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Contents

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EVIDENCE REVIEW

- 1 Inflammatory pseudotumor-like follicular dendritic cell sarcoma: Literature review of 67 cases
Wu H, Liu P, Xie XR, Chi JS, Li H, Xu CX

REVIEW

- 12 Exosomes: A new frontier under the spotlight for diagnosis and treatment of gastrointestinal diseases
Naseer M, Hadi S, Syed A, Safdari A, Tahan V

MINIREVIEWS

- 29 Biofat grafts as an orthobiologic tool in osteoarthritis: An update and classification proposal
Macedo RDR, Fonseca LFD, Lana JFSD, Mosaner T, Purita J, de Andrade M, Rodrigues LM, Centurion P
- 40 Non-invasive diagnosis of Crohn's disease: All that glitters is not gold
Khorshid M, Elkady MAK, Abdelkarim R, El-Nady M
- 45 Magic and forensic psychiatry: A case study and review of the literature
Vyshka G, Simoni S
- 51 Should we use full analgesic dose of opioids for organ procurement in brainstem dead?
Charlier P, Rebibo JD, Benmoussa N
- 54 Risk factors, manifestations, diagnosis and treatment of cholelithiasis in children
Xu ZR, Dan HL, Yu F

SYSTEMATIC REVIEWS

- 64 Mortality of critical care interventions in the COVID-19: A systematic review
Davis J, Leff R, Patel A, Venkatesan S

META-ANALYSIS

- 74 Efficacy and safety outcomes with remdesivir in COVID-19 patients: A meta-analysis
Patel TK, Patel PB, Barvaliya M, Vijayalaxmi, Bhalla HL
- 88 Health-related quality of life in patients that have undergone liver resection: A systematic review and meta-analysis
Ishinuki T, Ota S, Harada K, Tatsumi H, Harada K, Miyanishi K, Nagayama M, Takemasa I, Ohyanagi T, Hui TT, Mizuguchi T

ABOUT COVER

Xiao Long, MD, Chief Doctor, Deputy Director, Professor, Surgeon, Department of Plastic and Reconstructive Surgery, Peking Union Medical College Hospital of Peking Union Medical College and Chinese Academy of Medical Sciences, No. 1 Shuaifuyuan, Dongcheng District, Beijing 100730, China. pumclongxiao@126.com

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Risk factors, manifestations, diagnosis and treatment of cholelithiasis in children

Zheng-Rong Xu, Han-Lei Dan, Fan Yu

ORCID number: Zheng-Rong Xu 0000-0002-4869-7455; Han-Lei Dan 0000-0002-2629-2887; Fan Yu 0000-0003-3531-2285.

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Zheng-Rong Xu, Han-Lei Dan, Fan Yu, Department of Surgery, Hospital of PLA Unit 63820, Mianyang 621000, Sichuan Province, China

Corresponding author: Fan Yu, MM, Chief Physician, Surgeon, Department of Surgery, Hospital of PLA Unit 63820, West Section of Jianmen Road, Fucheng District, Mianyang 621000, Sichuan Province, China. l_fish@126.com

Abstract

Cholelithiasis in children refers to cholelithiasis or choledocholithiasis in newborns, infants and adolescents, including a series of symptoms and complications related to stones. The incidence rate of cholelithiasis in children is far lower than that in adults. However, the detection rate of cholelithiasis in children has risen in recent years. The aetiology of cholelithiasis in children is complex, and the pathogenesis is still unclear. According to existing studies, cholelithiasis in children may be related to sex and hormones, obesity, drugs, haemolytic diseases, genetic factors, chemokines, abnormal biliary tract formation, ileal surgery, total parenteral nutrition and other factors. In addition, there is a large occurrence of idiopathic cholelithiasis in children with unknown aetiology. The clinical manifestations of cholelithiasis in children are not completely the same as those in adults, mainly due to the different ages and causes. At present, there is no consensus on the clinical treatment of cholelithiasis in children. Follow-up and observation, drug dissolution and surgical treatment are all treatment methods for children with cholelithiasis. This study reviewed the related literature reports of cholelithiasis in children and summarized the risk factors, clinical manifestations, diagnosis and treatment of cholelithiasis in children to improve the understanding, diagnosis, and treatment of cholelithiasis in children.

Key Words: Cholelithiasis; Children; Risk factors; Diagnosis; Treatment

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Core Tip: The aetiology of cholelithiasis in children is complex, which may be related to sex and hormones, obesity, drugs, haemolytic diseases, genetic factors, chemokines, abnormal biliary tract formation, ileal surgery, total parenteral nutrition and other factors. The clinical manifestations of cholelithiasis in children are not completely the

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same as those in adults, mainly due to the different ages and causes. The treatment of cholelithiasis in children is individualized. Follow-up and observation, drug dissolution and surgical treatment are all treatment methods for children with cholelithiasis.

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INTRODUCTION

In recent years, the incidence rate of cholelithiasis in children has increased^[1-4]. According to a recent literature review^[5], the incidence of cholecystectomy in children under the age of 16 in England increased from 0.78 in 1997 to 2.7 per 100000 in 2012. The incidence of cholecystectomy in subjects under 18 years old increased from 8.8 per 100000 person-years in 1993 to 13.0 per 100000 person-years in 2012, and a 9-year retrospective study in the United States ending in 2012 also showed that the incidence of cholecystectomy in children had increased by 216%. The incidence rate of cholelithiasis in children under 19 years old is 0.13%-2%^[6,7], but it is still lower than the incidence of cholelithiasis in adults. The pathogenesis of cholelithiasis in children is not clear, and there is no uniform standard for treatment. Its complications or surgical consequences may affect children's social adaptability and healthy growth. Therefore, cholelithiasis in children has attracted increasing attention.

RISK FACTORS FOR CHOLELITHIASIS IN CHILDREN

Gallstone formation is secondary to local factors (*i.e.*, impaired smooth muscle function, wall inflammation and intraluminal mucin accumulation) and bile (*i.e.*, cholesterol supersaturation and solid crystal precipitation) and "extra-gallbladder" features, such as genetic polymorphisms, epigenetic factors, hormonal factors, multilevel alterations in cholesterol metabolism, altered intestinal motility, and variations in gut microbiota^[5]. What are the characteristics of the causes of cholelithiasis in children? Early studies mostly indicate that there is a large proportion of children with cholelithiasis from blood system diseases. With the accumulation of cases and increased research, cholelithiasis in children is also related to many factors, such as total parenteral nutrition, ileal disease and long-term fasting^[2,8-10]. Among the risk factors for cholelithiasis in children, haemolytic factors account for 20%-30%, and other known causes account for 40%-50% (including total parenteral nutrition, ileal diseases, congenital biliary diseases, *etc.*). Other idiopathic cholelithiasis accounts for 30%-40% of cases^[11]. In the infant stage, cholelithiasis often does not have a clear predisposing factor. In the childhood stage, the onset of cholelithiasis is often associated with chronic haemolytic disease or ileal disease. In the adolescent stage, idiopathic cholelithiasis accounts for the majority of cases, which is similar to adult cholelithiasis^[6]. Risk factors for cholelithiasis in children are shown in [Table 1](#).

Sex and oestrogen

Female patients are more common in children with cholelithiasis^[12]. One study from Turkey showed that among 254 children with cholelithiasis with an average age of 8.9 ± 5.2 years, the proportion of female patients was 52.8%^[13]. Another study reported that women accounted for 63.8% of children with cholelithiasis diagnosed at Bialystok Medical University within 4 years^[14]. To a large extent, this imbalance is due to the significant increase in the proportion of adolescent women with gallstones related to oestrogen. There are key enzymes involved in oestrogen inactivation and activation and the expression of oestrogen receptors α and β in normal gallbladder mucosa, which regulates the concentration of oestrogen in the human gallbladder^[15]. The increase in oestrogen levels may lead to stone formation by increasing the secretion of cholesterol and reducing the synthesis of bile acid^[16]. Overall, the incidence of gallstones in women is 2 times that of men. The increase in oestrogen levels during pregnancy will lead to significant metabolic changes in the liver and gallbladder

Table 1 Risk factors for cholelithiasis in children

Serial number	Risk factors	
1	Sex and oestrogen	
2	Obesity	
3	Drugs	
4	Haemolytic diseases	
5	Genetic factors	
6	Other known factors	Family history of cholelithiasis
		Chemokines
		Abnormal biliary tract formation
		Biliary ascariasis
		Ileal surgery
7	Idiopathic cholelithiasis	Total parenteral nutrition

system, including the formation of cholesterol supersaturation and slow gallbladder motion. These two factors promote gallstone formation^[17]. Through the activation of 5- β -hydroxylase, oestrogen in adolescence can increase the synthesis of cholesterol, which makes supersaturated cholesterol precipitate in the bile to form cholesterol stones, which is the main risk factor for the increased prevalence of gallstones in adolescent women.

Obesity

In a comparative study on the body mass index (BMI) of children with and without cholelithiasis, the median age of 98 children with simple cholelithiasis (75 cases) and children with common bile duct stones (23 cases) was 16 years old. The BMI of children with simple cholelithiasis and choledocholithiasis was significantly higher than that of the normal control group, and the BMI of children with choledocholithiasis was significantly higher than that of children with simple cholelithiasis^[18]. Therefore, it can be seen that an increase in BMI is related to the occurrence of cholelithiasis or choledocholithiasis in children, and obesity is a risk factor for cholelithiasis and choledocholithiasis.

Drugs (ceftriaxone sodium)

Ceftriaxone sodium is an anion that can be 20 to 150 times more concentrated in bile than in serum. It easily forms insoluble salt (ceftriaxone calcium) with calcium and precipitates in the gallbladder. Because cholelithiasis caused by ceftriaxone is reversible and disappears after stopping treatment, it is called "pseudolithiasis". In different prospective studies, the incidence of ceftriaxone-induced pseudolithiasis ranged from 15% to 46%^[13]. Ceftriaxone is a commonly used antibiotic for the treatment of severe bacterial infections in paediatric hospitals. Cholelithiasis or cholestasis is more common in children than in adults. A review of ceftriaxone-associated cholelithiasis in children suggests that ceftriaxone's relation to cholelithiasis is dose-dependent^[19].

Haemolytic diseases

Studies have shown that 39% of children with cholelithiasis have haemolytic disease^[7]. A study conducted at the Universidade de Campinas found a higher incidence (45%) of cholelithiasis in patients with sickle cell disease (SCD) and a predominance of younger patients (< 15 years)^[20]. The incidence rate of cholelithiasis in children with SCD is significantly higher due to increased hemobilirubin levels and promotion of gallstone formation due to haemolysis^[21-24]. SCD is a common cause of cholelithiasis. A total of 261 SCD children aged 4 mo to 16 years from the Children's Emergency Hospital in Khartoum were followed up for 13 years. The total prevalence of cholelithiasis was 11.5% (30/261) and increased with age^[23]. Karayalcin *et al*^[25] diagnosed cholelithiasis in 47 children aged 2-18 years with cholelithiasis using oral cholecystography and cholecystography, and the prevalence of cholelithiasis was 17%

(8/47). In another study using abdominal ultrasound, 305 children with SCD with an average age of 10.45 years were screened for cholelithiasis, and the prevalence of cholelithiasis was 19.7%. A correlation was found between the occurrence of stones and increased children's age^[26]. In Jos, northern Nigeria, a prospective gallstone prevalence study was conducted in 65 children with SCD aged 5-13 years by abdominal ultrasound. The results showed that the prevalence of gallstones was 4.6%^[27]. The low prevalence of cholelithiasis in SCD patients in Senegal may be due to the tolerance of Senegalese haplotypes. Older children with SCD and severe chronic haemolysis are the main causes of cholelithiasis in children in Senegal^[28].

Genetic factors

Studies have confirmed that genetic variation in the UGT1A promoter region has a significant impact on serum bilirubin levels and symptomatic cholelithiasis in children with SCD^[29,30]. A study on the association between genetic factors and other factors [including haematological parameters, clinical severity, hydroxyurea (HU) treatment] and cholelithiasis in children with SCD suggested that genetic polymorphisms of UGT1A1 (TA) were not the only cause of cholelithiasis in children with SCD, and its occurrence was also affected by low basal reticulocyte RET count, number of alpha gene deletions, HU treatment, and frequency of vascular occlusion events^[21]. In addition, the incidence rate of cholelithiasis in children with hereditary spherocytosis (HS) is also high^[30], and the incidence rate is reported to be as high as 41%^[31]. Therefore, it is recommended that HS children start physical examinations every year at the age of 4. Gilbert's syndrome, as an autosomal dominant genetic disease, increases indirect bilirubin in the liver due to insufficient glucuronosyltransferase activity in liver microsomes, thus increasing the risk of cholelithiasis^[30,31]. Moreover, a recent study showed that the risk trait of cholesterol metabolism in childhood favouring cholesterol gallstone disease later in adulthood is influenced by risk variant 19H of ABCG8^[32]. The occurrence of cholelithiasis in children is related to genetic factors or genetic diseases.

Other known factors

Any disease that can cause changes in the structure and function of the biliary system may become part of the aetiology or a potential risk factor for cholelithiasis in children. For example, gallbladder fibrosis caused by chronic inflammation, chronic active hepatitis and other liver infections or metabolic diseases, pregnancy and postpartum pregnancy is accompanied by high levels of oestrogen and progesterone. Blood transfusion haemolysis can also increase the incidence of gallstones.

Family history of cholelithiasis: A Turkish study on cholelithiasis in children shows that the most common risk factor for cholelithiasis in children is a family history of cholelithiasis^[33]. Similar conclusions have also been found in other studies^[7,34]. In Frybova *et al*^[18]'s study, 24% of children with cholelithiasis had a family history of cholelithiasis.

Chemokines: A prospective study carried out by Zdanowicz *et al*^[35] showed that the serum level of chemokines in 54 non-obese children and adolescents with cholelithiasis was significantly higher than that of 26 healthy people of the same age, suggesting that chemokines may play a potential role in the development of cholelithiasis in children and adolescents.

Abnormal biliary tract formation: Some scholars believe that cholelithiasis in children can be caused by abnormal formation of the biliary tract^[36]. Congenital biliary dysplasia can cause stricture or dilatation of intrahepatic and extrahepatic bile ducts, cholestasis complicated with bacterial infection, and gradual gallstone formation.

Biliary ascariasis: Biliary ascariasis can not only cause bile duct obstruction and mucosal damage but also form stones as the core. In addition, the *E. coli* introduced by ascariasis lumbricoides also produces β -glucuronidase, which hydrolyses soluble conjugated bilirubin into unconjugated bilirubin and precipitates with calcium ions to form bilirubin stones.

Ileal surgery: Because 98% of bile salt is reabsorbed at the end of the ileum, resection of ileum or ileal lesions can interrupt the intestinal and hepatic circulation of bile salt, resulting in a relative increase in cholesterol and precipitation from bile to form stones. The incidence rate of cholelithiasis in patients undergoing ileostomy is 24.5%, which is 3 times that of normal people. In patients with an ileal resection over 10 cm, the incidence of cholelithiasis is significantly higher^[37]. However, there was no

cholelithiasis in the paediatric group in this study, which may be related to the continued growth of children's intestinal tract.

Total parenteral nutrition: Total parenteral nutrition (TPN) is commonly used in the treatment of neonatal congenital malformations, necrotizing enterocolitis, severe malnutrition, premature infants and other situations. However, TPN may damage intestinal and hepatic circulation and the role of cholecystokinin, resulting in bile stasis, bile sludge and stone formation^[38]. The longer the duration of TPN treatment, the higher the risk of cholelithiasis. With ileum resection or ileal disease, the risk of long-term TPN cholelithiasis in children is increased^[39], and the same is true for newborns. The incidence of bile sludge in newborns treated with TPN is significantly increased^[40].

Idiopathic cholelithiasis in children

In addition to the abovementioned risk factors, the causes of cholelithiasis in many children are unknown with no clear risk factors before onset. This issue is called idiopathic cholelithiasis in children. A study of cholelithiasis in children showed that 56.6% of cases in 254 children with cholelithiasis (mean age: 8.9 ± 5.2 years) were idiopathic^[13]. Similarly, in a study on the efficacy of laparoscopic surgery for cholelithiasis in children, only 5 (27.8%) of the 18 children had definite aetiological risk factors for cholelithiasis, and the remaining 13 (75.2%) had idiopathic cholelithiasis^[41]. A study from Turkey also showed that no risk factor for stone formation was encountered in 50% of 70 children with cholelithiasis^[42].

MANIFESTATIONS AND DIAGNOSIS

Pigment stones are the most common type of gallstones in children^[41]. However, in adolescents, idiopathic cholesterol gallstones account for the majority of stone, which is similar to adults. At the same time, cholecystolithiasis accounted for 80%-90% of cases, and choledocholithiasis accounted for 10%-20% of cases^[6]. Abdominal pain is the most common symptom of cholelithiasis^[13,43], and often manifests as right upper abdominal colic or abdominal distension pain, which is also the situation in most children with cholelithiasis. In a retrospective study from Pittsburgh Children's Hospital, 197 children with symptomatic cholelithiasis (age 13.89 ± 0.26) had abdominal pain for 3.52 ± 0.56 mo, followed by nausea and vomiting (33.0%), weight loss (3.6%), diarrhoea (2.5%), abdominal distension (0.5%) and constipation (0.5%)^[44]. However, several special types of cholelithiasis in children are usually asymptomatic, such as ceftriaxone-associated cholelithiasis. Only in a few cases may abdominal pain, nausea and vomiting occur. When complications from ceftriaxone-related cholelithiasis are suspected, ultrasound examination should be performed^[19]. In addition, children with sickle cell disease are often asymptomatic when they are diagnosed with cholelithiasis. A 13-year follow-up study of 26 children with SCD cholelithiasis from Sudan showed that only one patient developed symptoms 3 years later and received surgical treatment. The remaining 25 patients had no symptoms of cholelithiasis^[23]. Cholelithiasis in children can also cause complications. It has been reported that the incidence of cholecystitis, choledocholithiasis and acute pancreatitis was 27.7%, 10.6% and 23.4%, respectively. In the differential diagnosis of abdominal pain, even the youngest child should pay attention to cholelithiasis, especially premature infants, low-birth-weight infants and very-low-birth-weight infants^[14]. In symptomatic cholelithiasis in children, 47.9% of the patients were complicated with cholecystitis by pathological examination after laparoscopic cholecystectomy^[45].

Other diseases of the gallbladder often cause abdominal pain, which is easily confused with cholelithiasis in children, such as chronic cholecystitis, biliary ascariasis, and biliary dyskinesia. Among 1611 patients aged 9-17 who underwent LC identified from the 2012 to 2013 American College of Surgeons' National Surgical Quality Improvement Program Paediatrics data, the most frequent indications for surgery were cholelithiasis/biliary colic (34.3%), chronic cholecystitis (26.9%), and biliary dyskinesia (18.2%)^[44]. Biliary dyskinesia is one of the main differential diagnoses of cholelithiasis in children. It attributes intermittent right upper abdominal pain to abnormalities in gallbladder function^[46]. Ultrasound is the first choice for the diagnosis of cholelithiasis in children. It is not only relatively simple but also easy to obtain the child's cooperation. In a follow-up study of 185 children with SCD conducted in Trousseau Children's Hospital (Paris), 26 cases of cholelithiasis were examined by ultrasonography, and abdominal ultrasonography was recommended for patients

under 7 years old with sickle cell anaemia^[24]. A Senegalese study also recommended systematic abdominal ultrasound at least once a year in patients with SCD over the age of five^[28]. It was recommended that repeated ultrasonography be used to observe gallstone formation in children with high-risk factors for gallstone disease for at least 10 years^[47]. When common bile duct stones are found, it is necessary to exclude choledochal cysts with abnormal connections of the pancreaticobiliary duct. Magnetic resonance cholangiopancreatography should be performed first^[6].

THERAPEUTIC TACTICS

The treatment strategy for cholelithiasis in children is a particularly difficult problem. Some scholars believe that different treatment methods can be adopted for different age groups^[4,48].

Observation

For asymptomatic cholelithiasis in children, especially in newborns and infants, an observation method suitable for individuals should be adopted according to the underlying disease and the degree of illness, including follow-up, regular clinical data collection, regular ultrasound or blood test. The duration of observation should also be heterogeneous, ranging from months to years and even to adulthood in some children. One study reported that 82% of children with atypical symptoms of gallstones improved through diet control and had no complications during an average follow-up period of 21 mo. This study concluded that children with asymptomatic or atypical symptoms could be safely followed up^[49]. Some children's cholelithiasis manifests in the form of bile sludge, which is often caused by long-term fasting (especially during total parenteral nutrition). After the patients resume an oral diet, the sludge and gallstones may disappear^[50].

Bile acid dissolution therapy

Ursodeoxycholic acid (UDCA) is controversial in the treatment of cholelithiasis because it is not effective at preventing symptoms and complications that subsequently occur as there is a high long-term recurrence rate^[50]. UDCA can significantly reduce cholesterol saturation by 40%-60% by inhibiting the absorption and secretion of cholesterol sterols. In adults, clinical studies have shown that the stone dissolution rate is 30%-60%^[33]. Some studies believe that UDCA in the treatment of children with gallstones, in addition to alleviating symptoms, has no obvious effect^[51]. Most children responded to UDCA treatment in the first six months, but children with haemolytic diseases showed no response to UDCA. Therefore, UDCA treatment may be useful before surgery in asymptomatic patients with cholelithiasis without haemolytic diseases^[33]. The dissolution rate of cholelithiasis was higher in younger children and those with biliary sludge formation and ceftriaxone-related cholelithiasis but lower in older children and haemolytic, anaemia-related cholelithiasis^[13]. Ceftriaxone-associated cholelithiasis gradually disappeared after withdrawal of ceftriaxone for a period of time (days to months). Therefore, conservative treatment and long-term follow-up are recommended^[19]. In a study by Serdaroglu *et al*^[42], the results showed that ursodeoxycholic acid had no effect on stone dissolution, but diagnosis under 2 years old, having a single stone and small stone size (less than 5 mm) were influential factors.

Extracorporeal shock wave lithotripsy

As early as the 1980s and 1990s, studies showed that gallstone disease may be treated successfully and without serious adverse effects by extracorporeally generated shock waves in selected patients^[52,53]. Evidence from randomized controlled trials, systematic reviews and cohort studies shows that extracorporeal shock wave lithotripsy, similar to bile acid dissolution therapy with UDCA alone, has a low cure rate^[50].

Surgical therapy

According to European Association for the Study of the Liver Clinical Practice Guidelines on the prevention, diagnosis and therapy of gallstones, cholecystectomy is recommended for symptomatic gallbladder stones but not routinely for asymptomatic gallbladder stones. However, asymptomatic patients with porcelain gallbladder may undergo cholecystectomy^[50]. Surgical decisions in children with cholelithiasis are more complicated. In a comparative study of cholelithiasis and biliary sludge in children, the authors suggest that cholecystectomy should not be routinely performed in

children with cholelithiasis or sludge but should be performed after careful selection of patients at risk for complications^[7]. With laparoscopic cholecystectomy (LC) becoming the gold standard for the treatment of gallstones, an elective LC procedure is recommended for cholelithiasis in children with SCD to prevent potential complications of biliary colics, acute cholecystitis, and choledocholithiasis^[54-57]. LC is a safe and effective method for the treatment of cholelithiasis in children^[22], and obesity is an independent risk factor for increased operative time in children undergoing LC^[44]. In addition, cholecystolithotomy is used in the treatment of cholelithiasis in children, and 14 of the 15 patients were not symptomatic with normal echography controls^[58]. Minimally invasive cholecystolithotomy using laparoscopy combined with choledochoscopy is a safe and viable technique, which can be successfully applied in pediatric surgery on the premise of mastering the indications, and has incomparable advantages over LC^[59]. Treatment of secondary common bile duct stones includes interventional radiologic, endoscopic or surgical procedures. Stone extraction may be performed with endoscopic retrograde cholangiopancreatography with or without sphincterotomy combined with LC^[6]. The sequential approach of endoscopic sphincterotomy and stone extraction followed by LC is a safe and effective approach for the management of cholelithiasis and choledocholithiasis in children^[60].

CONCLUSION

Cholelithiasis in children should be paid more attention in clinic. The aetiology of cholelithiasis in children is complex, which may be related to sex and hormones, obesity, drugs, haemolytic diseases, genetic factors, chemokines, abnormal biliary tract formation, ileal surgery, total parenteral nutrition and other factors. The clinical manifestations of cholelithiasis in children are not completely the same as those in adults, mainly due to the different ages and causes. The management of cholelithiasis in children is individualized. Follow-up and observation, drug dissolution and surgical treatment are all treatment methods for children with cholelithiasis, which can be individualized according to different ages and causes of onset. Through the review of the etiology, diagnosis and treatment of cholelithiasis in children, we can distinguish it from adult cholelithiasis, which will help us to improve the understanding and management of cholelithiasis in children.

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