Cirrhosis in children and adolescents: An overview

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Abstract

Several conditions, especially chronic liver diseases, can lead to cirrhosis in children and adolescents. Most cases in clinical practice are caused by similar etiologies. In infants, cirrhosis is most often caused by biliary atresia and genetic-metabolic diseases, while in older children, it tends to result from autoimmune hepatitis, Wilson’s disease, alpha-1-antitrypsin deficiency and primary sclerosing cholangitis. The symptoms of cirrhosis in children and adolescents are similar to those of adults. However, in pediatric patients, the first sign of cirrhosis is often poor weight gain. The complications of pediatric cirrhosis are similar to those observed in adult patients, and include gastrointestinal bleeding caused by gastroesophageal varices, ascites and spontaneous bacterial peritonitis. In pediatric patients, special attention should be paid to the nutritional alterations caused by cirrhosis, since children and adolescents have higher nutritional requirements for growth and development. Children and adolescents with chronic cholestasis are at risk for several nutritional deficiencies. Malnutrition can have severe consequences for both pre- and post-liver transplant patients. The treatment of cirrhosis-induced portal hypertension in children and adolescents is mostly based on methods developed for adults. The present article will review the diagnostic and differential diagnostic aspects of end-stage liver disease in children, as well as the major treatment options for this condition.

Key words: Cirrhosis; Liver diseases; Nutrition; Pediatric patients; Portal hypertension

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Core tip: The investigation and management of pediatric cirrhosis presents several challenges. The etiology of the condition may vary according to patient age. In many cases, cirrhosis is a predictable consequence of the progression of several chronic liver diseases, such as biliary atresia, although it may also be detected when splenomegaly is discovered on routine examination, or during the investigation of conditions such as hypersplenism, anemia, thrombocytopenia, leukopenia, petechiae and/or ecchymosis. The present article will discuss the diagnostic and treatment aspects of cirrhosis in children and adolescents.

Pinto RB, Schneider ACR, da Silveira TR. Cirrhosis in...
INTRODUCTION

Harvey Cushing - “A physician is obligated to consider more than a diseased organ, more than even the whole man - he must view the man in his world”.

General considerations

Cirrhosis is a diffuse process characterized by fibrosis and nodular regeneration, which lead to the disorganization of liver architecture. Cirrhosis was long thought to be irreversible and associated with limited life expectancy. However, it is now considered a dynamic condition, which can be reversed if adequately treated.

According to data from the Brazilian Unified Health System, between 2001 and 2010, liver diseases were the eighth leading cause of death in Brazil[1]. Cirrhosis was the main cause of hospital admissions and death from liver disease in Brazil, especially in the South region of the country. Little is known about its incidence in children.

Studies of the natural history of cirrhosis have found that the disease tends to present with a silent clinical course, followed by the onset of liver dysfunction and portal hypertension. The most important predictor of decompensation is the increase in hepatic venous pressure gradient (HVPG), which is seldom measured routinely in children and adolescents. In clinical practice, mortality risk is generally estimated on the basis of albuminemia, MELD (Model for End-Stage Liver Disease)/PELD (Pediatric End-Stage Liver Disease)/Child-PughTurcotte scores and body mass index. Advances in diagnostic and treatment technology, especially liver transplant surgery, have contributed significantly to the management of these cases. Currently, the majority of children diagnosed with cirrhosis in the first years of life can grow, develop and reach adulthood.

Biliary atresia and inherited syndromes of intrahepatic cholestasis are the most frequent causes of chronic liver disease in children[2]. The most common causes of cirrhosis in the first years of life are biliary atresia and genetic-metabolic diseases, whereas in older children, cirrhosis is usually caused by chronic viral hepatitis and autoimmune diseases (Table 1). Cirrhosis can be classified in several ways, based on morphological, histological, etiological and clinical criteria. As cirrhosis is the final stage of several types of progressive liver disease, etiological classification is often crucial for treatment planning. Despite the long list of possible etiologies shown in Table 1, the cause of cirrhotic disease is not always possible to determine.

As a result, the condition is considered cryptogenic in 5%-15% of cases. Cryptogenic cirrhosis in pediatric patients may result from the progression of fatty liver disease or from the effects of complex metabolic syndromes, such as mitochondrialopathies[3].

Biliary atresia

Biliary atresia (BA) occurs exclusively in childhood, and is the most common cause of chronic cholestasis and liver transplantation in children. It occurs in the first weeks of life and is characterized by complete obstruction of the biliary tract. Portal hypertension and biliary cirrhosis tend to occur early in the course of illness, and can be detected by 2 to 3 mo of age. Two forms of the disease have been identified: the congenital or “fetal” form, which accounts for 10% to 20% of cases of BA, and the perinatal or “acquired” form, which is responsible for 80% to 90% of cases. The fetal form usually manifests as jaundice at birth, and,

| Table 1 Diseases potentially resulting in cirrhosis in children and adolescents |
|-----------------------------------------------|
| Biliary obstruction                           |
| Biliary atresia                              |
| Choledochal cysts                            |
| Gallstones                                   |
| Bile duct stenosis                           |
| Familial intrahepatic cholestasis            |
| Alagille syndrome                            |
| FIC1 deficiency (AT1B81)                     |
| BSEP deficiency (ABCB11)                     |
| MDR3 deficiency (ABCB4)                      |
| Defects of bile acid synthesis               |
| Hepatotropic viral infections                |
| Hepatitis B and D                            |
| Hepatitis C                                  |
| Hepatitis E                                  |
| Inherited genetic-metabolic diseases         |
| α1-antitrypsin deficiency                    |
| Glycogenosis type III and IV                 |
| Galactosemia                                 |
| Fructosemia                                  |
| Tyrosinemia type 1                           |
| Wilson’s disease                             |
| Mitochondrial hepatopathies                  |
| Late cutaneous porphyria                     |
| Cystic fibrosis                              |
| Hemochromatosis                              |
| Wolman disease                               |
| Drugs and toxins                             |
| Total parenteral nutrition                   |
| Isoniazid                                    |
| Methotrexate                                 |
| Vitamin A intoxication                       |
| Autoimmune diseases                          |
| Autoimmune hepatitis                         |
| Primary sclerosing cholangitis               |
| Vascular alterations                         |
| Budd-Chiari syndrome                         |
| Veno-occlusive disease                       |
| Congenital cardiopathy                       |
| Congestive heart failure                     |
| Constrictive pericarditis                    |
| Other: Fatty liver disease, Neonatal hepatitis, Zellweger disease |

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in 15%-30% of patients, may also involve extrahepatic anomalies (vascular malformations, variant abdominal organ positioning, heart disease, etc.). In acquired BA, jaundice occurs later, after the first or second week of life, resulting in a jaundice-free period between the onset of physiological jaundice and biliary obstruction. Congenital extrahepatic anomalies are rare in this form of the disease. Studies involving the surgical removal of biliary obstruction have revealed that, in most cases, the preformed bile ducts are affected by inflammatory processes, the causes of which are still poorly understood. BA may represent a phenotype resulting from factors which lead to biliary obstruction and include developmental anomalies, infections, vascular alterations and exposure to toxins[2,4,5]. Treatment for this condition is surgical (Kasai portoenterostomy and its modifications, performed before the first 8 wk of life). The degree of restoration of biliary flow is inversely proportional to the age when surgery is performed. Without treatment, patients do not generally survive past 18-24 mo.

**Choledochal cysts**

This condition consists of congenital dilatation of the biliary ducts. Choledochal cysts are rare, with a prevalence of 1 per 13000-15000 live births in Western countries, although they are more common in Japan. Choledochal cysts are more common in females (5:1) and can be diagnosed antenatally by ultrasound. The cysts can be classified into five types: I, cystic dilatation of the common bile duct; II, diverticulum of the common bile duct; III, choledochocoele; IV, multiple cysts; and V, intrahepatic fusiform dilatation[6]. Most patients present with the typical symptom triad of abdominal pain, jaundice and palpable masses in the right upper quadrant. Surgical treatment consisting of cyst excision and biliopenic and stomy and its modifications, performed before the first 8 wk of life). The degree of restoration of biliary flow is inversely proportional to the age when surgery is performed. Without treatment, patients do not generally survive past 18-24 mo.

**Alagille syndrome**

Alagille syndrome is the most common cause of familial progressive intrahepatic cholestasis[7], and occurs in approximately 1:100000 live births. Most patients have mutations in the JAG1 gene, located on the short arm of chromosome 20. The syndrome is diagnosed on the basis of clinical symptoms, which can be difficult to detect in the first months of life, especially if the clinical picture is not yet clear. Histological examination may reveal a reduction of interlobular bile ducts in addition to cholestasis. Its main clinical features are cholestasis, a characteristic facies, cardiac abnormalities, vertebral arch defects and posterior embryotoxon. Supportive management is required in approximately 50% of cases. Alagille syndrome progresses to secondary biliary cirrhosis in 20%-25% of cases. The differential diagnosis must include other causes of ductopenia such as alpha-1-antitrypsin deficiency; the Zellweger, Pinto RB et al. Cirrhosis in children and adolescents
In a study conducted by Bortolotti et al.\textsuperscript{(15)}, only 6 (1.8%) of the 332 children evaluated developed cirrhosis after a period of 10 years. The incidence of hepatitis symptoms and severe liver disease was low\textsuperscript{(15)}. In a separate study performed in 80 Spanish and Italian children, only one presented with cirrhosis\textsuperscript{(16)}. More recently, a study of 121 children with chronic hepatitis C and a mean age of 10 years found that cirrhosis was only present in 2% of the sample\textsuperscript{(17)}.

**Alpha-1-antitrypsin deficiency**

Alpha-1-antitrypsin (AAT) is a glycoprotein produced in large quantities in the liver to inhibit the neutrophil proteases associated with inflammation. The classical form of the disease is caused by homozygosity for the Z mutation ("PiZZ" genotype for SERPINA1). Over 100 mutations in the AAT gene have been described, although the Z mutant is that most closely associated with liver disease\textsuperscript{(18)}. The clinical course is variable, and may involve neonatal cholestasis, liver dysfunction, liver failure and cirrhosis. Liver transplantation is often required. Approximately 20% of "PiZZ" patients develop cholestasis in the first weeks of life, and have a 5% risk of developing more severe forms of the disorder in childhood/adolescence. These patients are also more likely to develop hepatocellular carcinoma. There is no specific treatment or prevention against this condition, save for liver transplantation.

**Wilson's disease**

This autosomal recessive disease affects 1 in every 30000 live births. It is caused by mutations in the \textit{ATP7B} gene (chromosome 13), which encodes the protein responsible for the metabolism, transport and biliary excretion of copper. The clinical presentation of Wilson’s disease (WD) involves abnormal liver function tests, acute hepatitis, liver failure, portal hypertension, gallstones and cirrhosis. Copper accumulates in the liver, brain and cornea, and hepatic manifestations occur after the first 3 years of life. In adolescents, the diagnosis of WD is often based on signs and symptoms of chronic liver disease. Patients often have a family history of WD, and approximately 25% of cases are diagnosed as a result of the investigation of asymptomatic relatives. If left untreated, WD usually carries a bad prognosis.

**Cystic fibrosis**

This autosomal recessive disease occurs in approximately 1 in 2000-4000 live births in Caucasian populations. Cystic fibrosis (CF) is caused by mutations in the \textit{CFTR} transmembrane regulator gene, which is expressed in the apical membrane of biliary epithelial cells. This condition leads to severe and progressive impairment in the respiratory and digestive systems. Most patients do not present with liver damage in the early phase of the disease, although hepatic impairment is present in 10%-30% of cases. In older children and adolescents, CF liver disease manifests as hepatosplenomegaly and/or portal hypertension. Gallstones and micro-gallbladder are the most common biliary abnormalities in these patients. Portal hypertension is the major hepatic complication in CF.

**Fatty liver disease**

Given the high prevalence of obesity and metabolic syndrome in the general population, non-alcoholic fatty liver disease has become the most common cause of liver disease in both adults and children\textsuperscript{(19)}. It is a common, albeit under diagnosed, condition. Most cases are associated with obesity and type 2 diabetes mellitus. The risk of liver disease tends to increase with weight\textsuperscript{(20)}. Most patients are asymptomatic, and the disease is often discovered during routine examinations (by ultrasound or biochemical screening). Progression to cirrhosis is not common in childhood, but may occur in young adults.

**Autoimmune diseases**

Autoimmune liver diseases include sclerosing cholangitis, primary biliary cirrhosis, and autoimmune hepatitis (AIH), with the latter being the most autoimmune liver condition in children and adolescents. Primary biliary cirrhosis is rare in this age range, although sclerosing cholangitis has been increasing in prevalence, often accompanied by inflammatory bowel disease.

AIH is a chronic inflammatory liver disease, with
variable onset and duration. The prevalence of this condition in children is not yet known. There are few publications regarding this disease in patients from South America. In Brazil, AIH is still considered unusual, accounting for only 5%-10% of cases of liver disease in the major medical centers of the country. There are particular human leukocyte antigen (HLA) specificities associated with AIH in Latin Americans. HLA-DQ2 and DR52 seem to be risk factors, whereas DR5 and DQ3 appear to have a protective effect in this population. The trigger of the autoimmune process is not yet known. AIH can be classified into two subtypes, according to the non-organ specific antibodies present: type I (AIH-1) is associated with anti-nuclear (ANA) and anti-smooth muscle (ASMA) antibodies, whereas type II (AIH-2) is associated with positivity for anti-liver/kidney microsomal (LKM-1) antibodies. AIH-2 manifests earlier, in the first years of life, while AIH-1 generally occurs in older children and adolescents.

Primary sclerosing cholangitis (PSC) is a chronic, progressive liver disease of unknown cause. There is strong evidence to suggest that PSC is the result of alterations in the immune response to certain antigens. Cases with a well-defined etiology (e.g., cytomegalovirus infection, trauma, ischemic lesion) are diagnosed as “secondary sclerosing cholangitis”. PSC is characterized by oblitative fibrosis of the intra- and/or extrahepatic biliary tree. Concentric fibrosis is very common, and may lead to narrowing of the bile ducts and, eventually, to biliary cirrhosis and its complications. Sclerosing cholangitis may present soon after birth, in which case it must be distinguished from other causes of neonatal cholestasis, or later, with manifestations ranging from asymptomatic to decompensated cirrhosis.

Mitochondrial diseases

Mitochondrial diseases, or mitochondrialopathies, are inherited disorders of energy metabolism associated with a vast range of presentations, symptoms, severities and outcomes. Combined, they form one of the commonest groups of inherited metabolic diseases. Mitochondrial diseases occur due to dysfunction of the respiratory chain (RC) with resultant cellular ATP deficiency, increased production of reactive oxygen species and toxic metabolites and, ultimately, cell death. Disorders of mitochondrial energy metabolism result from mutations of nuclear or mitochondrial DNA. The exact prevalence of hepatic mitochondrial disease is not known, although it has been estimated that 10%-20% of patients with RC deficiencies have hepatic dysfunction. The three main defects associated with liver disease are almost always fatal: deficiency of RC enzymes, DNA depletion syndrome and Alpers syndrome. Liver involvement occurs frequently in childhood-onset mitochondrial disease, particularly in cases presenting in the neonatal period and early infancy. Liver transplantation is contraindicated in children with severe, life-threatening multiorgan extrahepatic mitochondrial disease due to poor post transplant neurological outcome.

EVALUATION OF CHILDREN AND ADOLESCENTS WITH CIRRHOSIS

The assessment of pediatric cirrhosis involves a thorough investigation of the child’s clinical history and physical examination findings (Table 3).

CLINICAL HISTORY

Investigation of the medical history of a child with chronic liver disease must cover not only the presence of previous hepatic disease, but also the history of blood or plasma transfusions, use of drugs and neonatal intercurrent clinical conditions such as cholestasis, infections, surgery and prolonged parenteral nutrition (PN). Neonatal cholestasis has been described in patients with alpha-1 antitrypsin deficiency. Prolonged PN can cause several types of liver damage which may progress to cirrhosis, especially in patients with intestinal failure. The source of patient referral must always be investigated, as knowledge of the regional prevalence of certain diseases can facilitate investigation of the etiological factors involved in cirrhosis. The maternal history of systemic diseases such as hepatitis B or C must always be investigated. Additionally, in adolescents, the presence of tattoos or piercings must be investigated due to their association with hepatitis C virus infection. In patients with inflammatory bowel disease, the presence of sclerosing cholangitis and/or AIH must also be considered. When investigating the clinical history of older children, it is also important to inquire as to the family history of neuropsychiatric diseases and/or hemolytic anemia. A family history of such conditions may raise suspicion of WD, which tends to affect children older than 5 years. Consanguinity and familial liver diseases must also be investigated. A history of jaundice in relatives may suggest the presence of PFIC. In children with pruritus associated with cholestasis and normal GGT levels, PFIC type 1 or 2 must be considered once other common causes of cholestasis have been ruled out.

CLINICAL FINDINGS

The clinical presentation of cirrhosis depends on the primary cause of liver disease and on whether the cirrhosis is compensated or decompensated. In up to 40% of cases, patients may be asymptomatic before liver failure occurs. In decompensated cirrhosis, there may be a cascade of progressive complications such as gastrointestinal bleeding, ascites and hepatic encephalopathy. The diagnosis is often predictable,
endocrine abnormalities may also be caused by the absence of hormonal conjugation or alterations in hormone metabolism, such as hepatic osteodystrophy, which may lead to fractures; rickets due to vitamin D deficiency; and spinal abnormalities. A heart condition associated specifically with cirrhosis, termed “cirrhotic cardiomyopathy”, has also been recently described. Some patients may also present with structural heart abnormalities, especially those with BA, Alagille syndrome, glycogen storage disorders and mitochondrial disease.

**INVESTIGATION**

In children and adolescents with cirrhosis, clinical investigations should be performed so as to determine the cause of the disease and identify any complications. The investigation techniques employed may vary according to patient age, as etiological factors vary widely between age ranges. In infants, cirrhosis is most often caused by BA and genetic-metabolic diseases, while in older children, it tends to result from AIH, WD, alpha-1-antitrypsin deficiency and PSC.

Laboratory investigation of cirrhosis should be comprehensive and designed to detect both infectious and genetic-metabolic diseases. Imaging modalities - abdominal ultrasound, computed tomography, and magnetic resonance imaging (MRI) - can be used to detect more advanced liver disease, but are not sensitive for detection of hepatic fibrosis. Esophagogastroduodenoscopy (EGD) and abdominal ultrasound can identify both gastroesophageal varices and portal hypertension. Liver biopsy is still the “gold-standard” method for diagnosis of cirrhosis, and can also contribute to etiological investigations. HVPG measurements are not usually included in the assessment of pediatric patients. Noninvasive methods such as transient elastography can also be used for the detection of fibrosis in patients with chronic liver disease. Studies of pediatric patients have produced favorable evidence regarding the use of these techniques. A study evaluating the use of transient elastography in children with chronic liver disease found that this method had good capacity to discriminate between significant fibrosis, severe fibrosis and cirrhosis. Pediatric MR elastography has also begun to be used in recent years. However, the reproducibility of these tests has yet to be evaluated in patients with cirrhosis of different causes.

**ROUTINE BIOCHEMISTRY**

Laboratory examinations are important for the assessment of liver function, the detection of hypersplenism and the identification of the causal factors underlying liver disease (Table 4). Aminotransferases are sensitive indicators of hepatocellular lesions. Alanine aminotransferase has been used as a specific

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**Table 3 Evaluation of children and adolescents with cirrhosis**

| Clinical history | Age, sex, ethnicity |
|-----------------|---------------------|
| Pregnancy and birth data: Adverse events during pregnancy, maternal serologies, birthweight, neonatal cholestasis, surgery, TPN |
| Signs and symptoms of systemic disease: anorexia, fatigue, muscle weakness, failure to thrive |
| Nausea, vomiting, abdominal pain, diarrhea, dyspepsia |
| Jaundice, pruritus, discoloration of urine and feces |
| Abdominal distension |
| Peripheral edema |
| Bleeding - nose, gums, skin, gastrointestinal tract |
| Bone pain, fractures |
| Adolescence: Menstrual history |
| Previous medical history: Jaundice, hepatitis, drug use, blood transfusions, inflammatory bowel disease |
| Social behaviors (adolescence): Use of alcohol or other drugs, tattoos, piercings |
| Family history: Consanguinity, liver disease, autoimmune disease |
| Physical examination: General: Anthropometric data (malnutrition or obesity), fever |
| Skin and extremities: jaundice, flushing or pallor, spider nevi, telangiectasias, palmar erythema, clubbing of the nails, xanthoma, Terry’s nails |
| Abdomen: Distension, prominent blood vessels, liver and spleen alterations (reduced liver size, splenomegaly) |
| Neurological alterations: Academic performance, sleep, asterixis, positive Babinski sign, mental status changes |
| Miscellaneous: Pubertal delay, gynecomastia, testicular atrophy, feminization |

Adapted from: McCormick, 2011; Högler et al, 2012; Hsu, 2014. TPN: Total parenteral nutrition.

since it is part of the natural progression of chronic liver conditions such as BA. However, cirrhosis may already be present when diseases such as AIH are diagnosed. Approximately 44%-80% of children with AIH present with cirrhosis.

The symptoms of cirrhosis in children and adolescents are similar to those experienced by adults. Poor weight gain is a common early symptom of cirrhosis in pediatric patients, who may also present with nonspecific symptoms such as anorexia, fatigue, muscle weakness, nausea and vomiting. Abdominal pain may also be present as a result of ulcers, gastritis or gallstones. The liver may be normal or reduced in size, and be covered by hardened or nodular tissue. The presence of ascites may also cause abdominal distension. The collateral vessels observed on the abdomen develop as a result of portal hypertension. Wide pulses and warm extremities are often indicative of high cardiac output. The identification of classical signs of chronic liver disease, such as spider nevi, visible abdominal circulation and palmar erythema, may also contribute to the diagnosis. Other cutaneous manifestations of cirrhosis include susceptibility to bruising, telangiectasias of the face and back and recurring epistaxis. Digital clubbing may also be detected by physical examination. Patients with chronic cholestasis may also present with pruritus, which can be so severe as to affect quality of life, as in the case of PFIC type 2 or Alagille syndrome. Several
marker of hepatocyte injury\(^4^6\). In obstructive liver damage, levels of canicular enzymes - alkaline phosphatase and gamma glutamyl transferase (GGT) - are usually elevated, as are bilirubin concentrations. However, these enzymes are not associated with hepatic synthesis and have no prognostic value\(^3^1\).

Presence of hypoalbuminemia and deficiency of coagulation factors correlate well with reduced hepatic synthesis, and are better predictors of survival\(^3^9\). An increased prothrombin time, despite vitamin K administration, suggests impaired liver synthesis and decompensated hepatocellular disease. Low levels of factors V, VII, XIII or plasminogen are indicative of poor prognosis\(^3^1\).

Abdominal ultrasound
Ultrasound is the ideal imaging method for the initial investigation of chronic liver disease in children and adolescents. The size of the spleen may provide indirect evidence of the presence or absence of portal hypertension, although it is not directly associated with measures of portal hypertension and is not an accurate indicator of the presence or absence of varices\(^3^3\). Ultrasound examination may also contribute to the diagnosis of gallstones, choledochal cysts and Caroli disease\(^4^7\). The use of Doppler techniques can complement ultrasound evaluations and help determine the perfusion and direction of blood flow in the portal system and hepatic artery. This method also allows identification of portal malformations. Cavernous transformation of the portal vein is a diagnostic feature of portal vein thrombosis.

Endoscopy
Endoscopy is the best method for evaluation of the presence, size and extension of gastric, esophageal and, more rarely, duodenal varices, and can help diagnose hypertensive gastropathy\(^4^8,4^9\). A prospective study of endoscopic findings in children with BA found that the presence of red signs and gastric varices was associated with increased risk of gastrointestinal bleeding\(^5^0\). Gastric mucosal damage, or hypertensive gastropathy, is characterized by the dilatation or ectasia of vessels in the mucosa and submucosa in the absence of inflammatory alterations, as identified by endoscopy or histological examination\(^5^1,5^2\). Although these criteria are not always used in children, a study of endoscopic findings in 51 children with portal hypertension found this condition in 59\% of 28 children with cirrhosis\(^5^3\). Endoscopy is also important to exclude other causes of gastrointestinal bleeding, such as gastric or duodenal ulcers and Mallory-Weiss tears\(^5^1\). In a study of 76 children with cirrhosis candidates for liver transplantation, gastric or duodenal ulcers were diagnosed in 8/21 (38\%) of children with gastrointestinal bleeding\(^5^4\). Studies of noninvasive methods to identify high risk of esophageal varices in children with chronic liver disease found that splenomegaly and hypoalbuminemia\(^5^5\), as well as platelet counts, Z scores of spleen size and albumin levels, predicted the presence of varices in patients with cirrhosis\(^5^6\).

Liver biopsy
Liver biopsy is still considered the gold-standard diagnostic method for cirrhosis. When required, it should be performed after thorough laboratory tests and imaging. The biopsy specimen should be evaluated by a pediatric hepatology specialist. The interpretation of results may be limited by several factors, especially

### Table 4 Investigation of chronic liver disease and cirrhosis in childhood and adolescence

| Hematology |  |
|------------|---|
| Hemoglobin, leukocyte and platelet count, prothrombin time (INR) |  |
| Coombs test, blood type, Rh factor |  |
| Biochemistry |  |
| Bilirubins |  |
| Transaminases |  |
| Alkaline phosphatase |  |
| Gamma-glutamyl transferase |  |
| Albumin and globulin |  |
| 25-OH vitamin D, parathyroid hormone, calcium, phosphorus, magnesium |  |
| Urea, creatinine |  |
| Lactic acid, fasting blood glucose, uric acid |  |
| Serum transferrin and ferritin saturation |  |
| Serum ceruloplasmin and copper, 24 h urinary copper (if age > 3 yr) |  |
| Alpha-1-antitrypsin phenotype |  |
| If ascites present |  |
| Paracentesis (in case of fever or sudden-onset ascites): |  |
| Cell count, albumin, total protein, neutrophil count |  |
| Amylase, cytology, PCR and mycobacterial culture (according to clinical suspicion) |  |
| Serum sodium, potassium, bicarbonate, chloride, urea and creatinine |  |
| Urinary sodium excretion |  |

| Immunology |  |
| Smooth muscle, mitochondrial, anti-nuclear, anti-LKM-1 antibodies |  |
| Hepatitis B antigen |  |
| Anti-HCV |  |
| α-fetoprotein |  |
| Immunoglobulins |  |
| HIV serology |  |
| Genetic-metabolic diseases |  |
| Metabolic screen (urine and serum amino acids, urine organic acids) |  |
| Genetic tests (if alpha-1-antitrypsin deficiency, Alagille syndrome, etc., suspected) |  |
| Sweat electrolytes test |  |
| Urine and serum analysis for bile acid and acid precursors (if PFIC suspected) |  |
| Bone marrow examination and skin fibroblast culture (if glycogen storage disease suspected) |  |
| Other: |  |
| Endoscopy (if prophylactic treatment is considered) |  |
| Abdominal ultrasound (computed tomography or MRI in selected cases) |  |
| Needle liver biopsy (if blood coagulation permits) |  |
| E EG (if neuropsychiatric changes present) |  |

Adapted from: McCormick\(^3^1\), 2011; Högl er et al\(^3^3\), 2012. LKM-1: Liver/kidney microsomal; PFIC: Progressive familial intrahepatic cholestasis; MRI: Magnetic resonance imaging; INR: International normalized ratio; HIV: Human immunodeficiency virus.
when suction biopsy is performed. These include small specimen size, sampling error or fragmented biopsy specimens\(^{57}\).

Other tests
In adults, HVPG measurements are the best method of assessing the presence and severity of portal hypertension, and can be used to monitor the efficacy of medical treatment\(^{58,59}\). However, this is still not a routine procedure in children.

Miraglia et al\(^{61}\) consider multidetector computed tomography scans and abdominal MRI crucial for the pretransplant assessment of patients with BA\(^{60}\). These imaging modalities permit identification of congenital anomalies or cirrhosis-related alterations (porto-systemic shunts, portal thrombosis) which may require modification of surgical techniques\(^{60}\). Most of these methods have not been studied extensively in children due to their invasive nature. Angiographic examinations are usually only performed in children as part of the preoperative assessment of surgical porto-systemic shunts or liver transplantation\(^{61}\).

### COMPLICATIONS OF PEDIATRIC CIRRHOSIS AND THEIR MANAGEMENT

#### Nutritional alterations
Malnutrition is an important prognostic factor, which may influence the clinical course of chronic liver disease\(^{62}\) and is associated with greater morbidity and mortality in both the pre- and post-transplant periods\(^{63}\). In children and adolescents, the increased energy demands associated with anorexia and nausea may complicate the management of malnutrition\(^{64-66}\).

A comprehensive clinical history and general physical examinations of the child/adolescent must be included in routine clinical practice\(^{67}\), and special attention must be paid to changes in muscle mass and body fat depots, both of which reflect important aspects of patient nutritional status. In clinical practice, anthropometry is the most widely used method for nutritional diagnosis. Regular patient follow-up also enables early detection of nutritional impairments. Given the high prevalence of water retention and organomegaly in pediatric cirrhosis, body weight is an unsatisfactory marker of nutritional status. In addition to measuring the weight, height/length and head circumference of children younger than 3 years, it is important to follow their long-term growth using reference curves. Triceps skinfold thickness and upper arm circumference measurements are also important to assess fat and protein reserves and can allow early detection of alterations in the nutritional status of pediatric patients with liver disease\(^{68,69}\). Subjective global assessments of nutritional status, performed on the basis of interview and physical examination findings, can also help identify factors which may influence the progression or regression of nutritional abnormalities\(^{70}\).

#### Nutritional treatment
Children or adolescents with chronic liver disease have increased nutritional needs. Patients at risk of malnutrition require 20%-80% more calories than healthy children to achieve normal growth\(^{26}\). These recommendations aim to ensure that children have sufficient energy to meet daily requirements, address the nutritional deficits caused by the increased energy demands of cirrhotic liver disease and prevent protein catabolism\(^{71}\).

Protein intake should not be restricted in the absence of hyperammonemia\(^{26}\). Cirrhotic infants with cholestasis require a protein intake of approximately 2-3 g/kg per day to achieve normal growth and endogenous synthesis. Supplementation with up to 4 g/kg per day is generally safe and necessary to maintain normal growth and avoid excessive catabolism.

Lipids are an especially important dietary component in children with liver disease, and should account for approximately 30%-35% of total calories in the diet. Medium-chain triglycerides (MCTs) should be included in the diet. Medium-chain triglycerides (MCTs) should account for 30%-50% of lipid intake, as these are absorbed directly by the intestinal epithelium and do not require bile salts for digestion and absorption\(^{59-72}\). Although MCT supplementation is crucial for the nutritional management of children with cholestasis, long-chain triglycerides should not be eliminated from the diet, as these substances provide essential fatty acids and contribute to the absorption of lipid-soluble molecules.

Deficiency of lipid-soluble vitamins is a common problem, especially in children with cholestasis; therefore, levels of these nutrients must be carefully monitored\(^{73,74}\).

Oral nutrition should always be preferred, although enteral or parenteral supplementation may be necessary if not all nutritional requirements can be met by oral feeding\(^{69}\). Enteral supplementation is generally recommended when oral intake provides less than 60% of recommended energy needs or in cases of severe malnutrition\(^{70}\).

#### Infections
Patients with cirrhosis are especially susceptible to infection, the most common of which is spontaneous bacterial peritonitis (SBP)\(^{76}\). Urinary and respiratory infections are also common\(^{311}\). In patients with cirrhosis, infections can lead to complications such as encephalopathy, ascites and hepatorenal syndrome.

Recommended preventive measures include nutritional supplementation, vaccination and prophylactic antibiotics for invasive procedures\(^{37}\). Pneumococcal and meningococcal vaccines are recommended for children with functional asplenia due to portal hypertension\(^{77}\). In children with cirrhosis candidates for liver transplantation, accelerated vaccination programs...
Deterioration of renal function. Excess fluid loss can lead to plasma depletion and blood urea nitrogen and urinary sodium levels. Be performed to verify serum electrolytes when the patient is stable, frequent laboratory testing should be performed. Thiazide diuretics can be used for treatment with a loop diuretic such as furosemide (1-6 mg/kg per day). The combination with furosemide lowers sodium levels below 125 mEq/L recommended in case of hypokalemia with serum sodium levels below 125 mEq/L. When diuretics are required, spironolactone (1-6 mg/kg per day) should be preferred and, if necessary, combined with a loop diuretic such as furosemide (1-6 mg/kg per day). The combination with furosemide lowers the risk of hyperkalemia due to increased potassium excretion. Thiazide diuretics can be used for treatment maintenance. During diuretic treatment and until the patient is stable, frequent laboratory testing should be performed to verify serum electrolytes, creatinine, blood urea nitrogen and urinary sodium levels. Excess fluid loss can lead to plasma depletion and deterioration of renal function.

Patients with refractory ascites or respiratory impairment can be treated by large-volume paracentesis. Up to 100 mL/kg of liquid can be removed at one time with the help of a post-paracentesis albumin infusion (25% albumin at 1 g/kg). Albumin and furosemide infusions can be used to treat patients with serum albumin below 2 mg/dL. In severe or recurrent refractory ascites, a transjugular intrahepatic portosystemic shunt may be performed as a bridge to liver transplantation. However, this procedure may be associated with increased risk of renal failure and encephalopathy.

Some medications should be avoided by patients with ascites. Aminoglycoside antibiotics, for instance, may increase the risk of renal failure, and non-steroidal anti-inflammatory drugs pose a high risk of sodium retention, hyponatremia and renal failure.

Ascites

Ascites is a common complication in pediatric cirrhosis, especially in younger children with terminal liver disease. This is generally associated with a poor prognosis. Pediatric patients with a sudden increase in ascites or new episodes of water retention should undergo paracentesis. Analysis of the ascitic fluid enables differentiation of ascites from portal hypertension of other causes of ascites. A serum-ascites albumin gradient - calculated by subtracting the albumin concentration of the ascitic fluid from the serum albumin level - greater than 1.1 g/dL can diagnose portal hypertension with 97% accuracy. Tests such as amylase, cytology, polymerase chain reaction and mycobacterial cultures should also be performed in case of diagnostic uncertainty or when pancreatic ascites, malignant tumors or tuberculosis are suspected.

Management

In most cases, cirrhotic ascites is resolved through dietary sodium restriction and the use of diuretics. However, children and adolescents ingesting low-sodium diets must be carefully monitored, since these restrictions often make the diet unpalatable and reduce food intake. Fluid restriction is strongly recommended in case of hyponatremia with serum sodium levels below 125 mEq/L. When diuretics are required, spironolactone (1-6 mg/kg per day) should be preferred and, if necessary, combined with a loop diuretic such as furosemide (1-6 mg/kg per day). The combination with furosemide lowers the risk of hyperkalemia due to increased potassium excretion. Thiazide diuretics can be used for treatment maintenance. During diuretic treatment and until the patient is stable, frequent laboratory testing should be performed to verify serum electrolytes, creatinine, blood urea nitrogen and urinary sodium levels. Excess fluid loss can lead to plasma depletion and deterioration of renal function.

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SBP

SBP refers to a bacterial infection of ascites without evidence of intestinal perforation or other intra-abdominal sources of infection. Infection is usually monomicrobial and caused by E. coli, Klebsiella spp. and Enterococcus faecalis. Polymicrobial infections are indicative of intestinal perforation or secondary peritonitis. SBP is a relatively common and potentially fatal complication in children with ascites. The presence of portal hypertension in patients with cirrhosis increases susceptibility to bacteremia and SBP. These phenomena are likely caused by the translocation of intestinal bacteria and of immune system deficits associated with cirrhosis, such as alterations in complement fixation and opsonization, decreased Kupffer cell function and neutropenia. Bacterial overgrowth and alterations in intestinal permeability probably play a role in bacterial translocation. Studies have found that detection of bacterial DNA in the ascitic fluid of children with portal hypertension is superior to cell cultures in diagnosing SBP, but cannot differentiate between infection and ascitic fluid colonization.

SBP must always be considered in children with cirrhosis and ascites who present with fever, abdominal pain or leukocytosis. Risk factors for SBP include ascites, hypoalbuminemia, gastrointestinal bleeding, pediatric intensive care unit admission and recent endoscopic examinations.

Management

Children with SBP are usually treated with a third-generation intravenous cephalosporin, such as cefotaxime, for 14 d. As a preventive measure, antibiotics should always be used during invasive procedures. If SBP recurs, the use of oral prophylactic antibiotics such as co-trimoxazole, ciprofloxacin or norfloxacin can be considered.

Hepatic encephalopathy

Hepatic encephalopathy (HE) is an alteration in brain function characterized by changes in mental status and neurological examination, as well as by increased ammonia levels in the blood. It is caused by the translocation of intestinal bacteria and of immune system deficits associated with cirrhosis, such as alterations in complement fixation and opsonization, decreased Kupffer cell function and neutropenia. Bacterial overgrowth and alterations in intestinal permeability probably play a role in bacterial translocation.
function caused by liver insufficiency and/or porto-systemic shunts\textsuperscript{(85)}. Infection is the main cause of HE. Gastrointestinal bleeding, excessive doses of diuretics, electrolyte imbalance and constipation are also commonly associated with this condition\textsuperscript{(85)}. HE can also be caused by excess protein intake, anesthetics and sedatives\textsuperscript{(86)}. Patients with HE may present with several neurological and psychiatric manifestations, ranging from subclinical alterations to coma\textsuperscript{(85)}. In children and adolescents, the first symptoms of HE are subtle, and include developmental delays, academic difficulties, lethargy or sleep inversion. Older children may also exhibit personality changes, intellectual impairments, obtundation (clouding of consciousness), stupor and coma.

Diagnosis of HE in children involves a high index of suspicion. Mild HE is even more difficult to diagnose, given the difficulty of administering psychometric tests to children and the absence of measures validated for use in this age range. Children are usually diagnosed on the basis of clinical symptoms. Psychometric tests evaluate memory and neuromotor function, and have been widely used to assess patients with mild encephalopathy. In children and adolescents, the most commonly used such tests are the Wechsler Intelligence Scales and the Dutch Child Intelligence test\textsuperscript{(87)}. The critical flicker frequency test, a simple and reliable test for the assessment of low-grade HE, can also be used in children older than 8 years\textsuperscript{(87)}.

Neuroimaging studies are important to exclude other causes of encephalopathy, but cannot be used to diagnose the condition\textsuperscript{(88)}. MR spectroscopy has proved to be as useful as neuropsychometric tests for the diagnosis of mild HE in adults\textsuperscript{(89)}. According to Foerster \textit{et al}\textsuperscript{(90)}, the alterations in cerebral metabolism observed in pediatric patients with suspected mild HE are similar to those observed in adults.

Management
Sedatives (especially benzodiazepines and opiates) should be avoided, as these drugs may worsen encephalopathy. Identification and treatment of the underlying cause of HE are crucial for the cure of the disease in approximately 90% of cases\textsuperscript{(85)}. Prolonged use of low-protein diets should be avoided. When protein restriction is required, protein intake should be reduced to 2-3 g/kg per day\textsuperscript{(37)}. Nonabsorbable disaccharides are the treatment of choice for patients with HE\textsuperscript{(31,87)}. In children, the optimal dose of lactulose is 0.3-0.4 mL/kg, two to three times a day\textsuperscript{(31)}. In adolescents and adults, the ideal dose can range from 10-30 mL three times a day, although treatment may begin with 25 mL/kg twice daily\textsuperscript{(85)}. A study of lactulose therapy in 22 children with cirrhosis and HE revealed complete recovery in 73% of patients\textsuperscript{(91)}. Several antibiotics, such as neomycin, vancomycin, metronidazole and rifaximin, have been used to reduce the number of ammonia-producing bacteria in the gastrointestinal tract\textsuperscript{(87)}. A case report of a 9-year-old girl with cirrhosis and HE described positive clinical results with the use of rifaximin\textsuperscript{(92)}.

Acute-on-chronic liver failure
Acute-on-chronic liver failure (ACLF) is the acute deterioration of liver function in patients with cirrhosis resulting from extra- or intrahepatic causes. Data on the epidemiology of ACLF are rare\textsuperscript{(93)}. In a study that evaluated a cohort of 192 patients admitted to the emergency department of a Brazilian tertiary hospital due to acute decompensation of cirrhosis, 46 (24%) fulfilled the EASL-CLIF Consortium criteria for ACLF. Bacterial infections were observed in 50%-94%. In children, the most common precipitating factor is infection. ACLF can progress to decompensation and multiple organ failure, resulting in high mortality rates. Mortality among inpatients with cirrhosis is strongly associated with infection. Patients with cirrhosis who acquire viral hepatitis, for instance, exhibit very rapid deterioration of liver function.

Hepatopulmonary syndrome
Hepatopulmonary syndrome (HPS) is a common complication in patients with portal hypertension and cirrhosis. It is characterized by intrapulmonary vasodilation, which results in insufficient oxygenation\textsuperscript{(95)}. The diagnosis of HPS should only be made when clinical suspicion is high, since clinical manifestations are subtle in the early stages of the disease. The presence of three symptoms – liver dysfunction, arteriovenous shunts and reduced O2 saturation - is required for diagnosis\textsuperscript{(96)}. The clinical picture can be reversed by liver transplantation, although the presence of HPS may interfere with tolerance to anesthesia and preclude transplant\textsuperscript{(96)}.

HPS is distinct from pulmonary hypertension, another underdiagnosed circulatory condition associated with pediatric cirrhosis. Pulmonary hypertension (also known in this setting as portopulmonary hypertension) has a vasoconstrictive etiology. Mild to moderate hypertension can be corrected by liver transplantation\textsuperscript{(97)}.

Hepatorenal syndrome
Patients with cirrhosis exhibit a progressive deterioration of renal function. Two types of hepatorenal syndrome (HRS) have been described: Type 1 HRS is associated with rapidly progressive kidney failure and a very low survival expectancy, the median survival time being only 2 wk if it is not treated; type 2 HRS is associated with slowly progressive kidney failure and has a better prognosis than type 1 HRS. Children also could exhibit alterations in renal function after liver transplantation, especially due to treatment with calcineurin inhibitors\textsuperscript{(98)}.

Hematological alterations
The basic laboratory tests of coagulation used to evaluate the risk of hemorrhage, such as prothrombin time and partial activated thromboplastin time, are only weakly associated with the incidence or duration
of bleeding after liver biopsy or other potentially hemorrhagic procedures\textsuperscript{[99]}. Nevertheless, patients with cholestatic disease and prolonged prothrombin time should receive parenteral vitamin K supplementation. The recommended dosage for children is 2-10 mg IV once daily for 3 d, or 5 to 10 mg IM per week\textsuperscript{[100]}. Fresh frozen plasma infusions (5-10 mL/kg) and cryoglobulin and/or platelet transfusions can also be used as treatment for bleeding episodes or prophyaxis against bleeding during procedures such as liver biopsy\textsuperscript{[100]}.

Chronic anemia is common in patients with cirrhosis, and can be caused by blood loss, iron deficiency and low folic acid levels due to sodium and water retention and hemolysis secondary to hypersplenism\textsuperscript{[111]}.

**Hepatocellular carcinoma**

Hepatocellular carcinoma (HCC) is also observed in patients with chronic liver disease. In pediatric patients, HCC can result from the progression of cholestatic, metabolic or viral diseases\textsuperscript{[101]}. Its pathogenesis is complex and involves both genetic and environmental factors. The usual symptoms are abdominal discomfort and distention and eating difficulties. Abdominal masses may also be detected on physical or ultrasound examinations\textsuperscript{[102]}. Alpha-fetoprotein levels may be elevated\textsuperscript{[102]}. An Italian study found HCC to be present in 2% of 103 children with cirrhosis who underwent primary liver transplantation. Despite the early age of onset, prognosis after liver transplantation was excellent, and recurrence was not observed\textsuperscript{[103]}.

HCC has also been reported in children with BA and Alagille syndrome\textsuperscript{[104,105]} and in adolescents with chronic hepatitis B\textsuperscript{[106,107]} or C\textsuperscript{[108]}.

Children with cirrhosis of any etiology should undergo abdominal ultrasound examinations and alpha-fetoprotein measurements every 6 mo or at least on a yearly basis\textsuperscript{[109,109]}.

**CONCLUSION**

End-stage liver disease or cirrhosis in children and adolescents has a multifactorial etiopathogenesis, and is usually the result of longstanding disease. Causes also vary in consequence of different factors, including patient age and prevalence of specific diseases in different regions. In clinical practice, the majority of cases are due to a limited repertoire of etiological factors, mainly BA, genetic-metabolic disorders and viral and AIH. In pediatric patients, special attention should be paid to the nutritional alterations caused by cirrhosis, as children and adolescents have higher nutritional requirements for growth and development. Malnutrition can have severe consequences for both pre- and post-liver transplant patients. Treatment of the complications of cirrhosis in children and adolescents is mostly based on methods developed for use in adults. Future research should focus on gaining a better understanding of the pathophysiology of cirrhosis in children, as well as improve non-invasive diagnostic tests for hepatic fibrosis and the management of pediatric patients with cirrhosis.

**REFERENCES**

1. Nader LA, de Mattos AA, Bastos GA. Burden of liver disease in Brazil. *Liver Int* 2014; 34: 844-849 [PMID: 24422599 DOI: 10.1111/liv.12470]
2. Santos JL, Choquette M, Bezerra JA. Cholestatic liver disease in children. *Curr Gastroenterol Rep* 2010; 12: 30-39 [PMID: 20425482 DOI: 10.1007/s11894-009-0081-8]
3. Mollsten JP, Sokol RJ, Karnsakul W, Mielke A, Horslen S, Magge JC, Romero R, Squires RH, Van Hove JL. Evaluation of the child with suspected mitochondrial liver disease. *J Pediatr Gastroenterol Nutr* 2013; 57: 269-276 [PMID: 23783016 DOI: 10.1097/MPG.0b013e31829ef7a]
4. Garcia-Barceló MM, Yeung MY, Miao XP, Tang C, Cheng G, So MT, Nguen ES, Lui VC, Chen Y, Liu XL, Hui KJ, Li LI, Guo WH, Sun XB, Tou JF, Chan KW, Wu ZX, Song YQ, Chan D, Cheung K, Chung PH, Wong KK, Sham PC, Cherry SS, Tam PK. Genome-wide association study identifies a susceptibility locus for biliary atresia on 10q24.2. *Hum Mol Genet* 2010; 19: 2917-2925 [PMID: 20460270 DOI: 10.1093/hmg/ddq196]
5. Hayashida M, Nishimoto Y, Matsuura T, Takahashi Y, Kohashi K, Souzaki R, Taguchi T. The evidence of maternal microchimerism in biliary atresia using fluorescent in situ hybridization. *J Pediatr Surg* 2007; 42: 2097-2101 [PMID: 18082716]
6. de Vries JS, de Vries S, Aronson DC, Bosman DK, Rauws EA, Bosma A, Heij HA, Gouma DJ, van Gulik TM. Choleodochal cyst: age of presentation, symptoms, and late complications related to Todani’s classification. *J Pediatr Surg* 2002; 37: 1568-1573 [PMID: 12407541]
7. Alagille D, Odièvre M, Gautier M, Dommergues JP. Hepatic ductular hypoplasia associated with characteristic facies, vertebral malformations, retarded physical, mental, and sexual development, and cardiac murmur. *J Pediatr Surg* 1975; 86: 63-71 [PMID: 803282]
8. Rumbo C, Fawaz RL, Emre SH, Suchy FJ, Kerkar N, Morotti RA, Schneider BL. Hepatitis C in children: a quaternary referral center experience. *J Pediatr Gastroenterol Nutr* 2006; 43: 209-216 [PMID: 16789787]
9. Ministério da Saúde - Secretaria de Vigilância em Saúde - Departamento de DST, Aids e Hepatites Virais. Boletim epidemiológico Hepatites virais, 2012: ano III v. 01
10. Bortolotti F, Jara P, Crivellaro C, Hierro L, Cadrobbi P, Frauca G, Pinto RB et al. Hepatitis C in children: a quaternary referral center experience. *J Pediatr Gastroenterol Nutr* 2002; 34: 137-142 [PMID: 11992574]
11. Iorio R, Giannattasio A, Cirillo F. Long-term outcome in children with chronic hepatitis B: a 24-year observation period. *Clin Infect Dis* 2007; 45: 943-949
12. European Association For The Study Of The Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. *J Hepatol* 2012; 57: 167-185 [PMID: 22436845]
13. González-Peralta RP, Langham MR, Andres JM, Mohan P, Colombani PM, Alford MK, Schwarz KB. Hepatocellular carcinoma in 2 young adolescents with chronic hepatitis C. *J Pediatr Gastroenterol Nutr* 2009; 48: 630-635 [PMID: 19412012 DOI: 10.1097/MPG.0b013e318170af04]
14. Dal Molin G, D’Agaro P, Ansaldui F, Ciana G, Fertz C, Alberico S, Campello C. Mother-to-infant transmission of hepatitis C virus: rate of infection and assessment of viral load and IgM anti-HCV as risk factors. *J Med Virol* 2002; 67: 137-142 [PMID: 11992574]
15. Bortolotti F, Verucchi G, Cammina C, Cavanna G, Zancan L, Indolfi G, Giacchino R, Marcellini M, Marazzi MG, Barbera CA, Maggiore S, Vajro P, Bartolacci S, Balli F, Maccabruni A, Guido M. Long-term course of chronic hepatitis C in children: from viral clearance to end-stage liver disease. *Gastroenterology* 2008; 134: 1900-1907
Complications in chronic liver disease and after liver transplantation in children. *J Pediatr Gastroenterol Nutr* 2012; 54: 313-321 [PMID: 22064631 DOI: 10.1097/MPG.0b013e31823e9412]

36 Timoh T, Protona MA, Wagnam G, Bloom M, Vittorio TJ. A perspective on cirrhotic cardiomyopathy. *Transplant Proc* 2011; 43: 1649-1653 [PMID: 21693251 DOI: 10.1016/j.transproceed.2011.01.188]

37 Leonis MA, Balistersi WE. Evaluation and management of end-stage liver disease in children. *Gastroenterology* 2008; 134: 1741-1751 [PMID: 18471551 DOI: 10.1053/j.gastro.2008.02.029]

38 Miraglia R, Luca A, Maruzzelli L, Spada M, Riva S, Caruso S, Maggiore G, Grudelli B, Bosch J. Measurement of hepatic vein pressure gradient in children with chronic liver diseases. *J Hepatol* 2010; 53: 624-629 [PMID: 20615572 DOI: 10.1016/j.jhep.2010.04.027]

39 Kim MY, Jeong WK, Baik SK. Invasive and non-invasive diagnosis of cirrhosis and portal hypertension. *World J Gastroenterol* 2014; 20: 4300-4315 [PMID: 10.3748/wjg.v20.i15.4300]

40 Fitzpatrick E, Quaglia A, Veillas vanesvaran S, Basson MS, Dhawan A. Transient elastography is a useful noninvasive tool for the evaluation of fibrosis in pediatric chronic liver disease. *J Pediatr Gastroenterol Nutr* 2013; 56: 72-76 [PMID: 22922372 DOI: 10.1097/MPG.0b013e31826760]

41 de Ledinghen V, Le Bail B, Rebouissoux L, Fournier C, Foucher J, Miette V, Castéra L, Sandrin L, Merrouche W, Lavrand F, Lamireau T. Liver stiffness measurement in children using FibroScan: feasibility study and comparison with Fibrotest, aspartate transaminase to platelets ratio index, and liver biopsy. *J Pediatr Gastroenterol Nutr* 2007; 45: 443-450 [PMID: 18030211]

42 Nobili V, Vizzutti F, Arena U, Abraldes KG, Marra F, Pietrobellati A, Fruhwirth R, Marcellini M, Pinzani M. Accuracy and reproducibility of transient elastography for the diagnosis of fibrosis in pediatric nonalcoholic steatohepatitis. *Hepatology* 2008; 48: 442-448 [PMID: 18563842 DOI: 10.1002/hep.22576]

43 Malbrunot-Wagner AC, Bridoux L, Noussebaum JB, Rou C, Driou A, Ginies JL, Maurage C, Cagnard B, Pelatan C, Dubade A. Transient elastography and portal hypertension in pediatric patients with cystic fibrosis. *J Cyst Fibros* 2011; 10: 338-342 [PMID: 21550861 DOI: 10.1016/j.jcf.2011.04.004]

44 Binkovitz LA, El-Youssef M, Slavik J, Yin M, Binkovitz AK, Ehman RL. Pediatric MR elastography of hepatic fibrosis: principles, technique and early clinical experience. *Pediatr Radiol* 2012; 42: 402-409 [PMID: 22120578 DOI: 10.1007/s00247-011-2299-6]

45 Xanthakos SA, Podbersky DJ, Serai SD, Miles L, King EC, Balisetersi WF, Kohli R. Use of magnetic resonance elastography to assess hepatic fibrosis in children with chronic liver disease. *J Pediatr* 2014; 164: 186-188 [PMID: 24064151 DOI: 10.1016/j.jpeds.2013.07.050]

46 Lamireau T, McLevin N, Nobili V, Vajo P. A practical approach to the child with abnormal liver tests. *Clin Res Hepatol Gastroenterol* 2014; 38: 259-262 [PMID: 24736033 DOI: 10.1016/j.clinre.2014.02.010]

47 Pinto RB, Lima JP, da Silveira TR, Scholl JG, de Mello ED, Silva G. Caroli’s disease: report of 10 cases in children and adolescents in southern Brazil. *J Pediatr Surg* 1997; 33: 1531-1535 [PMID: 9802807]

48 Sherlock S, Dooley J. Diseases of the liver and biliary system. In: Sherlock S, Dooley J, editors. 10th ed, London: Blackwell Scientific Publications, 1997: 135-140

49 Whittington PF. Portal hypertension in children. *Pediatr Ann* 1985; 14: 494-495, 498-499 [PMID: 3875070]

50 Duchê M, Ducot B, Tournay E, Fabres M, Cohen J, Jacquier M, Bernard O. Prognostic value of endoscopy in children with biliary atresia at risk for early development of varices and bleeding. *Gastroenterology* 2010; 139: 1952-1960 [PMID: 20637201 DOI: 10.1053/j.gastro.2010.07.004]

51 Viggiano TR, Gostout CJ. Portal hypertensive intestinal vasculopathy: a review of the clinical, endoscopic, and histopathologic features. *Am J Gastroenterol* 1992; 87: 944-954 [PMID: 1642217]
cirrhosis, and complications: Part 2: Hepatic encephalopathy and other systemic effects. In: Disease of the liver in children. Evaluation and management. Eds. Murray KF, Horslen S. New York, Springer, 2014: 497-516

88 Srivastava A, Yadav SK, Lal R, Yacha SK, Thomas MA, Saraswat VA, Gupta RK. Effect of surgical portosystemic shunt on prevalence of minimal hepatic encephalopathy in children with extrahepatic portal venous obstruction: assessment by magnetic resonance imaging and psychometry. J Pediatr Gastroenterol Nutr 2010; 51: 766-772 [PMID: 20890215]

89 Ross BD, Jacobson S, Villamí F, Korula J, Kreis R, Ernst T, Shonk T, Moats RA. Subclinical hepatic encephalopathy: proton MR spectroscopic abnormalities. Radiology 1994; 193: 457-463 [PMID: 7972763]

90 Foerster BR, Conklin LS, Petrou M, Barker PB, Schwarz KB. Minimal hepatic encephalopathy in children: evaluation with proton MR spectroscopy. AJNR Am J Neuroradiol 2009; 30: 1610-1613 [PMID: 19569075 DOI: 10.3174/ajnr.A165]

91 Sharma P, Sharma BC. Profile of hepatic encephalopathy in children with cirrhosis and response to lactulose. Saudi J Gastroenterol 2011; 17: 138-141 [PMID: 21372353 DOI: 10.4103/1319-3767.77246]

92 Malla I, Cerino VT, Villa A. Rifaximina para encefalopatía hepática en ninos. Caso clinico. Arch Argent Pediatria 2011; 109: e113-e115

93 Jalan R, Gines P, Olson JC, Mookerjee RP, Moreau R, Garcia-Tsao G, Arroyo V, Kamath PS. Acute-on-chronic liver failure. J Hepatol 2012; 57: 1336-1348 [PMID: 22750750 DOI: 10.1016/j.jhep.2012.06.026]

94 Silva PE, Fayad L, Lazzarotto C, Ronsoni MF, Bazzo ML, Colombo BS, Dantas-Correa EB, Narciso-Schiavon JL, Schiavon LL. Single-center validation of the EASL-CLIF Consortium definition of acute-on-chronic liver failure and CLIF-SOFA for prediction of mortality in cirrhosis. Liver Int 2014 May 20; Epub ahead of print [PMID: 24840673 DOI: 10.1111/liv.12597]

95 Sari S, Oguz D, Sucak T, Dalgic B, Atasever T. Hepatopulmonary syndrome in children with cirrhotic and non-cirrhotic portal hypertension: a single-center experience. Dig Dis Sci 2012; 57: 175-181 [PMID: 21792618 DOI: 10.1007/s10620-011-1832-6]

96 Barbe T, Losay J, Grimón G, Devictor D, Sardet A, Gauthier F, Houssin D, Bernard O. Pulmonary arteriovenous shunting in children with liver disease. J Pediatr 1995; 126: 571-579 [PMID: 7699535]

97 Hoepfer MM, Krowka MJ, Strassburg CP. Portopulmonary hypertension and hepatopulmonary syndrome. Lancet 2004; 363: 1461-1468 [PMID: 15121411]

98 Jara V P, Llanillo LH. Transplante hepático pediátrico. In Silva L, Ferreira CT, Carvalho E. Hepatologia em Pedriatria. Bauru: Editora Manole, 2012: 77-96

99 Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med 2011; 365: 147-1956 [PMID: 21751907 DOI: 10.1056/NEJMoa1011170]

100 Shepherd RW. Complication and management of chronic liver disease. In: Kelly D. Disease of the liver and biliary system in children, 3th ed. Maiden, Mass: Wiley-Blackwell, 2008

101 Walthier A, Tiao G. Approach to pediatric hepatocellular carcinoma. Clin Liver Dis 2013; 2: 219-222 [DOI: 10.1002/cld.260]

102 Haddie N, Finegold MJ. Liver neoplasia in children. Clin Liver Dis 2011; 15: 443-462, vii-x [PMID: 21689623 DOI: 10.1016/j.cld.2011.03.011]

103 Romano F, Stroppa P, Bravi M, Casotti V, Luciannetti A, Gazzotti M, Sonzogni A, Colledan M, D’Antiga L. Favorable outcome of primary liver transplantation in children with cirrhosis and hepatocellular carcinoma. Pediatr Transplant 2011; 15: 573-579 [PMID: 21797955 DOI: 10.1111/j.1399-3046.2011.01528.x]

104 Bhadri VA, Stormon MO, Arbuckle S, Lam AH, Gaskin KJ, Shun A. Hepatocellular carcinoma in children with Alagille syndrome. J Pediatr Gastroenterol Nutr 2005; 41: 676-678 [PMID: 16254531]

105 Kim B, Park SH, Yang HR, Seo JK, Kim WS, Chi JG. Hepatocellular carcinoma occurring in alagille syndrome. Pediatr Res Pract 2005; 201: 55-60 [PMID: 15807312]

106 Wen WH, Chang MH, Hsu HY, Ni YH, Chen HL. The development of hepatocellular carcinoma among prospectively followed children with chronic hepatitis B virus infection. J Pediatr 2004; 144: 397-399 [PMID: 15009156]

107 Bortolotti F, Guido M, Bartolacci S, Cadrabbi P, Crivellaro C, Noventa F, Morisca G, Moriondo M, Gatta A. Chronic hepatitis B in children after e antigen seroclearance: final report of a 29-year longitudinal study. Hepatology 2006; 43: 556-562 [PMID: 16946323]

108 Strickland DK, Jenkins JJ, Hudson MM. Hepatitis C infection and hepatocellular carcinoma after treatment of childhood cancer. J Pediatr Hematol Oncol 2001; 23: 527-529 [PMID: 11878782]

109 Mack CL, Gonzalez-Peralta RP, Gupta N, Leung D, Narkiewicz MR, Roberts EA, Rosenthal P, Schwarz KB. NASPGHAN practice guidelines: Diagnosis and management of hepatitis C infection in infants, children, and adolescents. J Pediatr Gastroenterol Nutr 2012; 54: 838-855 [PMID: 22487950 DOI: 10.1097/MPG.0b013e318258326d]

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