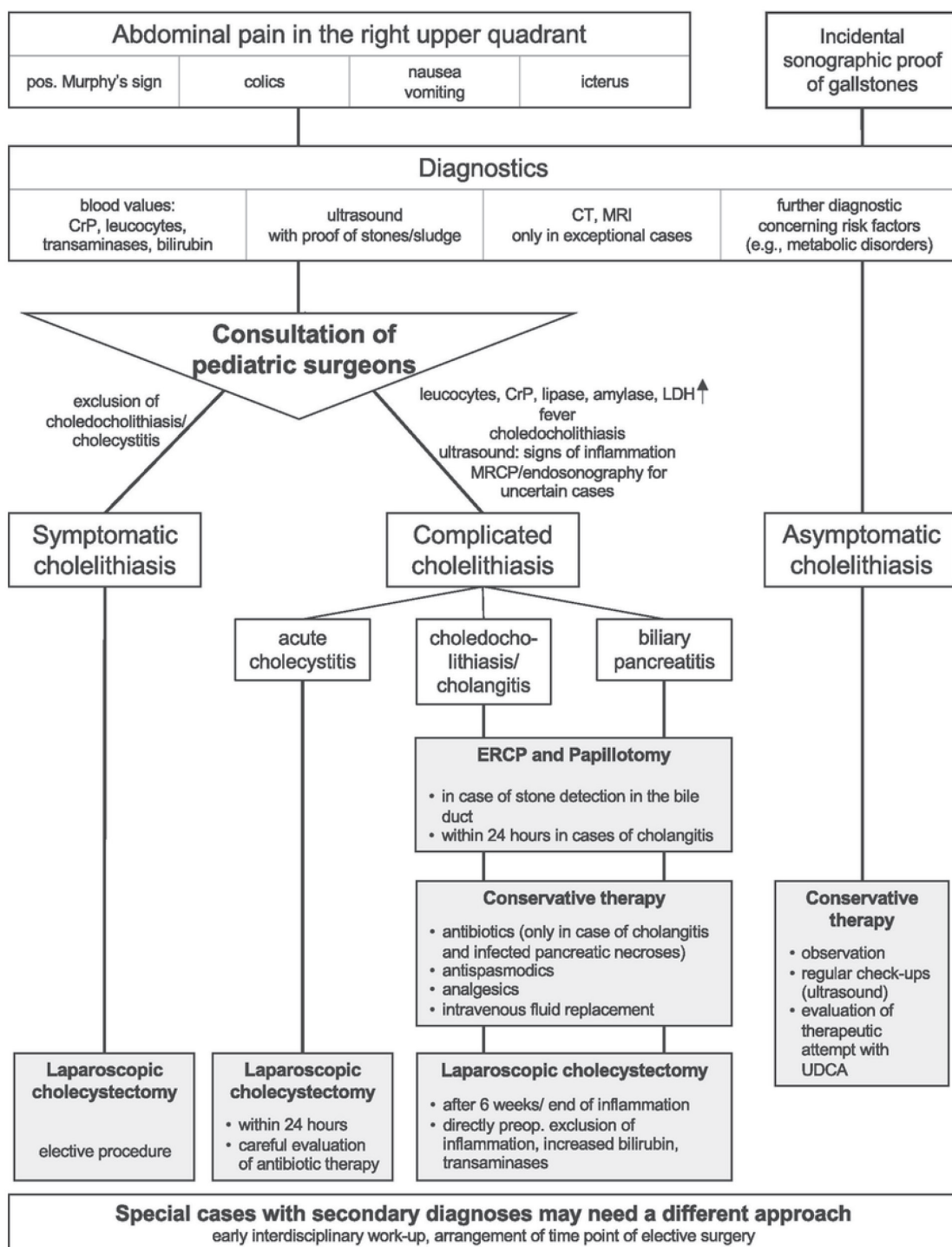


Figure 2. Guidelines for treatment of pediatric cholelithiasis published in BMC Gastroenterology 2021 by Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Pediatric Surgery, Department of Surgery, University Hospital Erlangen, Erlangen, Germany.

Open cholecystectomy

Classical open cholecystectomy is usually performed when there is a lack of the necessary experience, skill or equipment for the performance of a safe laparoscopic pediatric cholecystectomy.

Laparoscopic cholecystectomy

Most cholecystectomies are performed in cases of biliary colic, but also in acute cholecystitis, although it takes longer, has a higher conversion rate to an open procedure, and a higher risk for choledochal duct conversion³⁵. The main advantages of the laparoscopic approach are shorter hospitalization stay, better esthetic appearance, less operative pain, and a quicker return to daily activities. These advantages are the result of the smaller incision and less tissue trauma in comparison to open procedures¹⁵. Contraindications for laparoscopic procedures are the failure to tolerate general anesthesia, and the terminal stage of liver disease, with portal hypertension and coagulopathy. Since the laparoscopic procedure requires a pneumoperitoneum created using CO₂, severe obstructive pulmonary disease with decreased gas exchange and congestive heart insufficiency (ejection fraction <20%) are relative contraindications^{35,36}.

Laparoscopic cholecystectomy is performed in several phases: creating the pneumoperitoneum, trocar, camera and optics insertion, identification of anatomic structures, cholecystectomy, removal of the gallbladder with gallstones from the abdominal cavity, drain placement, sutures and /or possible conversion to an open procedure⁵⁰.

A nasogastric tube is placed in the stomach to ensure the stomach and duodenum are empty, to minimize the risk of duodenal injury due to dissection of the Calot triangle with monopolar hook cautery. The position of the trocars depends on the child's age. In toddlers and small children, it is possible to place an abdominal incision on the lower right, and the epigastric trocar should be placed more to the left side to ensure more space between instruments. In

preschool patients, the umbilical incision is 5 mm, and in older children 10 mm. Through this position CO₂ is insufflated into the abdomen^{15,16}.

In children it is rarely necessary for CO₂ to be insufflated with pressure higher than 12mmHg because it can lead to the inability to move the diaphragm during respiration, and there is no visible increase in the intra-abdominal volume⁴⁶. The recommendations for CO₂ insufflation in the pediatric population are teenagers with BMI > 30kg/m² – 16 mmHg, teenagers with average BMI – 14mmHg, children aged 8-12 years – 12mmHg, and children younger than 7 years – 10mmHg³⁰.

The position of the trocar and instruments depends on the children's age. For all ages the umbilical port is 5mm in size. In toddlers, two right side ports sized 3mm are made for instrument insertion, and an umbilical port 5mm in size for insertion of the telescope and the epigastric port should be located more to the left side. In children aged 3-10 years there are also two right side ports sized 3mm for instruments, and the umbilical instruments can be 5mm in size but they are usually 10mm. In adolescents, the ports are placed in the same way as in adults – two right-hand ports sized 5mm and an umbilical port sized 10mm¹⁶. In children, placement of the first trocar and creation of the pneumoperitoneum are performed using the minimally invasive Hasson procedure (we perform this in all our patients due to the fact that when using Veress the possibility of a lesion of the abdominal organs is higher and in the Hasson procedure it is lower, although there are disadvantages, such as gas leakage and it is time consuming), whereas in adult surgery the pneumoperitoneum is created using a Veress needle⁵¹.

The continuation of the procedure is performed as usual. To minimize the risk to the main bile duct, the “critical view of safety” method is recommended for visualization of the cystic duct and artery during laparoscopic cholecystectomy. There are three criteria for this – removal of the fat and connective tissue from the Calot triangle, continuation of dissection until the lower third of the gallbladder is separated from the

liver, and then removal of the surrounding tissue from the tubular structures – if the infundibulum is rotated laterally and then medially, only two structures should be seen that enter in the gallbladder. This is known as the “critical view of safety”^{35,52,53}.

Identification of the Rouviere sulcus (2-5cm in length to the right of the liver hilum and in front of the lobus quadratus hepatis) is an additional strategy to minimize injury to the main bile duct⁴⁹. If necessary, intraoperative cholangiography can be performed¹⁵. The clips used in ligation are usually 5mm in length, although in older children those sized 10mm can be used (Figures 3, 4, 5, 6, 7).

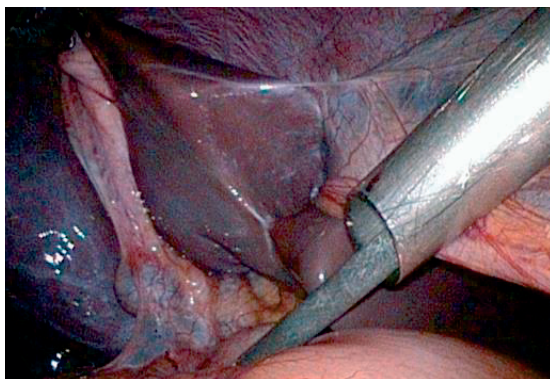


Figure 3. The gallbladder is retracted using graspers and Calot's triangle is cleared.

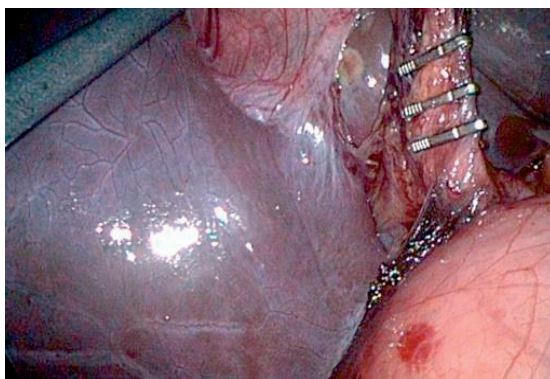


Figure 4. The endoscopic clip applicator is used to apply titanium clips in a dumbbell formation separately to the cystic duct and the cystic artery.



Figure 5. Using scissors, both the tissues are individually divided and checked for leaks.



Figure 6. The gallbladder is dissected using electrocautery bipolar scissors from the cystic duct end.



Figure 7. After the gallbladder is dissected free, it is extracted through the 10-mm port and removed.

Postoperative care

The average hospital stay after laparoscopic cholecystectomy is 36 hours, and after an open procedure it is 3 days. Prevention of deep vein thrombosis is managed with low molecule heparin or a compression stocking³⁶. A follow-up examination should be performed 2 weeks after a cholecystectomy. The patient is observed for postoperative fever, jaundice, ileus, pancreatitis, bile leakage or urinary retention⁴⁵. Early moderate postoperative physical activity is recommended, but strenuous activity should be avoided after laparoscopic cholecystectomy until the cessation of pain, or 4 weeks after an open cholecystectomy⁴⁵.

Complications

Postoperative complications

Main postoperative complications of cholecystectomy can be divided into biliary and nonbiliary. Biliary complications are injuries of the bile ducts, residual gallstones in the choledochal duct, bile leak, and development of fistulas, pancreatitis, and ileus. Nonbiliary complications are those connected to any abdominal operation, such as bleeding and infection³⁴. The frequency of wound infection and cardiopulmonary complications is significantly lower in laparoscopic treatment in comparison to open procedures³⁶. In the pediatric population, postoperative complications, such as obstruction of the choledochal duct, are more common in disorders such as sickle cell anemia.

Main bile duct injury

One of the most severe complications during surgery in the upper right quadrant that is quite common is iatrogenic injury of the main bile duct. More than 80% of all iatrogenic injuries of the main bile duct occur during cholecystectomy, and it may occur in both approaches. In children, the incidence of this injury is similar to that in adults where younger children are at greater risk. The risk of ductal injury increases from 0.1-0.2% in open procedures to 0.5-1% in laparoscopic procedures²¹. In comparison to

adults, use of intraoperative cholangiography is not connected to any reduced probability of injuries to the main bile duct⁵⁶. Inflammation, unclear bile duct anatomy, inadequate structure presentation, aggressive hemostasis and an inexperienced surgeon are risk factors for these injuries³⁵. When there are choledochal duct injuries, benign structures can develop that require corrective surgical intervention, because if left untreated they can lead to biliary cirrhosis and liver insufficiency³⁴. Although bile duct injury can be seen in both approaches, it is more commonly seen in the laparoscopic approach⁴⁵. Injury of the main bile duct can be noted during the operation but is usually recognized postoperatively. It is commonly believed that only 10% of strictures of the main bile duct are recognized in the first 2 weeks and 70% in the first 6 postoperative months³⁵. Iatrogenic injuries of the bile duct are recognized due to the severe pain and fever caused by peritonitis due to bile leakage. Afterwards, at the site of the stricture or injury, jaundice occurs with the increase in alkaline phosphatase and bilirubin³⁵. When the surgeon suspects that there has been an injury to the main bile duct during an operation, conversion to an open procedure is advised. When there is an injury, resection of the injured part with implantation of part of the jejunum is advised (Roux mucosa-mucosa anastomosis)³⁵. In every patient where injury of the main bile duct is suspected after the operation, thorough diagnostics should be conducted: CT is the best option. After this kind of injury all measures for inflammation control and infection prevention should be taken³⁵. The next step is cholangiography (percutaneous) for biliary tree anatomy representation. Reconstruction is performed after the inflammation has subsided³⁵.

Other complications

When significant fluid accumulation is seen during the postoperative period, percutaneous aspiration under ultrasound control should be performed. If there is blood in this fluid and the patient is hemodynamically stable and does not need transfusion, it is sufficient to conduct micro bacterial analyses of the fluid and to observe the patient. If there is bowel

content in the fluid, urgent laparotomy is required. If there is bile accumulation, with worsening of the patient's condition, urgent laparotomy should be considered, and if the patient is stable, MRCP or ERCPO should be performed to locate the site of leakage and to assess the state of the extrahepatic biliary tree⁴⁹. The greatest risk for postoperative bile leaks is in the case of acute cholecystitis. Clips placed on the cystic duct may move due to inflammation and fibrosis around the cystic duct where leakage can occur. This usually happens in the first postoperative week. If there is bile leaking from the cystic duct stump, endoscopic sphincterotomy with or without stenting of the main bile duct is required^{35,49}. Postoperative fever is a common complication of laparoscopic cholecystectomy and can be sign of a complication such as bile leakage from the biloma (bile collection)⁴⁹. Residual gallstones in the main bile duct may be identified for up to two years after cholecystectomy. They can be primary (originated from the main bile duct) or secondary (originated from the gallbladder). Secondary gallstones are usually symptomatic for a few weeks after the operative procedure and cause fever, jaundice, and severe pain under the right rib cage. In these patients, removal of these gallstones by laparoscopy is advised³⁵.

Intraoperative complications

During a laparoscopic procedure there may be complications such as injury caused by the Veress needle or a trocar, thermal injuries, and errors in the operative technique itself⁵⁰.

Postcholecystectomy syndrome

Post cholecystectomy syndrome is a preliminary diagnosis until the real cause is determined. The clinical presentation has a wide range of symptoms, such as: colic pain (93%), fever (38%), diarrhea (36%), jaundice (24%) and flatulence (14%). In one multicentric study, the incidence of this syndrome was only 4.7% in children after cholecystectomy⁸. There are many causes of post cholecystectomy syndrome,

but the most common are functional disorders (increased pressure in the papilla Vateri). The increase in pressure in the bile ducts and pancreatic duct due to intermittent obstruction of the sphincter of Oddi can be a consequence of an organic cause (papillary fibrosis) or a functional disorder of the sphincter mechanism. Normal values are below 30mmHg and an increase in the value above 40mmHg indicates stenosis or spasm of the sphincter³⁴. This syndrome also includes symptoms caused by the "loss" of the gallbladder as a reservoir, and changes in bile flow after cholecystectomy. After cholecystectomy there is a continuing increase in bile flow in the upper part of the gastrointestinal canal that can lead to gastritis and esophagitis, and at the level of the lower part of the alimentary canal, diarrhea may occur^{34,37}.

Conclusion

There are certain specific features of the diagnosis and treatment of cholelithiasis in the pediatric population that should be taken in consideration.

Children (but not adolescents who usually have the same causes for cholelithiasis as adults) may have cholelithiasis due to hereditary hemolytic and non-hemolytic diseases, medication such as ceftriaxone, and total parenteral nutrition due to the existence of ICUs where babies now survive but need this kind of treatment, if it is not a case of transient cholelithiasis.

Pediatric cholelithiasis is more prone to complications in some cases so its presentation may occur with symptoms of these complications.

Unlike in adults, where it is not recommended to treat cholelithiasis immediately, in the pediatric population cholelithiasis should be treated as soon as it is diagnosed due to the possible and frequent complications.

When it comes to treatment, although there are some studies that show that there is a higher percentage of bile duct injuries in the pediatric population when it comes to pediatric laparoscopy, this method of treatment is the gold standard for treatment of pediatric cholelithiasis.

Conflict of interests

The author has no relevant financial or non-financial interests to disclose.

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