NICOLAE TESTEMITANU STATE UNIVERSITY OF MEDICINE AND PHARMACY OF THE REPUBLIC OF MOLDOVA

Tatiana RABA, Svetlana LIUBARSCAIA,
Olga TIHAI, Ninel REVENCO

CYTOLYSIS SYNDROME IN CHILDREN MANAGEMENT OF THE PEDIATRIC PATIENT

Diagnostic and Clinical Management Guideline

Methodological and Didactic Guide for Pediatric Residents and Medical Specialists

Chișinău
2026

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ABBREVIATIONS

ALT	– alanine aminotransferase
AST	– aspartate aminotransferase
HbsAg	– hepatitis b surface antigen
Anti-Hbe	– antibodies to hepatitis b “e” antigen
Anti-HBc total	– total Hepatitis B Core Antibody (IgM and IgG)
Anti-HBs	– antibodies to Hepatitis B Surface Antigen
Anti-HAV IgM	– anti-Hepatitis A Virus IgM Antibody
ANA	– antinuclear antibodies
Anti-SLA	– anti-soluble liver antigen antibodies
Anti-tTG IgA/IgG	– anti-tissue transglutaminase antibodies (IgA or IgG)
ASMA	– anti-smooth muscle antibodies
IBD	– inflammatory bowel disease
CMV	– cytomegalovirus
DIC	– disseminated intravascular coagulation
CT	– computed tomography
CK	– creatine kinase
ERCP	– endoscopic retrograde cholangiopancreatography
MRCP	– magnetic resonance cholangiopancreatography
EBV	– virus Epstein-Barr
G6PD deficiency	– glucose-6-phosphate dehydrogenase deficiency
AIH	– autoimmune hepatitis
HDL	– high-density lipoprotein
HSV	– herpes simplex virus
HTRA	– hypertransaminasemia
IgM	– immunoglobulin M
IgG	– immunoglobulin G
LDL	– low-density lipoprotein
LDH	– lactate dehydrogenase
MASLD	– metabolic dysfunction-associated steatotic liver disease
p-ANCA	– perinuclear anti-neutrophil cytoplasmic antibodies
MRI	– magnetic resonance imaging
TSH	– thyroid-stimulating hormone
T4	– thyroxine

SUMMARY OF THE GUIDELINE

Elevated serum transaminases represent a challenging scenario in both primary and hospital medical care. Their etiology is heterogeneous, ranging from hepatic to extrahepatic origins, and from transient hepatic dysfunction to chronic hepatitis. Elevated liver enzymes in children are often detected incidentally, either through laboratory evaluation requested by a physician or out of parental curiosity. Although in most cases these abnormalities are transient, returning to normal values over time, a subset of children will eventually be diagnosed with acute or chronic liver diseases. Differential diagnosis of cytolysis syndrome in the pediatric population must be comprehensive and multilayered, requiring a systematic and multidisciplinary approach.

This guideline presents the most recent and relevant clinical, paraclinical, and instrumental approaches, organized stepwise, to support clinicians particularly young practitioners in the accurate evaluation of cytolysis syndrome and in determining its etiological cause in children. Measurement of serum ALT and AST values is a standard component of biochemical testing in children, regardless of whether clinical manifestations are present. Aminotransferases serve as laboratory markers that indicate hepatocellular or extrahepatic cellular injury. ALT values increase predominantly in acute or chronic hepatic diseases (hepatitis), whereas AST elevation is more commonly observed in muscular, cardiac, renal, pulmonary diseases, and in acute or chronic pancreatitis.

This guideline is designed as a practical tool to provide method-logical support for both young and experienced clinicians. It addresses a common issue in medical practice and offers information regarding the definition, etiological causes, and principles of efficient and stepwise management of cytolysis syndrome and abnormal liver blood tests. Identifying the etiological cause of cytolysis in an evaluated child represents a crucial step in establishing the final clinical diagnosis. This methodological guideline is the first of its kind developed in national pediatric practice and is based on updated recommendations from international pediatric guidelines, including: *Guidelines on the Management of Abnormal Liver Blood Tests, 2017* (Prof.

Philip N. Newsome, NIHR Birmingham Biomedical Research Centre and Centre for Liver Research, University of Birmingham, UK); Updated recommendddations of the *European Society for Paediatric Gastroenterology, Hepatology, and Nutrition* (ESPGHAN).

Globally, a similar guideline was first published in 2000 and later revised by members of a Guideline Development Group (BSG), with contributions from: British Liver Trust, Liver4Life, PBC Foundation, PSC Support, patient and caregiver representatives, elected members of the British Society of Gastroenterology (including representatives from Scotland and Wales), British Association for the Study of the Liver (BASL), Specialist Advisory Committee on Clinical Biochemistry (Royal College of Pathology), the Association for Clinical Biochemistry, BSPGHAN, Public Health England, the Royal College of General Practice, BSGAR, and the Society for Acute Medicine.

The quality of evidence and grades of recommendation in this guideline were evaluated using the AGREE II instrument. These directives address specifically the management of abnormal liver blood tests in children and adults across primary care, secondary and tertiary public medical institutions, and private practice. Whenever a practitioner identifies abnormal liver test results including cytolysis he or she must initiate a systematic paraclinical evaluation to determine the underlying cause of cytolysis, guided by the following questions:

1. Are the standardized liver blood test results within age-appropriate reference limits, or are they abnormal?
2. What constitutes the standardized initial and supplementary liver test panel in cytolysis syndrome?
3. When and how frequently should abnormal liver blood tests be reassessed in pediatric patients?
4. Do the magnitude and duration of abnormal liver test values indicate the need for further investigations?
5. What is the appropriate clinical strategy for managing a pediatric patient with abnormal liver blood test results?

6. What is the institutional, stepwise referral pathway for pediatric patients diagnosed with cytolysis syndrome in outpatient and inpatient settings?

The recommendations in this guideline are not intended to manage underlying chronic liver diseases directly. Instead, they aim to clarify the etiological cause leading to cytolysis and to guide the correct, stepwise application of international pediatric algorithms and standards according to the presumptive diagnosis.

PREFACE

Cytolysis syndrome in children represents an important medical concern, involving both acute and chronic liver pathology, and frequently presents a diagnostic and management challenge for pediatricians and all specialists providing medical care to children across all levels of healthcare. This guideline is dedicated to the stepwise and efficient management of cytolysis, with particular emphasis on identifying its etiological cause and establishing the final diagnosis. The information presented herein is tailored to meet the practical needs of clinicians who encounter these challenges on a daily basis. Within this guideline, readers will find essential and up-to-date information on the precise definition of cytolysis syndrome, its etiology, diagnostic methods, and evidence-based strategies for diagnostic evaluation and clinical management. Our approach is grounded in the most recent scientific evidence and the collective international and national experience of leading specialists in pediatrics, gastroenterology, and pediatric hepatology. The primary aim of this guideline is to provide a clear and well-structured methodological framework for the identification and management of cytolysis syndrome in children, encouraging a holistic and integrated approach to each individual case. We hope that this methodological guide will serve as a valuable resource for young clinicians (including pediatric residents and clinical trainees), as well as for experienced professionals –pediatricians, gastroenterologists, hepatologists, family physicians, and experts from related fields – supporting their continuous professional development and their essential role in safeguarding child health across all levels of medical care. We extend our gratitude for your dedication and commitment to ensuring optimal and highly effective care for children affected by cytolysis syndrome. Together, we can contribute to enhancing the quality of pediatric medical services and making a meaningful impact on the lives of young patients and their families.

With respect,
The Authors

INTRODUCTION

Cytolysis syndrome in children represents one of the pathological manifestations of hepatic injury and is a major concern in medical practice. This syndrome is characterized by hepatocellular damage and the release into the bloodstream of specific liver enzymes, such as AST (aspartate aminotransferase), ALT (alanine aminotransferase), and LDH (lactate dehydrogenase), which indicate impairment of hepatic function.

Compared with adults, the occurrence of cytolysis syndrome in children presents additional challenges due to its potential impact on growth and development. Children may be affected by a wide spectrum of liver disorders, including viral infections, metabolic diseases, and congenital conditions, all of which may be associated with cytolysis and require appropriate diagnostic and therapeutic management. It is estimated that 3.5 % to 12.4 % of asymptomatic adolescents present with elevated liver enzymes. However, the prevalence and etiology of hypertransaminasemia across all pediatric age groups remain insufficiently understood, likely due to underrecognition of the condition. Furthermore, a standardized approach to the management of cytolysis syndrome in primary care is currently lacking, and few studies provide methodological recommendations for evaluating hypertransaminasemia in the pediatric population.

The aim of this guideline is to provide a comprehensive analysis of the potential causes of cytolysis syndrome in children, including its pathophysiological mechanisms, associated risk factors, clinical signs and symptoms, diagnostic pathways, relevant investigations, and age-specific therapeutic management strategies. A step-by-step algorithm has been developed to support frontline clinicians in accurately identifying the true etiological cause of cytolysis in pediatric patients. A deeper understanding of the condition enables earlier diagnosis, timely therapeutic intervention, and effective management of hepatic and metabolic disorders among children. This integrative approach is essential for ensuring optimal care and high quality of life for children affected by cytolysis syndrome.

This guideline is based on current medical literature and recommendations from experts in pediatrics and pediatric hepatology. Our goal is to provide pediatric residents, specialists, young practitioners, and those undergoing continuous professional training with a valuable resource for the efficient and comprehensive management of cytolysis syndrome in children. Together, we hope to contribute to improved clinical approaches and better outcomes for children affected by this complex and heterogeneous condition.

DEFINITION AND GENERAL CHARACTERISTICS OF CYTOLYSIS SYNDROME IN CHILDREN

Definition. Cytolysis represents a polyetiological clinical and laboratory syndrome characterized by elevated serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), compared with age-adjusted reference values provided by the laboratory. This syndrome reflects the response of hepatocytes to various hepatic and extrahepatic injurious factors that lead to their destruction. The condition is commonly associated with other pathological syndromes such as cholestasis, mesenchymal-inflammatory syndrome, and autoimmune inflammation. Cytolysis may be present in several hepatic (acute or chronic) and extrahepatic diseases, as well as in acute or chronic liver failure [16].

Multiple studies report that the prevalence of abnormal liver enzyme values varies by country, dietary patterns, hygiene and sanitation conditions, season, and quality of medical care in the region. It is estimated that between 3.5 % and 12.4 % of asymptomatic adolescents have elevated liver enzymes. In low-income countries, the most frequent cause of cytolysis is acute viral infection caused by hepatitis A virus (HAV). In contrast, in high-income countries, the leading cause is metabolic dysfunction–associated steatotic liver disease (MASLD), although hepatobiliary, genetic, and autoimmune disorders also significantly contribute to the development of hepatic cytolysis.

However, the prevalence and etiology of hypertransaminasemia among European children of all age groups remain poorly defined, likely due to underrecognition of the condition. In addition, few studies provide clear guidance for evaluating asymptomatic hypertransaminasemia in the pediatric population. At present, there is no standardized approach within primary or hospital pediatric care for managing cytolysis syndrome [16].

Several international studies (Yuan et al., 2022) indicate a high prevalence of hepatic cytolysis in children with *Helicobacter pylori* infection, highlighting the significant burden of this infection in the pediatric population [17].

In clinical pediatric gastroenterology, several groups of etiological factors are recognized as causes of cytolysis, each leading to hepatocellular injury and release of hepatic enzymes into the bloodstream.

Pediatric patients with elevated liver enzymes (ALT and AST) are often identified incidentally during routine testing or laboratory investigations performed for unrelated clinical concerns. Although most children may have transient and/or benign abnormalities, a subset may harbor subclinical or asymptomatic liver disorders that can persist for months or years. Differential diagnosis of cytolysis syndrome in children is complex and requires a systematic and broad investigative approach, especially regarding laboratory evaluation. This guideline reviews the most recent and relevant scientific data to provide a comprehensive overview of the main pathological processes associated with hypertransaminasemia in children. Lastly, we propose a practical, stepwise diagnostic approach to guide clinicians in evaluating abnormal liver enzyme values in both asymptomatic and symptomatic pediatric patients. The first step involves obtaining a complete medical history and performing a thorough physical examination to identify any red flags that necessitate urgent consultation with a pediatric gastroenterologist or hepatologist.

Acute and chronic infectious processes. Viral hepatitis A, B, C, D, and E; liver involvement in CMV infection; herpes simplex virus (HSV) infection; and Epstein-Barr virus (EBV) infection represent the most frequent causes of hepatic parenchymal injury, often accompanied by hepatocellular destruction leading to cytolysis and predominant elevation of ALT and, to a lesser extent, AST. Cytolysis occurs in both acute hepatic inflammation and exacerbations of chronic hepatitis, liver cirrhosis, or hepatocellular carcinoma. Cytolysis can also be diagnosed in children with intestinal, hepatic, and extraintestinal parasitic infections such as amebiasis, giardiasis, echinococcosis, alveococcosis, *Larva Migrans Visceralis*, opisthorchiasis, and fascioliasis.

Metabolic dysfunction–associated steatotic liver disease (MASLD). Metabolic steatotic liver disease, whether nonalcoholic (MASLD) or alcohol-related, is the leading noninfectious cause of

cytolysis in older children and adolescents. Hepatic tissue destruction is driven by the toxic effects of lipoproteins or ethanol metabolites entering the liver in increased quantities through the portal circulation.

Cholestatic disorders. Cytolysis and cholestasis frequently coexist in intrahepatic or extrahepatic biliary lithiasis. When bile secretion is impaired, cytolysis occurs alongside elevated cholesterol and alkaline phosphatase levels. Hepatocellular injury is mediated by the toxic effects of bile acids.

Toxic liver injury induced by drugs, medications, or non-pharmaceutical toxic substances. Unsupervised self-medication, combined drug use with cumulative effects, pharmacological synergism, and polypharmacy – especially in critically ill children – frequently lead to drug-induced or toxic hepatitis, with a reported prevalence of 2-5 %. Most cases are subclinical, but cytolysis may manifest with markedly elevated liver enzymes and may progress to acute liver injury with potentially fatal prognosis in the absence of liver transplantation.

A significant elevation of ALT and AST is also characteristic of various extrahepatic conditions, including myopathies, inherited metabolic diseases, rheumatologic diseases, cardiac or renal disorders, muscle necrosis, and acid-base imbalances. Hyperlipidemia, cytolysis, and metabolic syndrome observed in hereditary storage diseases (Gaucher disease, Niemann-Pick disease, Wilson disease, hereditary hemochromatosis, etc.) are considered key laboratory features of these disorders. In adolescents and older children with behavioral disturbances – including excessive consumption of fried or fatty foods, intake of contaminated water, alcohol use, smoking, or substance abuse cytolysis may also occur and requires early and effective management.

Cytolysis syndrome is not an independent nosological entity. It is observed in various gastrointestinal, hepatobiliary, and extra-digestive disorders. In some instances, when the etiological agent cannot be identified, the condition is referred to as „nonspecific hepatitis," highlighting its inflammatory nature. The true incidence of cytolysis in children is unknown, as many cases are detected incidentally during unrelated medical evaluations.

From a biochemical perspective, AST and ALT are essential enzymes synthesized primarily in the liver and, to a lesser extent, in muscle tissue. They participate in key metabolic pathways, including the citric acid cycle and amino acid transamination, which are critical for energy production and metabolic homeostasis. Elevated ALT and AST levels indicate increased enzyme release due to hepatocellular injury. Under normal conditions, serum transaminase levels reflect the balance between physiological hepatocyte turnover and enzyme clearance from the body.

Indicators of hepatic injury and cytolysis include elevations in:

- Alanin aminotransferase (ALT, GPT);
- Aspartate aminotransferase (AST, GOT);
- Lactate dehydrogenase (LDH, fractions 4 and 5) and gamma-glutamyltransferase (GGT);
- Specific hepatic enzymes (sorbitol dehydrogenase, aldolase, ornithine carbamyltransferase);
- Mitochondrial enzymes (glutamate dehydrogenase, succinate dehydrogenase);
- Total bilirubin and its fractions (particularly due to an increase in the direct fraction, and in some cases, the indirect fraction).

Significance of Specific Hepatic Enzymes

Alanine aminotransferase (ALT), also known as glutamate-pyruvate transaminase (GPT), is a cytoplasmic enzyme found predominantly in hepatocytes, making it more specific to liver disease. Smaller amounts of ALT are also present in cardiac muscle, skeletal muscle, pancreas, spleen, and lungs. Its primary function is to catalyze the transfer of the amino group from alanine to α-ketoglutarate, resulting in the formation of pyruvate and glutamate. Elevated ALT levels in the bloodstream may be associated with a variety of hepatic disorders or processes that involve cellular destruction.

ALT is considered a more specific marker of hepatic injury compared with AST (aspartate aminotransferase). Increased ALT levels may be observed in acute viral hepatitis, chronic hepatitis, and other liver

diseases. Recent studies highlight the importance of carefully evaluating and actively managing patients with mildly elevated ALT values, as such abnormalities may represent early indicators of chronic liver disease or subtle hepatocellular injury.

Aspartate aminotransferase (AST), also known as glutamate - oxaloacetate transaminase (GOT), is a cytoplasmic enzyme present predominantly in hepatocytes and myocytes, but it is also expressed in several other tissues. AST catalyzes the transfer of the amino group from aspartic acid to α-ketoglutarate, forming oxaloacetate and glutamate (a reaction requiring pyridoxal phosphate).

Its highest activity is found in the myocardium, liver, skeletal muscle, nervous tissue, and kidneys, with lower expression in the pancreas, spleen, and lungs. AST exists in two cellular fractions: mitochondrial (≈2/3) and cytoplasmic (≈1/3). Because AST is predominantly mitochondrial, its serum concentrations rise less markedly in liver injury compared with ALT. Clinically, AST is frequently used for early diagnosis of myocardial infarction in adults, although its specificity is limited. Elevated AST levels may indicate extensive tissue injury and involvement of multiple organs, including the liver.

Common causes of AST elevation include myocardial infarction, acute rheumatic fever, pulmonary embolism, cardiac surgery, coronary angiography, severe angina attacks, muscular injuries, myopathies, and acute pancreatitis. In children, elevated AST holds particular significance in dermatomyositis. Moderate increases can also occur in hemolytic conditions, severe muscle injury, and acute pancreatitis, while intense physical exertion may transiently raise AST levels.

Gamma-glutamyltransferase (GGT) is released from hepatocytes into plasma through bile, with enzyme activity in bile being ten times higher than in plasma. A small proportion is degraded in the kidneys and excreted in urine. Excessive hepatic synthesis of GGT may be induced by cholestasis, chronic alcohol consumption, or therapeutic doses of certain drugs. Serum GGT concentrations are elevated in hepatoma cells, in hepatocytes compressed by hepatic tumors, and in regenerative nodules in cirrhotic liver. GGT is a specific marker of injury to the liver

and biliary ducts and correlates with elevated alkaline phosphatase values.

Elevated GGT levels may be encountered in the following conditions:

- acute viral hepatitis – GGT increases less than other hepatic enzymes (GGT/AST = 0.1-0.2) but normalizes last; in cholestatic forms, GGT/AST = 1;
- chronic active hepatitis (viral or autoimmune) – can exceed the upper limit of normal by >7-fold (GGT/AST = 1-3);
- acute alcoholic hepatitis – GGT/AST > 6;
- liver cirrhosis – approximately 2-fold elevation in post-hepatitic cirrhosis; up to 10-fold in alcoholic cirrhosis;
- primary sclerosing cholangitis – GGT increases parallel to alkaline phosphatase before jaundice appears, rising ≥13-fold above normal;
- fatty liver disease alcohol-related GGT ~2× normal and remains elevated long after abstinence; non-alcoholic/metabolic: mild aminotransferase elevation predominates;
- hepatic tumors and metastases – cytolysis progression parallels rising alkaline phosphatase; GGT may exceed normal by up to 14-fold; elevated in 90 % of patients with hepatic metastases; normal levels virtually exclude metastasis; serial measurement may indicate chemotherapy response;
- hepatic congestion – especially chronic; GGT may rise 5-fold; acute congestion (e.g., portal vein thrombosis) shows smaller increases relative to AST and LDH;
- isolated GGT elevation – anticonvulsant medication (values >3× upper limit are usually unrelated to therapy), fatty liver, subclinical biliary obstruction, space-occupying hepatic lesions, congestive heart disease, alcoholic etiology;
- other causes: acute pancreatitis (≈5× normal), acute myocardial infarction, acute renal failure, nephrotic syndrome, renal graft rejection (moderate elevation), diabetes mellitus (mild elevation), brain tumors and hemorrhages (mild elevation), neoplasms especially malignant melanoma, breast cancer, and lung cancer.

Aldolase is an essential enzyme in carbohydrate metabolism, participating in glycolysis. It catalyzes the conversion of fructose-1,6-bisphosphate into dihydroxyacetone phosphate and glyceraldehyde-3-phosphate, a crucial reaction for cellular energy production. Aldolase is present in all tissues but is highly concentrated in the liver, skeletal muscle, and brain. There are three major isoforms: A, B, and C. Isoform B is most specific for hepatocellular injury because it is found exclusively in the liver and is not normally detectable in blood. However, aldolase isoform testing is not yet commonly implemented in routine clinical practice.

Alpha-glutathione-S-transferase (α-GST) belongs to the glutathione-S-transferase (GST) family and plays a key role in cellular detoxification. GSTs facilitate conjugation of glutathione (GSH) with various hydrophobic substrates, enabling the elimination of toxins and xenobiotics. α-GST is predominantly expressed in the liver but is also present in kidneys and intestine. It is a highly sensitive biomarker of hepatocellular injury and useful for early diagnosis of hepatic disorders. Because α-GST is mainly cytosolic, it is released rapidly into the bloodstream following hepatocyte injury often earlier than ALT or AST. Its clinical measurement is not yet widely adopted, despite its superior diagnostic sensitivity in cytolysis.

Coding of Elevated ALT/AST and Abnormal Liver Tests (ICD-10 and ICD-11) When patient history, symptoms, or clinical context suggest an acute or chronic hepatic process, and when the etiology of cytolysis cannot be immediately determined, the following ICD-10 codes may be applied:

R94.5 – Abnormal results of liver function studies.

K75.9 – Inflammatory liver disease, unspecified.

K76.9 – Liver disease, unspecified.

K73.9 – Chronic hepatitis, unspecified.

With the introduction of ICD-11 (2024 revision) and the WHO Reference Guide (2022), coding specificity has significantly improved, allowing more accurate classification of established or excluded diagnoses.

Examples of ICD-11 codes (International Classification of Diseases for Mortality and Morbidity Statistics, 11th Revision; findacode.com/icd-11):

- DB9Z – Unspecified liver disease (includes hepatic dysfunction not classified elsewhere).
- DB95.0 – Toxic or drug-induced liver disease with acute hepatic necrosis or acute hepatitis.
- DB95.Z – Toxic or drug-induced liver disease, unspecified.
- DB95.2Z – Toxic or drug-induced liver disease with cholestasis, unspecified (drug-induced cholestatic injury with pruritus, jaundice, hyperphosphatemia).
- ME23 – Abnormal digestive system function tests, including abnormal liver function test results.

REFERENCE INTERVALS FOR SERUM ALT AND AST LEVELS IN CHILDREN

In children, the normal reference ranges for ALT and AST differ from those established for adults (*Table 1,2*). ALT values are generally considered normal when they are below two times the standard adult upper reference limit. However, no universally accepted pediatric reference intervals exist for ALT and AST. Transaminase levels may be classified as follows: mild elevation – up to 2× the upper limit of normal (ULN); moderate elevation – between 2× and 10× ULN; marked elevation – greater than 10× ULN

It is important to note that normal aminotransferase levels do not exclude underlying liver disease, as individuals with end-stage liver disease and minimal residual hepatic parenchyma may present with entirely normal transaminase concentrations.

These values vary according to age group and the specific reference ranges established by the testing laboratory. In general, children tend to have slightly higher upper reference limits than adults, due to increased metabolic activity during periods of growth and development [1,2,6].

Table 1

Upper reference limits for serum ALT levels (U/L), stratified by sex and age [2]

Age / Sex	0-18 months	> 18 months	12-17 years
Boys	60 U/L	40 U/L	25.8 U/L
Girls	55 U/L	35 U/L	22,1 U/L

Table 2.

Upper Reference Limits for Serum AST (U/L) Stratified by Age and Sex [2]

Age / Sex	> 12 months	1-4 years	5-8 years	9-18 years
Boys/Girls	>65 U/L	>55 U/L	>50 U/L	>40 U/L

ASSESSMENT OF THE SEVERITY OF CYTOLYSIS SYNDROME IN CHILDREN BASED ON ALT ELEVATION [2]

mild grade: increase between 2 and 5 times above the upper normal reference values.

moderate grade: increase between 5 and 10 times above the upper normal reference values.

severe grade: increase greater than 10 times above the upper normal reference values.

According to the data reported by Lamireau et al. (2014), England et al. (2009), and Schwimmer et al. (2010), the following age- and sex-specific upper reference limits for ALT in children are recommended:

- 3 months to 18 months: 60 U/L in boys and 55 U/L in girls;
- 18 months to 12 years: 40 U/L in boys and 35 U/L in girls;
- 12 to 15 years: 26 U/L in boys and 22 U/L in girls.

THE De RITIS RATIO AND ITS CLINICAL SIGNIFICANCE

The De Ritis ratio (AST/ALT ratio) is an important biochemical marker used in the diagnosis and management of various hepatic and extrahepatic disorders. The ratio was introduced in 1957 by the Italian physician Fernando De Ritis, who first described its usefulness in

differentiating viral hepatitis from alcohol-induced hepatitis. The ratio remains a valuable paraclinical tool because it provides information on the degree of hepatic injury, based on the proportion between AST and ALT. The normal mean value of the ratio is 1.33 ± 0.42, with a range of 0.91-1.75.In primary inflammatory liver diseases, ALT increases more prominently and the De Ritis ratio decreases to 0.2-0.5.

In secondary hepatic involvement, such as cardiogenic hepatic cytolysis, AST increases more prominently and the ratio rises above the upper normal limit. The De Ritis ratio is clinically relevant only when aminotransferase levels are elevated.

Clinical interpretation:

De Ritis ratio < 1: indicates acute hepatocellular injury, such as viral hepatitis A, B, C, D or metabolic dysfunction associated steatotic liver disease (MASLD). Higher ALT compared with AST reflects predominant hepatocellular damage. Most inflammatory liver diseases present with AST/ALT < 1.

De Ritis ratio > 1: usually associated with chronic liver diseases, including cirrhosis or acute alcohol-induced hepatitis in adolescents. Because AST is mainly mitochondrial, its predominance suggests more severe hepatic injury.

De Ritis ratio > 2: strongly indicative of alcohol-related liver injury, either acute or chronic.

ETIOLOGICAL CAUSES OF CYTOLYSIS SYNDROME IN CHILDREN

Cytolysis syndrome in children represents a condition of major clinical relevance. The presence of hepatic cytolysis, its degree of severity, and its etiological causes determine the strategy for both short-term and long-term management. Hepatic cytolysis most frequently develops as a result of hepatocellular injury, accompanied by dystrophy, increased permeability of the hepatocyte membrane, and hepatocellular necrosis of various etiologies.

Depending on the child's age group, different acute or chronic hepatic diseases may be more frequently identified in the presence of cytolysis syndrome (*Figure 1*).

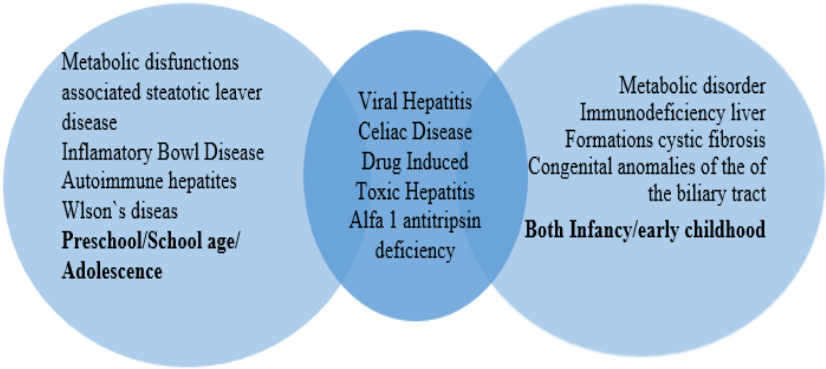

Figure 1. **The most common causes of hypertransaminasemia by age group [1]**

The most common acute and chronic diseases in children that evolve with cytolysis syndrome are presented in Table 3 [2,10,11].

Table 3

Hepatic causes	Extrahepatic causes
Viral: **Primarily hepatotropic viruses:** Hepatitis A, B, C, D, G, E. **Secondarily hepatotropic viruses:** Cytomegalovirus (CMV) Epstein-Barr virus (EBV) Herpes simplex virus (HSV) Varicella-zoster virus (VZV), Rubella virus, Adenovirus	**Myopathies:** Duchenne/Becker muscular dystrophy **Muscle injury:** Trauma Intense physical exertion
Toxic: **Drugs:** psychotropic drugs, anabolic steroids, oral contraceptives, salicylates, sulfonamides, antibiotics, immunosuppressive drugs, antineoplastic agents, anesthetic agents. **Alcohol consumption.**	**Hemolytic disorders:** Autoimmune hemolytic anemia Thalassemia Glucose-6-phosphate dehydrogenase (G6PD) deficiency Disseminated intravascular coagulation (DIC)
Metabolic: Boala hepatică steatozică asociată disfuncției metabolice (MASLD) Deficitul de alfa-1 antitripsină Boala Wilson-Konovalov Hemocromatoza Deficiențe enzimatice congenitale: galactozemia, tirozemia tip 1	**Macro – AST**
Autoimmune liver diseases: Hepatitis autoimmune (AIH) Primary sclerosing cholangitis (PSC)	**Cardiac diseases:** Cardiac anomalies Heart failure Cardiomyopathy
Disorders of bilirubin secretion and transport in cholestatic diseases	**Renal disorders (Nephropathies)**
Bacterial and parasitic diseases: Schistosomiasis Toxoplasmosis Leptospirosis *Entamoeba histolytica* infection	**Thyroid disorders:** Hypothyroidism
Cryptogenic hepatitis	**Adrenal insufficiency**
Neoplasms: Hepatoblastoma Hepatocellular carcinoma (HCC) Gastrinoma Intestinal lymphoma	**Neoplasms:** Lymphoma Leukemia Metastases
Others: Cystic fibrosis Budd-Chiari syndrome	**Others:** Bacterial sepsis Anorexia nervosa Celiac disease Inflammatory bowel disease (IBD)

In infants and young children, cytolysis syndrome is most commonly associated with metabolic disorders, primary immune-deficiencies, various hepatic masses, cystic fibrosis, congenital biliary tract anomalies, as well as viral hepatitis including perinatal infections with hepatitis B, hepatitis C, cytomegalovirus (CMV), herpesviruses, and others. Celiac disease may also manifest after the introduction of wheat-based complementary foods. Additional causes include drug-induced toxic hepatitis and alpha-1 antitrypsin deficiency. In preschool-aged children, school-aged children, and adolescents, the most common causes of cytolysis include viral hepatitis A, B, C, E, CMV, herpesviruses, and others, as well as celiac disease, drug-induced toxic hepatitis, and hepatitis caused by other toxic substances. Alpha-1 antitrypsin deficiency is a very rare cause in this age group. In older children and adolescents, additional etiologies include metabolic dysfunction-associated steatotic liver disease (MASLD), inflammatory bowel diseases (ulcerative colitis, Crohn's disease, eosinophilic colitis), autoimmune hepatitis, Wilson's disease, and hereditary hemochromatosis.

PATHOGENETIC MECHANISMS AND ETIOLOGICAL CAUSES OF HEPATIC CYTOLYSIS SYNDROME IN CHILDREN

Aminotransferases ALT and AST are universal enzymes distributed throughout all human organs and tissues, with the highest concentrations located within hepatocytes. Their release into the systemic circulation occurs through three mechanisms: direct destruction of liver cells, pathological increase in cell membrane permeability, and disruption of intracellular organelles within the hepatocyte cytoplasm (*Figure 2*).

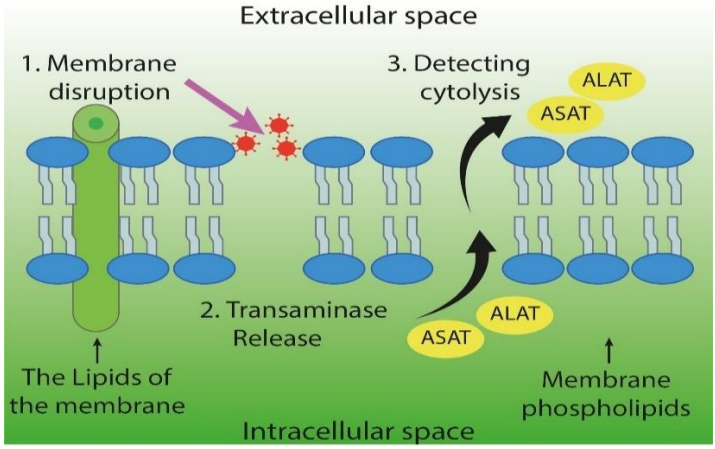

Figure 2. **Pathophysiological mechanism of cytolysis syndrome [3].**

The pathophysiological mechanism underlying the development of cytolysis syndrome depends on the action of certain causative factors (hepatotropic viruses; toxic effects of specific medications and/or alcohol consumption in adolescents; lipotoxicity in metabolic dysfunction associated steatotic liver disease; impaired synthesis and transport of bile acids in cholestatic liver diseases; disturbances in hepatic storage function; enzyme deficiencies; congenital and hereditary disorders;

parasitic liver diseases, and others), toxic injury occurs, leading to membrane disruption, degradation of membrane phospholipids, widening of transmembrane spaces, and release of intracellular hepatic enzymes (ALT and AST) into the extracellular space. Consequently, elevated serum levels of AST and ALT become detectable. In routine clinical practice, increased serum levels of these enzymes often indicate acute or chronic liver injury.

The pathogenetic mechanisms involved in the development of cytolysis syndrome in various diseases include:

1. Non-infectious and infectious inflammatory liver lesions: Viral infections (for example, hepatitis A, B, and C viruses) induce hepatocellular inflammation through activation of the immune system. These viruses penetrate hepatocytes and trigger cell death (apoptosis and hepatocyte necrosis), which leads to the release of hepatic enzymes into the bloodstream [8].

2. Oxidative stress and mitochondrial injury: Oxidative stress generated by free radicals in chronic liver injury, such as metabolic dysfunction-associated steatotic liver disease (MASLD), damages intrahepatic mitochondria and leads to the release of mitochondrial AST. This process exacerbates cytolysis and is associated with progression toward hepatic fibrosis [9].

3. Acute toxic induction of liver injury: Hepatotoxic substances, such as high doses of acetaminophen or alcohol, produce massive hepatic necrosis. These agents damage both the plasma membrane and the mitochondria of hepatocytes, causing cell death through necrotic and apoptotic mechanisms. In cases of severe intoxication, ALT and AST values are markedly elevated.

4. Autoimmunity and immune-mediated hepatic injury: In autoimmune liver diseases, such as autoimmune hepatitis, the immune system mistakenly attacks hepatocytes, leading to chronic inflammation and progressive self-destruction of liver cells. This autoimmune attack is driven by anti-hepatic autoantibodies targeting hepatocellular structures, causing long-term cytolysis.

5. Lipid metabolism dysfunction and impairment of hepatic functions: In the context of lipid metabolism disorders, particularly in metabolic dysfunction-associated steatotic liver disease (MASLD), the liver becomes the central organ responsible for processing an increased flux of lipids and lipoproteins, favoring the development of hepatocellular injury [9]. Lipoproteins play an important role in the pathogenesis of cytolysis syndrome, as they exert toxic effects on hepatocytes during their metabolism while passing through the liver.

In the intestine, fats are absorbed and, under the influence of the intestinal microbiota, enter the portal venous system before being distributed into visceral or subcutaneous fat depots or metabolized by the body. Excessive dietary intake of lipoproteins, which possess pro-inflammatory properties, activates hepatic stellate cells and stimulates the synthesis of tumor necrosis factor (TNF) and collagen. All these processes lead to inflammatory changes within the liver, steatosis and steatohepatitis, ultimately causing hepatic fibrosis. Hepatic cytolysis syndrome involves a complex combination of pathological mechanisms, including inflammation, oxidative stress, mitochondrial injury, and immune dysfunction. Understanding these mechanisms is essential for effective diagnosis and management of both severe acute liver diseases and chronic hepatic disorders.

CLINICAL AND PARACLINICAL EVALUATION OF THE PEDIATRIC PATIENT WITH CYTOLYSIS SYNDROME

The etiological diagnosis of cytolysis syndrome is a complex process that integrates clinical reasoning with paraclinical assessment. It requires a systematic review of the patient's medical and life history, an analysis of previous and current clinical manifestations, as well as a thorough evaluation of laboratory data obtained over time. Family and hereditary background must also be taken into account. This chapter outlines the principal components of a stepwise diagnostic approach, emphasizing the key stages and methods necessary to identify and assess the underlying causes of cytolysis syndrome.

Establishing the etiology of cytolysis syndrome in pediatric patients, and conducting the corresponding differential diagnosis, are essential steps in developing an appropriate diagnostic and therapeutic plan. A careful examination of the patient's history including disease onset and evolution, life circumstances, epidemiological exposures, and immunization status combined with clinical evaluation and laboratory testing, is fundamental. Beyond measuring ALT and AST, assessment of albumin, coagulation factors (Quick time), and the international normalized ratio (INR) provides valuable information regarding both causation and the severity of hepatic injury. A wide range of potential contributing conditions, either acute or chronic, must be considered, together with specific biomarkers that allow differentiation among possible etiologies of cytolysis in children.

When elevated transaminases are identified, the first diagnostic question is whether the cytolysis is of hepatic origin or secondary to extrahepatic conditions, most notably muscular injury. If a hepatic source is suspected, the next step is to determine whether cholestasis is present, as this distinction helps clarify the extent and nature of liver involvement. Once these elements are defined, the underlying cause must be identified to guide appropriate management for treatable conditions.

A comprehensive medical history and detailed clinical examination remain the cornerstone of evaluation. Relevant elements include personal and family histories of hepatic or muscular disorders, metabolic or autoimmune diseases, and any known consanguinity. The clinician should carefully review prior illnesses, associated comorbidities, the timeline of cytolysis, growth and developmental status, anthropometric parameters, dietary habits (such as avoidance of specific food groups), exposure to medications or toxins, and accompanying symptoms. Clinical manifestations vary widely, from asymptomatic cases to acute presentations with nonspecific signs such as fatigue, nausea, vomiting, diarrhea, and weight loss. Jaundice and pruritus may indicate liver involvement, whereas hepatomegaly, splenomegaly, or telangiectasias may suggest chronic liver disease.

Hepatic versus extrahepatic origin of cytolysis. The distinction between elevated transaminase levels of hepatic versus extrahepatic origin is essential. In muscular disorders and myopathies, AST elevation typically predominates, as seen after intense physical exercise, in muscular dystrophies, or in drug-induced muscle injury. Biochemical profiles may assist in this differentiation: a more pronounced increase in ALT compared with AST suggests a hepatic source, whereas the reverse pattern favors an extrahepatic, predominantly muscular origin. In addition, elevated serum creatine phosphokinase (CPK) levels support the presence of a myopathy.

Investigation for macro-AST using polyethylene glycol precipitation and/or electrophoresis is recommended in asymptomatic children with persistently isolated AST elevation. Macro-AST represents a benign macromolecular complex formed by the association or autopolymerization of AST with plasma proteins, most commonly immunoglobulin G (IgG). Due to its large molecular size, macro-AST is not filtered by the renal glomeruli and remains in the circulation. Although clinically benign, it frequently represents a source of diagnostic uncertainty.

Evaluation of liver involvement in patients with cytolysis. If a hepatic origin of the elevated transaminases is suspected, it is necessary to expand the assessment of liver involvement by determining cholestasis markers and evaluating hepatic synthetic function, as well as performing an abdominal ultrasound to identify possible changes in the liver parenchyma such as diffuse hyperechogenicity and to exclude a focal lesion. The primary first-line investigations required, along with their recommended order in the evaluation of elevated aminotransferases in children, are listed below:

- complete blood count (including reticulocyte count);
- C-reactive protein;
- diurnal blood glucose;
- serum electrolytes and acid - base balance;
- evaluation of renal function with serum urea and creatinine, and urinalysis;

- serum creatine phosphokinase;
- hemolysis markers: lactate dehydrogenase, haptoglobin, unconjugated bilirubin;
- cholestasis markers: total and conjugated bilirubin, gamma-glutamyltransferase, alkaline phosphatase, serum bile acids;
- hepatic synthetic function markers: prothrombin time, international normalized ratio (INR), serum albumin, activated partial thromboplastin time, fibrinogen;
- abdominal ultrasound.

SPECIFIC INVESTIGATIONS FOR DETERMINING THE ETIOLOGY OF CYTOLYSIS SYNDROME IN CHILDREN

Once a comprehensive clinical and biochemical profile consistent with hepatic involvement has been established, the next step is to identify the underlying etiology *(Table 4)*.

The child's age is a critical factor, as hypertransaminasemia in newborns and infants may have different causes compared with those in older children.

1. CLINICAL SIGNS AND SYMPTOMS OF CYTOLYSIS IN CHILDREN

1.1. Clinical signs and symptoms.

Cytolysis syndrome may manifest through a wide range of clinical signs and symptoms, which include:

- jaundice of the visible mucous membranes and/or the skin;
- abdominal pain or discomfort in the right upper quadrant;
- fatigue and generalized weakness;
- dark urine;
- pale or acholic stools in the presence of jaundice;
- dyspeptic symptoms: nausea, vomiting, loss of appetite;
- hepatomegaly and/or splenomegaly;
- ascites and lower-limb edema.

1.2. Patient History.

One of the fundamental aspects in diagnosing cytolysis syndrome

is obtaining a complete and accurate patient history. This is of crucial importance, as incorporating detailed information from the patient's medical background may provide significant clues regarding the origin and evolution of the syndrome. Understanding and evaluating risk factors including alcohol consumption, the use of certain medications or drugs, exposure to toxic substances, the presence of comorbidities, and other individual characteristics constitutes an essential component of the diagnostic process.

1.3. Physical Examination of the Patient.

The clinical examination in cytolysis syndrome must be complete and rigorous in order to assess all relevant aspects of the patient's condition and to guide the subsequent investigations and appropriate therapeutic management.

Examination of the skin and mucous membranes should be performed carefully to identify the presence or absence of jaundice, cutaneous rashes, telangiectasias, palmar erythema, or other clinical signs associated with cytolysis.

Examination of the digestive system, with emphasis on abdominal palpation, is essential for detecting the presence or absence of hepatomegaly and/or splenomegaly, ascites, as well as for identifying the presence or absence of pain in the upper abdominal region, which may indicate hepatic or splenic involvement.

Clinical examination and assessment of other organs and systems are important in severe cases of cytolysis in order to identify and manage associated complications:

a) cardiovascular system: examination is essential for detecting cardiac complications such as tachycardia, hypotension, acute and

chronic carditis, and acute or chronic heart failure;

b) respiratory system: cytolysis may represent a secondary manifestation of respiratory involvement, and examination of the respiratory system is important for identifying respiratory symptoms;

c) nervous system: examination is necessary to evaluate possible neurological diseases and complications associated with cytolysis. This may include assessing the level of consciousness, identifying

neurological symptoms (such as confusion or seizures), and detecting meningeal signs;

d) other organs and systems: in severe cytolysis, other internal organs and systems may also be involved, such as the renal, musculoskeletal, hematopoietic, or other extrahepatic or extradigestive systems. Comprehensive examination and evaluation of their functional status are important for identifying and managing complications that may be associated with cytolysis syndrome.

2. LABORATORY INVESTIGATIONS REQUIRED FOR THE EVALUATION OF CYTOLYSIS SYNDROME

2.1. Laboratory Investigations.

Laboratory investigations are essential for determining the etiology and severity of cytolysis syndrome, as well as for evaluating the degree of hepatic inflammation and core liver functions [7]. The initial assessment includes the stepwise evaluation of the following parameters:

Complete blood count:

***hemoglobin and hematocrit*:** decreased levels may indicate iron-deficiency anemia, autoimmune anemia, or anemia secondary to severe hepatic dysfunction, internal bleeding, or dehydration;

leukocyte count: leukocytosis may suggest inflammation or bacterial infection, whereas lymphopenia may indicate viral infection, severe hepatic insufficiency, or autoimmune disease;

***platelet count*:** thrombocytopenia may be present in cirrhosis or other advanced chronic liver diseases, reflecting impaired hepatic production and splenic sequestration. In advanced chronic liver disease, thrombocytopenia is consistent with hypersplenism.

Biochemical Blood Examination:

Total bilirubin and its fractions:

These tests are performed to evaluate disorders of bilirubin metabolism, the association of cytolysis with jaundice, and the severity of jaundice, which may accompany cytolysis syndrome.

An elevation in bilirubin levels indicates hepatic dysfunction or

biliary obstruction. Normal reference values for total bilirubin in children: ≤17-21 μmol/L or ≤1.2 mg/dL, predominantly due to the unconjugated (indirect) fraction.

Lactate dehydrogenase (LDH), total activity:

LDH is an intracellular enzyme present in the kidneys, myocardium, skeletal muscle, liver, brain, and lungs.

It consists of two subunits H (heart) and M (muscle) and is a nonspecific marker of tissue injury.LDH isoenzyme distribution (international medical terminology): LDH-1: cardiac muscle, red blood cells; LDH-2: reticuloendothelial system; LDH-3: lungs; LDH-4: liver, skeletal muscle, kidneys, pancreas; LDH-5: liver and skeletal muscle.

Elevation of: LDH-4 → hepatic, renal, skeletal muscle, pancreatic injury-LDH-5 → hepatocellular injury (cytolysis). Reference values in children remain unchanged (these are numeric, not terminologic).

Alkaline phosphatase (ALP):

Elevated in cholestasis or biliary obstruction. International name: „ALP", not FA or PAL. Pediatric reference intervals depend on age (values as in text). Prothrombin time (PT), International Normalized Ratio (INR), fibrinogen.

These tests evaluate hepatic synthetic function, specifically the liver's ability to produce coagulation factors: PT (Prothrombin Time) – international term, INR (International Normalized Ratio) – universally used. Reference values: PT: 11-13.5 seconds, INR: 0.8-1.1 in healthy children.

Albumin:

Albumin is synthesized in the liver and reflects hepatic synthetic capacity and nutritional status. Reference values remain the same; medical terminology is already standardized („serum albumin"). Urinalysis (urine dipstick and microscopy). International terms: *Bilirubinuria* – conjugated bilirubin in urine, *Increased urobilinogen* – suggests altered bilirubin metabolism or impaired hepatic clearance, *Dark brown* („tea-colored") *urine* – typical in direct hyperbilirubinemia.

2.2. Specific Immunoserologic and Biochemical Tests

A. Serologic markers of acute or chronic hepatic diseases required

for differential diagnosis:

Hepatitis B virus (HBV): HBsAg, anti-HBc IgM and total, anti-HBs, HBeAg, anti-HBe, HBV DNA (semiquantitative or quantitative), and intrahepatic cccDNA (covalently closed circular DNA, double-stranded).

Hepatitis C virus (HCV): anti-HCV IgM and total, HCV RNA (semiquantitative or quantitative).

Hepatitis A virus (HAV): anti-HAV IgM.

Cytomegalovirus (CMV) infection: anti-CMV IgM and IgG, CMV DNA in blood and urine.

Epstein–Barr virus (EBV) infectious mononucleosis: EBV VCA IgM and IgG, EBNA IgG, EBV EA IgG, and quantitative EBV DNA in blood.

Herpes simplex virus (HSV) infection: anti-HSV IgM and IgG.

Autoimmune hepatitis markers:

- antinuclear antibodies (ANA);
- anti-smooth muscle antibodies (ASMA);
- perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA);
- anti-liver kidney microsomal type 1 antibodies (anti-LKM-1);
- anti-LKM-3;
- anti-soluble liver antigen (anti-SLA);
- anti-liver cytosol antibodies (anti-LC).

B. Biochemical parameters for identifying metabolic causes:

- serum glucose;
- glycated hemoglobin (HbA1c);
- total protein and serum protein electrophoresis;
- albumin;
- triglycerides;
- total cholesterol, LDL cholesterol, HDL cholesterol.

Alpha-1 antitrypsin deficiency: Quantitative serum alpha-1 antitrypsin measurement.

Wilson disease (Wilson-Konovalov): Serum ceruloplasmin, serum copper, 24-hour urinary copper, ATP7B gene mutation testing.

Hereditary hemochromatosis: Serum iron, ferritin, HFE gene mutation analysis (C282Y, H63D).

Celiac disease: anti-tissue transglutaminase antibodies (anti-tTG IgA/IgG) anti-deamidated gliadin peptide antibodies (anti-DGP IgA/IgG), anti-endomysial antibodies (EMA IgA/IgG), HLA-DQ2 and HLA-DQ8 genotyping.

Gilbert syndrome: Unconjugated hyperbilirubinemia and UGT1A1 promoter mutation in the absence of hepatocellular cytolysis.

3. INSTRUMENTAL METHODS OF INVESTIGATION IN CYTOLYSIS SYNDROME IN CHILDREN

3.1. Non-invasive and minimally invasive methods

Instrumental methods of investigation are essential for diagnosing and monitoring cytolysis syndrome and can provide valuable information regarding the cause and severity of the associated hepatic condition. The use of these techniques within a comprehensive evaluation may assist in establishing an accurate etiological and clinical-evolutionary diagnosis.

Non-invasive methods

Abdominal ultrasonography: This non-invasive, first-line method uses sound waves to generate detailed images of the liver, gallbladder, portal system, and spleen. Ultrasonography may reveal structural abnormalities such as hepatomegaly or splenomegaly, which can be associated with cytolysis syndrome.

Computed tomography (CT), with or without contrast: Abdominal CT provides detailed images of the liver parenchyma, biliary tract, and abdominal organs. This method can detect hepatic lesions, biliary obstructions, or other conditions that may contribute to cytolysis.

Magnetic resonance imaging (MRI), with or without contrast, including MR cholangiography (MRCP): Abdominal MRI provides precise images of internal organs using magnetic fields and radiofrequency waves. It can offer detailed information on liver structure and function and may be useful for diagnosing chronic hepatic disorders presenting with cytolysis. MRI spectroscopy may provide additional

information regarding the chemical composition of the liver, including fat content, which may be useful for diagnosing and monitoring steatotic liver disease associated with metabolic disorders (MASLD).

Transient elastography (FibroScan): This technique uses ultrasound to measure hepatic tissue stiffness. Increased liver stiffness may be associated with hepatic fibrosis. FibroScan is used to evaluate the degree of fibrosis in chronic liver diseases such as chronic hepatitis or cirrhosis, expressed in kPa and staged as F0, F1, F2, F3, F4.

Minimally invasive methods

Minimally invasive methods of liver investigation involve obtaining liver tissue through biopsy during the patient's lifetime or performing special imaging studies with contrast administration to obtain detailed information about the structure and function of the liver and biliary tract. These methods may be necessary in certain cases for diagnosing and evaluating rare hepatic disorders and diseases of the extrahepatic or intrahepatic biliary tree.

Percutaneous liver biopsy: This procedure involves obtaining a small sample of hepatic tissue using a Menghini needle or a semi-automatic needle, or intraoperatively, for microscopic histologic examination. Liver biopsy remains the **„*gold standard*"** and is performed using a transcutaneous needle inserted blindly, under ultrasound guidance, or under CT guidance. The procedure allows for special staining (for detecting hepatic fibrosis or intracellular copper or iron accumulation), thus providing detailed information regarding the degree of hepatocellular injury, severity of hepatic fibrosis, and other relevant histological changes essential for establishing an accurate etiologic diagnosis, staging the disease, and evaluating prognosis.

Liver biopsy is recommended at 12-18 months after the initial detection of asymptomatic and persistent hypertransaminasemia, in the absence of other signs of chronic liver disease, in patients for whom previous paraclinical evaluation has not identified the cause of cytolysis.

Endoscopic retrograde cholangiopancreatography (ERCP): A minimally invasive procedure combining endoscopy with X-ray imaging

for the diagnosis and treatment of biliary and pancreatic duct obstructions.

Magnetic resonance cholangiopancreatography (MRCP): This MRI-based imaging method generates detailed images of the biliary tract. MRCP may be used for diagnosing biliary obstructions, gallstones, pancreatic stones, and other associated conditions that may present with cytolysis syndrome.

Invasive methods

Hepatic angiography: An invasive imaging method for evaluating hepatic blood vessels, used in hepatic tumors, thrombosis of hepatic vessels, vascular malformations, and portal blockages. The procedure requires the use of contrast under X-ray or magnetic field guidance.

Only a stepwise approach, guided by the chronological medical history of the disease, in correlation with clinical signs and paraclinical and instrumental findings, is essential for establishing the true etiology of cytolysis in children and selecting the correct therapeutic management.

In diagnostically or therapeutically difficult situations, in the presence of signs of acute liver failure and life-threatening risk, referral to specialized pediatric hepatology or toxicology centers- including intensive care is necessary, where extracorporeal detoxification techniques or liver transplantation may be applied when indicated.

INFECTIOUS ACUTE AND CHRONIC LIVER DISEASES

Infectious acute and chronic liver diseases represent an important group of conditions in which the etiologic cause is infection with various pathogens, predominantly hepatotropic viruses (Tables 4, 5, 6, 7). These infections may present in acute or chronic forms and have a significant global health impact, being among the most common causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma.

Acute infectious liver diseases include viral hepatitis A, B, C, D, and E, as well as bacterial, parasitic, and fungal infections that may affect the liver either directly or indirectly.

Viral hepatitis represents the best-known category of infectious liver diseases, characterized by varied modes of transmission- ranging from

exposure to infected blood or other body fluids in hepatitis B, C, and D, to ingestion of contaminated water or food in hepatitis A and E.

Hepatitis B and hepatitis C are particularly important from a public health perspective because they carry a high risk of progression to hepatic cirrhosis and hepatocellular carcinoma.

Hepatitis C, in particular, constitutes a major global health burden, affecting millions of individuals and representing one of the leading causes that frequently lead to liver transplantation due to advanced-stage chronic liver disease.

Besides viral causes, other bacterial and parasitic infections may also affect the liver.

Bacterial infections such as leptospirosis or pyogenic liver abscesses can trigger acute hepatic inflammation and severe acute liver failure.

Similarly, parasitic infections (e.g., schistosomiasis, amebiasis, malaria) are important causes of hepatomegaly and hepatic dysfunction in endemic regions, particularly in low- and middle-income countries.

Another key component of infectious liver diseases is chronic hepatitis. For example, chronic hepatitis B virus (HBV) infection may persist in hepatic tissue for decades, causing long-term inflammation that leads to hepatic fibrosis and eventually cirrhosis. Hepatitis D virus (HDV), a defective virus that requires HBV for replication, worsens the course of hepatitis B and increases the risk of hepatic failure. Hepatitis C virus is likewise characterized by a chronic course in most cases and may also lead to severe long-term complications.

Although hepatotropic viruses such as HBV, HCV, HDV, and HEV are the best studied, the liver can also be affected during systemic infections caused by viruses such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), and herpes simplex virus (HSV).

Table 4

Infectious Acute and Chronic Liver DiseasesAcute Viral Hepatitis in Children

Disease	Etiology	Clinical Manifestations	Criteria diagnostic	
			Specific Laboratory Test	Imaging Modalities
Acute Viral Hepatitis A (HAV)	HAV. It is transmitted through the fecal-oral route. The incubation period ranges from 2 to 6 weeks, with an average duration of about 28 days.	Fever, jaundice, nausea, abdominal pain, fatigue, dark urine, pale stools, hepatomegaly, and biochemical evidence of hepatocellular injury.	Anti-HAV IgM positive, total anti-HAV, HAV RNA detectable in stool samples.	Abdominal ultrasound
Acute Viral Hepatitis B (HBV)	HBV. Transmission occurs through blood and other bodily fluids, as well as via contaminated objects. Vertical transmission may occur from mother to infant, while horizontal transmission can arise from chronically infected household contacts. The average incubation period is approximately 90 days.	Abdominal pain, fever, arthralgia, nausea, vomiting, fatigue, jaundice, dark urine, hepatomegaly, or the infection may be asymptomatic.	HBsAg +; Anti-HBs −; Anti-HBc IgM +; Total anti-HBc; HBeAg +; Anti-HBe −; HBV DNA +.	Abdominal ultrasound
Chronic Hepatitis C Infection (HCV)	HCV. Transmission occurs through blood exposure, sexual contact, the use of shared or non-sterile needles and syringes, and, more rarely, perinatally. The incubation period ranges from 45 to 160 days.	Approximately 80% asymptomatic; in symptomatic cases: fatigue, jaundice, dark urine, hepatomegaly, hepatocellular injury.	anti-HCV IgM +/−; total anti-HCV +; HCV RNA +/−; genotype 1-6.	Abdominal ultrasound
Acute Viral Hepatitis E (HEV)	HEV. Transmission is fecal–oral for genotypes 1-2; zoonotic transmission of genotypes 3-4 occurs through the consumption of pork, or inadequately cooked meat. The incubation period ranges from approximately 15 to 60 days.	Symptomatic cases may present with fever, fatigue, arthralgia, edema, rash, nausea, vomiting, pruritus, jaundice, abdominal pain, anorexia, diarrhea, hepatomegaly; the infection may also be asymptomatic.	anti-HEV IgM +; HEV RNA in blood; HEV RNA in stool; genotypes 1, 2, 3, 4.	Abdominal ultrasound

Table 5

Chronic Viral Hepatitis in Children

Disease	Etiology	Clinical Manifestations	Criteria diagnostic	
			Specific Laboratory Test	**Imaging Modalities**
Chronic Hepatitis / Chronic Viral Hepatitis B	HBV, persistence of infection for more than 6 months.	Symptomatic: fatigue, with or without jaundice, hepatomegaly, hepatocellular injury. Asymptomatic: hepatomegaly with cytolysis.	HBsAg +; anti-HBs −; anti-HBc IgM −; total anti-HBc +; HBeAg +/−; anti-HBe +/−; HBV DNA + (low, moderate, or high viral load).	Abdominal ultrasound; Elastography (Fibroscan); FibroTest; abdominal MRI/CT.
Chronic Viral Hepatitis C	HCV, persistence of infection for more than 6 months.	In symptomatic cases: marked fatigue, jaundice, hepatomegaly, hepatocellular injury.	anti-HCV IgM −; total anti-HCV +; HCV RNA +.	Abdominal ultrasound; Elastography (Fibroscan); FibroTest; abdominal MRI/CT.
Chronic Hepatitis D (HDV Superinfection)	HDV transmitted through blood and body fluids, contaminated objects; in children, vertical transmission from mother to infant.	Fever, fatigue, jaundice, dark urine, hepatomegaly, splenomegaly.	HBsAg +; anti-HBs −; anti-HBc IgM −; total anti-HBc +; HBeAg +/−; anti-HBe +/−; HBV DNA +; anti-HDV IgM +/−; total anti-HDV +; HDV RNA + (variable viral load).	Abdominal ultrasound; Elastography (Fibroscan); FibroTest; abdominal MRI/CT.

Table 6

Viral Infections in Children Caused by Hepatotropic Viruses

Disease	Mode of Transmission	Clinical Manifestations	Criteria diagnostic	
			Specific Laboratory Test	Imaging Modalities
Cytomegalovirus (CMV) Infection	Transmission through direct contact with bodily fluids (blood, saliva); vertical transmission from a chronically infected mother; intrauterine transplacental transmission; postnatal transmission.	Prolonged fever or low-grade fever, severe fatigue, sore throat, lymphadenopathy, hepatomegaly or splenomegaly.	anti-CMV IgM +; anti-CMV IgG +; CMV DNA + in blood and urine.	Abdominal ultrasound; cranial ultrasound; brain MRI.
Epstein–Barr Virus (EBV) Infection, Acute Phase	Transmission through saliva or other human bodily fluids; incubation period 4–6 weeks.	Signs of infectious mononucleosis: tonsillitis, fever, regional lymphadenopathy, jaundice, hepatomegaly and/or splenomegaly, cutaneous rash.	Paul–Bunnell +; anti-EBV VCA IgM +; anti-EBV VCA IgG −; anti-EBV EA IgG +; anti-EBV EBNA IgG −; EBV DNA detectable in blood/urine/saliva.	Abdominal ultrasound.
Acute Herpes Simplex Virus (HSV) Infection – Type I and II	HSV-1 transmitted by direct contact with saliva or contaminated secretions; HSV-2 transmitted through sexual contact.	Rare hepatic involvement, mainly in neonates or immunocompromised children: fever, jaundice, severe hepatic necrosis, myocarditis.	anti-HSV IgM +; anti-HSV IgG −; HSV-1 antigen +; HSV-2 antigen +; HSV DNA + in blood or cerebrospinal fluid.	Abdominal ultrasound; cranial ultrasound; brain MRI/CT; EEG.

Table 7

Infectious and Parasitic Diseases Associated With Hepatic Involvement

Disease	Mode of Transmission	Clinical Manifestations	Criteria Diagnostic	
			Specific Laboratory Test	Imaging Modalities
Leptospirosis (Weil's Disease)	Zoonotic disease caused by Leptospira spp.; transmitted to humans through exposure to urine from infected animals.	Fever, cough, headache, myalgia, epigastric pain, non-pruritic rash, diarrhea, vomiting, chills, jaundice, iridocyclitis.	Anti-Leptospira IgM (detectable from day 8 of fever); anti-LeptospiraIgG −/+.	Abdominal ultrasound; chest X-ray; abdominal MRI/CT.
Toxoplasmosis (Toxoplasma gondii)	Zoonotic parasitic infection transmitted through ingestion of contaminated food/water, exposure to contaminated soil or cat feces; vertical transmission possible.	Lymphadenopathy, asthenia, rash, hepatosplenomegaly, fever, jaundice, myocarditis, chorioretinitis, retinal hemorrhages, meningoencephalitis, hydrocephalus.	Toxoplasma gondii IgM + and IgG +; Toxoplasma gondii DNA + in blood or other biological fluids.	Abdominal ultrasound; ophthalmologic examination; abdominal MRI/CT; brain MRI.
Schistosomiasis (Bilharziasis, Katayama Fever)	Parasitic infection caused by Schistosoma spp.; transmission through contact with water contaminated with parasites released by infected freshwater snails.	Abdominal pain, diarrhea, nausea, vomiting, bloody stools, hematuria, dysuria, hepatomegaly, splenomegaly, ascites (advanced stages).	Detection of Schistosoma eggs in stool or urine; blood culture; detection of specific antibodies to Schistosoma antigens in serum.	Abdominal ultrasound; additional imaging as clinically indicated.
Amebiasis (Entamoeba histolytica, Entamoeba dispar)	Fecal–oral transmission through ingestion of cysts in contaminated food or water.	Bloody diarrhea, hepatic or pulmonary abscesses, fever, right upper quadrant pain, hepatomegaly; jaundice (rare).	Stool microscopy; antigen or DNA detection of Entamoeba histolytica (ENHI) in stool; anti-E. histolytica IgG in blood.	Abdominal ultrasound; other investigations as clinically indicated.

CYTOLYSIS SYNDROME AND THE IMPACT OF SARS-COV-2 INFECTION IN CHILDREN

With the declaration of the SARS-CoV-2 pandemic by the World Health Organization (WHO) on March 11, 2020, it was demonstrated that the virus has clinical impact on all internal organs, such as the lungs, heart, kidneys, spleen, and liver. Globally, by May 2021, more than 158 million cases of COVID-19 and more than 3 million COVID-19-associated deaths had been confirmed [18,19]. Hepatic involvement was usually expressed through hepatic cytolysis and was reported, on average, in 50 % of patients hospitalized for COVID-19. Liver involvement in COVID-19 has no specific clinical signs and is confirmed by the presence of hepatic cytolysis syndrome in 14-76 % of cases [18,19]. Hepatic cytolysis has been reported in similar proportions regardless of whether or not the patient had pre-existing liver disease [18,19]. Liver involvement was identified more frequently in males, elderly individuals, and in those with a high body mass index (BMI > 30), predominating in patients with severe or critical forms of COVID-19 [18,19].

Possible pathogenic mechanisms involved in liver injury in COVID-19. SARS-CoV-2 may exert direct cytotoxic action on the liver, either through viral replication in hepatocytes/cholangiocytes or through induction of cellular necrosis or apoptosis. Arguments supporting this hypothesis include: a) hepatocytes and cholangiocytes possess specific receptors for SARS-CoV-2 (angiotensin-converting enzyme 2 – ACE2 receptors); b) liver involvement is present already at hospital admission, before administration of any hepatotoxic treatment; c) SARS-CoV-2 was detected in 68% of post-mortem liver biopsy samples collected from patients with COVID-19. The systemic inflammatory response syndrome associated with COVID-19 infection may trigger a nonspecific hepatic reaction, occurring in the second week of illness, concomitant with the „cytokine storm" [18,19]. Exacerbation of pre-existing liver disease may occur, such as chronic HBV or HCV infection, non-alcoholic

steatosis/steatohepatitis, alcoholic steatohepatitis, or metabolic dysfunction-associated steatotic liver disease (MASLD), etc.

Immunosuppressive treatments (corticosteroids, tocilizumab, etc.) used in COVID-19 may determine reactivation of a pre-existing asymptomatic chronic HBV infection. Drug hepatotoxicity associated with medications used in COVID-19 and drug interactions in cases of polypharmacy may lead to accumulation or potentiation of hepatotoxicity.

Hepatic cytolysis usually appears in the second week of COVID-19 evolution and is often present already at hospital admission. Patients do not present specific clinical symptoms. Elevation of ALT and AST values is frequently observed in COVID-19 (14-76 % of hospitalized cases), while elevation of bilirubin values is much more rarely reported (only in 10 % of hospitalized cases). Elevated GGT values have been identified in half of the cases, while alkaline phosphatase values are usually normal. Hepatic cytolysis may persist for a long period, and thus, at clinical improvement and hospital discharge, patients often still present elevated ALT and AST values [18,19]. The clinical implications of liver involvement in COVID-19 are variable, which is why long-term post-COVID-19 monitoring is recommended for patients who manifested hepatic involvement, in order to document its subsequent evolution.

In conclusion, infectious and parasitic liver diseases have major relevance in clinical practice due to their significant impact on hepatic function and the increased risk of progression toward end-stage liver disease. Early diagnosis and prompt therapeutic intervention are essential to prevent long-term complications, and vaccination programs, especially against hepatitis B, may significantly reduce the prevalence of these diseases.

NON-INFECTIOUS ACUTE AND CHRONIC LIVER DISEASES

Non-infectious acute and chronic liver diseases represent a broad spectrum of hepatic disorders that are not caused by an infectious agent. These conditions include metabolic, autoimmune, toxic, and genetic disorders that can lead to inflammation, necrosis, and hepatic fibrosis,

affecting the liver's vital functions (detoxification, synthesis, and nutrient metabolism). These diseases range from mild and reversible forms to severe forms that may progress to liver failure and cirrhosis.

Medical literature indicates that non-infectious liver diseases are caused by multiple factors. Autoimmune hepatitis and primary biliary cholangitis (PBC) are notable examples of autoimmune liver diseases that may cause significant hepatic damage. In autoimmune hepatitis, an aberrant immune response targets hepatocytes, leading to chronic inflammation and necrosis. This condition may progress rapidly if not diagnosed and treated appropriately with immunosuppressive therapy. Similarly, primary sclerosing cholangitis (PSC), a rare inflammatory disease of the bile ducts, can lead to chronic cholestasis and, ultimately, cirrhosis. In addition to autoimmune diseases, toxic hepatitis caused by exposure to hepatotoxic medications, alcohol, or chemical substances plays an important role in the development of liver injury. Alcoholic hepatitis and drug-induced hepatitis, particularly during adolescence, represent an important medical and social issue and a major cause of acute or chronic liver disease worldwide. Chronic alcohol exposure leads to hepatic steatosis, inflammation, and fibrosis, eventually culminating in cirrhosis and severe hepatic complications.Another important group of non-infectious disorders includes hereditary diseases such as cystic fibrosis, which may cause progressive liver damage if not properly managed. These metabolic diseases require early diagnosis and continuous monitoring in order to prevent severe complications. Non-infectious acute and chronic liver diseases constitute a heterogeneous group of conditions that require rapid diagnosis and careful management to prevent progression toward fulminant or advanced stages of liver disease (*Tables 8, 9*).

Table 8

Non-infectious Acute and Chronic Liver Diseases

Disease	Etiology	Clinical Manifestations	Diagnostics	
			Laboratory Tests	Imaging Studies
Toxic Liver Injury	Exposure to hepatotoxic medications (paracetamol, antibiotics, statins); alcohol; industrial toxins; toxic plants; poisonous mushrooms.	Fatigue, jaundice, abdominal pain, hepatomegaly.	ALT, AST, total and direct bilirubin, albumin, Quick test; toxicology tests for toxin detection.	Abdominal ultrasound; abdominal MRI/CT.
Autoimmune Hepatitis (AIH)	Autoimmune disease in which the immune system attacks hepatocytes; triggering factors include genetic predisposition and infections.	Fatigue, jaundice, joint pain, hepatomegaly.	ANA, ASMA, p-ANCA, anti-LKM1, anti-LKM3, anti-SLA.	Abdominal ultrasound; liver biopsy.
Primary Sclerosing Cholangitis (PSC)	Chronic inflammatory and fibrosing disease of the large and small bile ducts; etiology unknown.	Fatigue, jaundice, pruritus, recurrent episodes of cholangitis (intra- and extrahepatic).	C-reactive protein, ALP, GGT, total and direct bilirubin, ALT, AST, albumin, total protein, coagulation panel; ANA, ASMA, p-ANCA.	Abdominal MRI/CT; ERCP; abdominal ultrasound with color Doppler; liver biopsy; MRCP.
Cholestatic Disorders	Impaired bile flow due to primary biliary cholangitis (PBC), PSC, biliary tumors, or biliary lithiasis.	Jaundice, pruritus, hepatomegaly, cholestasis; possible cirrhosis.	ALT, AST, ALP, GGT, total and direct bilirubin, serum bile acids.	Abdominal ultrasound; abdominal MRI/CT; MRCP; ERCP.

Table 9

Cytolysis in Selected Rare Pediatric Liver Diseases

Disease	Etiology	Clinical Manifestations	Diagnostics	
			Laboratory Tests	Imaging Studies
Hepatic Neoplasms (Tumors)	Primary tumors (hepatocellular carcinoma, hepatoblastoma) or metastatic tumors (from colon, breast, lungs).	Abdominal pain, weight loss, jaundice, hepatomegaly.	ALT, AST, total and direct bilirubin, LDH, ALP, GGT, total protein, albumin; alpha-fetoprotein (AFP); organ-specific tumor markers.	Abdominal ultrasound; abdominal MRI/CT with or without contrast; liver biopsy.
Cryptogenic Hepatitis	Unknown cause; possible undetected autoimmune or metabolic factors.	Fatigue, jaundice, hepatomegaly, progressive hepatic cirrhosis.	ALT, AST, total and direct bilirubin, LDH, ALP, GGT, total protein, albumin; exclusion of other causes.	Abdominal ultrasound; abdominal MRI/CT; liver biopsy.
Cystic Fibrosis	Mutations in the CFTR gene affecting mucus production in exocrine glands.	Jaundice, hepatomegaly, liver failure, respiratory symptoms.	Sweat test; fecal elastase-1; ALT, AST, total and direct bilirubin, amylase, lipase; CFTR genetic testing.	Abdominal ultrasound; abdominal MRI/CT; pulmonary function test; liver biopsy (in severe cases); chest X-ray; chest CT scan.
Budd–Chiari Syndrome	Obstruction of hepatic veins due to thrombosis or external compression.	Acute abdominal pain, ascites, edema, hepatomegaly, jaundice, abdominal distension.	Coagulation panel, D-dimer, ALT, AST, total and direct bilirubin, ALP, GGT, albumin, Quick test, INR, fibrinogen, and others.	Abdominal ultrasound with color Doppler of portal vessels; abdominal MRI/CT; portal venography; portal vein angiography; liver biopsy.

CYTOLYSIS SYNDROME IN METABOLIC DISEASES IN CHILDREN

Metabolic liver diseases constitute a heterogeneous group of disorders characterized by disturbances in fundamental biochemical pathways, resulting either in the accumulation of hepatotoxic substrates or in metabolic defects that directly impair hepatocyte function. The liver is commonly involved given its central role in nutrient metabolism, detoxification processes, and the synthesis of essential proteins. Evidence indicates that several metabolic conditions are frequently associated with cytolysis, mediated either by inherited enzymatic defects or by the buildup of toxic metabolites. Representative disorders include Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency, and a range of lipid metabolism abnormalities. These conditions contribute to increased oxidative stress, chronic inflammatory activity, and progressive hepatocellular injury (Table 10).

Metabolic disorders may be classified according to the nature of the biochemical impairment, including disorders of metal metabolism such as iron overload in hemochromatosis and copper accumulation in Wilson's disease as well as abnormalities in carbohydrate and lipid metabolism. Metabolic dysfunction-associated steatotic liver disease (MASLD) illustrates the contribution of lipid accumulation to hepatic inflammation, necrosis, and subsequent cytolysis, which often reflects disease progression. In numerous cases, cytolysis precedes the development of advanced hepatic complications, including fibrosis, cirrhosis, and hepatocellular carcinoma.

Early identification of metabolic diseases associated with cytolysis and implementation of targeted therapeutic strategies are essential to prevent progression toward hepatic failure. Accurate diagnosis typically requires an integrated approach combining clinical assessment, biochemical evaluation, genetic testing, and both non-invasive and invasive imaging techniques to ensure appropriate disease characterization and to reduce the risk of long-term complications.

Table 10

Pediatric Metabolic Diseases Frequently Associated with Cytolysis

Disease	Etiology	Clinical Manifestations	Diagnostics	
			Laboratory Tests	**Imaging Studies**
Wilson's Disease	Autosomal recessive disorder caused by mutations in the ATP7B gene, leading to excessive copper accumulation in parenchymal organs.	Acute hepatitis, cirrhosis, neurological symptoms (tremor, muscle rigidity), Kayser–Fleischer rings.	Serum copper, ceruloplasmin, 24-hour urinary copper.	Abdominal ultrasound; liver biopsy; abdominal MRI.
Hereditary Hemochromatosis	Genetic disease caused by HFE gene mutations, resulting in excessive iron accumulation in parenchymal organs.	Hepatomegaly, fatigue, diabetes, advanced hepatic cirrhosis.	Ferritin, serum iron, transferrin.	Abdominal ultrasound; abdominal MRI; liver biopsy.
Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD)	Accumulation of fat within hepatocytes, associated with obesity, type 2 diabetes, dyslipidemia, metabolic syndrome.	Most patients are asymptomatic; may present fatigue, abdominal discomfort, hepatomegaly.	Glucose, albumin, triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol.	Abdominal ultrasound; transient elastography (FibroScan); MRI/CT; liver biopsy.
Alpha-1 Antitrypsin Deficiency	Genetic disorder caused by mutations in the SERPINA1 gene leading to hepatic accumulation of misfolded protein.	Hepatomegaly, jaundice, respiratory symptoms (emphysema).	Serum alpha-1 antitrypsin level.	Abdominal ultrasound; liver biopsy.
Galactosemia	Deficiency of the enzyme galactose-1-phosphate uridyltransferase (GALT), impairing galactose metabolism.	Neonatal jaundice, vomiting, hepatomegaly, liver failure, developmental issues.	Blood galactose level, GALT activity testing, newborn screening.	Abdominal ultrasound.
Tyrosinemia Type 1	Deficiency of fumarylacetoacetate hydrolase (FAH), leading to accumulation of hepatotoxic metabolites.	Hepatomegaly, liver failure, increased risk of cirrhosis and hepatocellular carcinoma.	Elevated urinary succinylacetone; genetic testing for FAH mutations.	Abdominal ultrasound.
Gaucher Disease	Deficiency of the enzyme glucocerebrosidase, causing accumulation of glucocerebrosides in liver and spleen.	Hepatosplenomegaly, anemia, thrombocytopenia, bone pain.	Quantitative glucocerebrosidase assay; GBA gene mutation testing.	Abdominal ultrasound.

Table 11

Extrahepatic Diseases in Children That Present With Cytolysis Syndrome

Disease	Etiology	Clinical Manifestations	Laboratory Tests, Instrumental Investigations
Myopathies: Duchenne/Becker muscular dystrophy Traumatic muscle injury: Hereditary hematologic disorders: Hereditary hemoglobinopathies (α- and β-thalassemia, sickle cell disease, methemoglobinemia), etc.; Hemolytic anemias (autoimmune, drug-induced, aplastic, hemolysis in glucose-6-phosphate dehydrogenase deficiency – G6PD); Coagulopathies (hereditary, disseminated intravascular coagulation – DIC).	Genetic muscle disorders that lead to the release of muscle enzymes into the bloodstream. Muscle trauma and excessive physical exertion may induce the release of AST from muscle cells. Hereditary defects of the hemoglobin molecule or of its synthesis rate. Increased destruction of erythrocytes.	Progressive muscle weakness, gait difficulties. Muscle pain, severe fatigue, muscle cramps, dark-colored urine. Mild to severe hemolytic anemia, jaundice, fatigue, pain crises/sickle cell crises, splenomegaly. Transfusion dependence in hemoglobinopathies or need for iron chelation therapy. Acute syndromes involving internal organ damage.	Marked elevation of ALT and AST, total creatine kinase (CK), LDH; genetic testing. Electromyography, muscle MRI, muscle biopsy with immunohistochemistry and immunofluorescence. Elevation of ALT, AST, and indirect bilirubin associated with hemolysis; abnormalities in the complete blood count, red blood cells and hemoglobin, platelet count; ferritin and transferrin saturation; G6PD deficiency. Deficiency of coagulation factors. Determination of genetic mutation types, testing for abnormal hemoglobin and DNA analysis.
Macro-aspartate aminotransferase (Macro-AST)	A rare benign condition in which AST binds to immunoglobulins and becomes less degradable. Its etiology is not clearly defined. AST appears elevated without true hepatic injury. It may be observed in MASLD.	This is not a disease and does not present symptoms or health risks.	Isolated elevation of AST caused by macro-AST, with normal ALT. Testing for macro-AST using polyethylene glycol (PEG) precipitation. Abdominal ultrasound.
Cardiac diseases: congenital heart defects, cardiomyopathies with heart failure	Chronic venous congestion leads to hepatic ischemia and cytolysis.	Peripheral edema, ascites, hepatomegaly, fatigue.	Significant elevations of ALT and AST associated with clinical, laboratory, and imaging evidence of cardiac involvement.

Malignant hematologic diseases: hepatic T-cell lymphoma, leukemia, hepatic metastases, myeloma (etc.).	Infiltration of the liver by neoplastic cells leads to hepatocyte destruction.	Fatigue, weight loss, jaundice, hepatomegaly, splenomegaly.	Elevated ALT and AST, increased LDH, associated with the corresponding clinical, laboratory, and instrumental findings.
Sepsis, septicemia	A severe bacterial or fungal condition with toxic involvement of the liver.	Loss of appetite, nausea, vomiting, pain, cold extremities, lethargy, anxiety, confusion, agitation, fever, severe general condition, hemorrhagic rash, jaundice. Signs of generalized infection, purulent foci.	Elevated ALT and AST. Complete blood count, CRP, positive blood cultures, bacteriological testing of urine samples, wound secretions, and respiratory secretions. X-ray imaging, CT scan, MRI, ultrasound of abdominal organs and lungs.
Anorexia nervosa	Severe malnutrition and catabolism impair hepatic metabolism, leading to steatosis and cytolysis.	Extreme weight loss, dry skin, fragility, behavioral and appetite disturbances, anxiety-related symptoms.	Moderate elevations of ALT and AST.
Celiac disease	Chronic autoimmune inflammation of the small intestine with intestinal villous atrophy, rarely with hepatic involvement, occurring in genetically predisposed individuals consuming gluten-containing foods.	Diarrhea or constipation, recurrent abdominal pain, intestinal malabsorption syndrome, weight stagnation and growth failure, osteoporosis, and other systemic manifestations.	Elevated ALT and AST associated with positive anti-tTG IgA, serologic IgG, anti-DGP IgA, anti-endomysium IgA, HLA-DQ2/DQ8 positivity, and intestinal villous atrophy (Marsh 1-3).
Inflammatory bowel disease: ulcerative colitis (UC), Crohn's disease (CD)	Systemic inflammation with colonic involvement in UC; involvement of any part of the gastrointestinal tract in CD, predominantly the distal small intestine and the proximal large intestine; hepatic involvement may occur, leading to cholangitis or cytolysis.	Abdominal pain, diarrhea, rectal bleeding, weight loss.	Elevated ALT and AST, increased GGT, associated with specific inflammatory markers: elevated calprotectin, positive anti-ANCA/anti-ASCA, colonoscopy with characteristic endoscopic and histomorphological changes, intestinal sonography, abdominal CT, MRI, video-colonoscopy.

Chapter IV

DIFFERENTIAL DIAGNOSIS OF CYTOLYSIS SYNDROME IN CHILDREN

Aminotransferases are essential enzymes involved in protein metabolism and play a key role in normal hepatic function. The two principal enzymes, ALT and AST, are widely used as serum biomarkers in the assessment of liver function. Elevated serum levels of these enzymes may serve as important indicators of hepatocellular injury but can also reflect a variety of systemic disorders. Therefore, establishing a differential diagnosis for aminotransferase elevation is crucial to identifying the underlying cause and initiating appropriate therapy.

Increased ALT and AST levels are not specific to liver disease; they may result from numerous conditions, including muscular, cardiovascular, metabolic, or renal disorders. Differentiating between hepatic and extrahepatic causes of aminotransferase elevation represents a frequent diagnostic challenge for clinicians.

Marked elevations of aminotransferases, typically exceeding 10–20 times the upper limit of normal, are most commonly associated with severe acute hepatic injury such as acute viral hepatitis, drug- or toxin-induced hepatitis, or ischemic hepatitis (*Table 11*). In these scenarios, a rapid rise in aminotransferases reflects extensive hepatocellular necrosis and requires urgent medical evaluation to prevent progression to acute liver failure. Conversely, a disproportionately higher AST compared with ALT may point toward a non-hepatic source, such as muscular disease (e.g., rhabdomyolysis) or cardiac pathology (e.g., congestive heart failure), as both tissues release AST.

In cases of cytolysis characterized by predominant ALT elevation and an AST/ALT ratio <1, the clinician must initially investigate to exclude or confirm the following conditions: drug-induced or toxin-induced hepatitis, acute viral hepatitis (A, B, C, D, E), and acute hepatocellular injury due to industrial toxins or accidental poisonings

(chemical agents, heavy metals). Once life-threatening conditions are ruled out, further targeted laboratory and imaging assessment is required to evaluate less common pediatric liver diseases such as autoimmune hepatitis, MASLD, Wilson disease (acute hepatic crisis), α1-antitrypsin deficiency, hereditary hemochromatosis, congestive hepatopathy, benign or malignant hepatic tumors, and hepatic metastases.

When cytolysis presents with predominant AST elevation and an AST/ALT ratio ≥1, differential diagnosis should include alcohol-related fatty liver disease, cirrhosis associated with MASLD, progressive chronic viral hepatitis (B, C, D), or untreated Wilson disease.

The diagnostic workup for cytolysis in children can be conducted according to the algorithm outlined in Table 11 and Figures 5 and 6.

Cytolysis in pediatric patients must be differentiated from conditions such as muscle injury due to abdominal trauma or excessive physical exertion, primary myopathies, heart failure and myocardial infarction in older children, hepatic ischemia occurring in adolescents with anorexia nervosa, thyroid disorders, and celiac disease (including celiac crisis). Cases of severe cytolysis warrant expedited diagnostic evaluation to rapidly identify or exclude the primary etiologies listed in Tables 11, 12, 13.

In conclusion, elevated aminotransferases are important serum indicators encountered in both hepatic and extrahepatic diseases. Determining the specific underlying cause requires a comprehensive evaluation that includes clinical history, physical examination, laboratory testing, imaging assessment, and serologic studies to exclude infectious, autoimmune, and metabolic disorders. Accurate diagnosis and differentiation of potential etiologies are essential for optimal management and prevention of complications.

Table 12

Causes of Severe Cytolysis with ALT >10× Upper Limit of Normal

Hepatic Diseases	**Extrahepatic Diseases**
Acute toxic injury: Acetaminophen (paracetamol) intoxication Idiosyncratic drug reactions Mushroom poisoning	**Facultative hepatotropic viruses:** Cytomegalovirus (CMV) Epstein-Barr virus (EBV) Herpes simplex virus (HSV) Varicella, Rubella, ECHO viruses
Wilson's disease	**Sepsis**
Partial hepatopathy	**Heat stroke**
Hepatitis: Viral hepatitis A, B, C, D, E Alcoholic fatty liver disease Autoimmune hepatitis Ischemic hepatitis	**Muscular disorders:** Acquired muscle disorders Polymyositis Muscle cramps Intense physical exertion Long-distance running
Budd-Chiari syndrome (hepatic veno-occlusive disease)	**Malignant tumors**: Breast cancer Small-cell lung cancer Lymphoma Melanoma or myeloma
Sinusoidal obstruction syndrome (hepatic veno-occlusive disease)	**HELLP syndrome**: Hemolysis Elevated liver enzymes Low platelet count

Table 13

Classification of Cytolysis According to the Main Causes in Children and the Recommended Investigations

Etiology	**Recommended Investigations**
Viral infections (HAV, HBV, HCV, HEV, CMV, EBV, HSV-1/2, HHV-6/7, enterovirus, adenovirus, rotavirus, parvovirus, echovirus)	Serological tests for acute and chronic phase antibodies; molecular tests (e.g., HBV DNA or HCV RNA using PCR).
Bacterial infections (Salmonella spp., tuberculosis, Bartonella, sepsis)	Blood cultures.
Toxic agents/drugs	Determination of serum/plasma concentrations of the suspected drug; RUCAM score to assess probability of drug-induced liver injury.
Metabolic diseases: Metabolic dysfunction-associated steatotic liver disease (MASLD), Wilson disease, Hereditary hemochromatosis	Blood glucose, lipids (cholesterol and fractions, triglycerides); serum ceruloplasmin, 24-hour urinary copper, slit-lamp exam, ATP7B gene testing; serum iron, ferritin, HFE genotyping (C282Y, H63D).
Other rare metabolic disorders: Alpha-1 antitrypsin deficiency, Inborn errors of metabolism: galactosemia, tyrosinemia, glycogen storage diseases, mitochondrial diseases, hereditary fructose intolerance, lysosomal acid lipase deficiency	Serum alpha-1 antitrypsin level, phenotype/genotype; blood glucose, blood gases, ammonia; plasma and urinary amino acid profile; urinary organic acids; serum succinylacetone; lysosomal acid lipase activity.
Endocrine disorders: (hypo-/hyperthyroidism, hypocortisolism, panhypopituitarism, growth hormone deficiency)	TSH, FT4, ACTH, serum cortisol, GH, IGF-1 (insulin-like growth factor-1).
Autoimmune hepatitis, sclerosing cholangitis	Serum IgG; autoantibodies: ANA, ASMA, anti-LKM1, anti-LC1; liver biopsy; MRCP (magnetic resonance cholangiopancreatography).
Celiac disease	Total serum IgA, anti-tTG IgA and IgG, anti-DGP IgA, anti-endomysium IgA.
Cystic fibrosis	Sweat chloride test; CFTR gene mutation analysis; imaging of hepatobiliary complications.

CONSEQUENCES OF CYTOLYSIS SYNDROME

Cytolysis, defined as the destruction of hepatic or extrahepatic cells, occurs through the action of antibodies directed against antigens within human cell membranes or against cells on which microbial or drug-related antigens have been deposited. Clinically, it may manifest as anemia, thrombocytopenia, autoimmune leukopenia, thyrotoxicosis, and acute or chronic glomerulonephritis, as well as pernicious anemia.

In the absence of appropriate etiopathogenetic treatment, all liver diseases that present with cytolysis may progress to fibrotic changes driven by acute or chronic-sometimes severe or fulminant-inflammation. According to the typical natural history of hepatic diseases, regardless of the underlying etiology, approximately 30 % of hepatitis cases with persistent cytolysis may progress over a 10-year period to liver cirrhosis, portal hypertension, ascites, esophageal or rectal varices, and chronic liver failure with hepatic encephalopathy.

Progressive hepatic necrosis reduces the number of functional hepatocytes and diminishes the effective liver mass, clinically manifesting as acute or chronic hepatic failure accompanied by dystrophic changes in multiple organs and tissues, as well as cachexia. Long-standing cytolysis with persistent inflammatory activity constitutes a risk factor for the development of hepatocellular carcinoma in 2-5 % of patients.

Chapter V

PRINCIPLES OF TREATMENT IN CYTOLYSIS SYNDROME IN CHILDREN

Cytolysis syndrome in children is not a standalone diagnosis but rather an indicator of an underlying pathological process affecting the liver. Management therefore requires both identification and treatment of the causal condition, as well as protection of the liver from further injury. According to current scientific literature, treatment of cytolysis in pediatric patients follows a multidisciplinary approach that includes etiologic therapy, hepatoprotective strategies, and adequate nutritional support. As outlined in previous chapters, a wide variety of conditions may lead to hepatocellular injury, including acute and chronic viral hepatitis, metabolic liver diseases, autoimmune hepatitis, and toxic or drug-induced hepatic injury. Consequently, therapy must be individualized and tailored to the specific etiology responsible for cytolysis.

The fundamental principles of treatment focus on eliminating the primary cause of hepatocellular damage through well-established therapeutic interventions such as antiviral agents in chronic viral hepatitis B, C, or D, or metal-chelating therapy in metabolic liver diseases such as Wilson disease and hereditary hemochromatosis. In severe cases, particularly when progression toward acute liver failure or life-threatening complications is observed, extracorporeal therapies including plasmapheresis, liver dialysis, hemodialysis, or liver transplantation - represent essential therapeutic options.

Supporting and preserving hepatic function through hepatoprotective agents and providing optimal nutritional care are key components in preventing disease progression and improving long-term outcomes in pediatric patients. Recent literature also highlights the importance of continuous monitoring to assess treatment response and to adjust therapeutic strategies according to the child's clinical evolution.

Thus, management of cytolysis syndrome in children is a complex process that requires early intervention and a holistic, evidence-based approach to prevent severe complications and improve quality of life.

The primary objective of therapy is to restore hepatocyte membrane integrity and reduce ongoing cytolysis, thereby limiting hepatic injury and lowering the risk of subsequent complications. Achieving this goal involves a multifaceted strategy incorporating several components detailed below.

Pathogenetic Treatment with Hepatoprotective Agents

According to the treatment standards of the European Association for the Study of the Liver (EASL) and ESPGHAN, hepatoprotective agents are recommended for the functional restoration of hepatocyte membranes and reduction of the cytolysis syndrome. Hepatoprotectors are medications or supplements used to protect and support liver function, particularly in the context of hepatic injury such as cytolysis syndrome. These substances act to reduce inflammation, prevent further destruction of hepatocytes, and promote regeneration of the affected hepatic tissue.

In children with cytolysis syndrome, hepatoprotective agents are often an integral part of the treatment plan, alongside etiologic therapy directed at the primary cause of the liver disease. These agents represent a diverse group of medications with different chemical structures and mechanisms of action. They include products of plant origin, homeopathic preparations, animal-derived products, and synthetic agents. Among hepatoprotectors, essential phospholipids, milk thistle preparations (silibinin), ademetionine, and ursodeoxycholic acid are most frequently distinguished. Ademetionine is not recommended for children under 18 years of age. The most commonly used hepatoprotective agents are described below.

Ursodeoxycholic Acid (UDCA)

Ursodeoxycholic acid is a choleretic hepatoprotector used especially in cholestatic liver diseases such as primary biliary cholangitis and primary sclerosing cholangitis. UDCA helps improve bile flow and protects hepatocytes from damage caused by the accumulation of toxic

bile acids. Mechanism of action: UDCA reduces the toxicity of hydrophobic bile acids and stimulates bile secretion. It also has anti-inflammatory and anti-apoptotic effects on hepatocytes. Indications: cholestasis, cholestatic liver diseases, and other conditions involving bile stasis; conservative lithotripsy in biliary lithiasis. Administration: administered orally, with the dose adjusted according to age and weight of the child and based on the underlying disease. In children and adolescents aged 1 month to 18 years, doses of 10-12-15-20 mg/kg are given as oral suspension 250 mg/5 ml in 2-3 doses or capsules 250 mg per capsule, for a duration determined individually, up to 3-6 months.

Silymarin (Milk Thistle Extract)

Silymarin is a complex of flavonoids extracted from *Silybum marianum* (milk thistle) and is well known for its antioxidant and anti-inflammatory properties. Mechanism of action: Silymarin stabilizes hepatocyte membranes and inhibits toxin penetration into hepatocytes. It also stimulates protein synthesis in the liver and promotes hepatocyte regeneration. Silymarin additionally has antioxidant effects, protecting the liver from free radical damage. Indications: chronic viral hepatitis, toxic hepatitis, metabolic liver diseases, and hepatic disorders associated with cytolysis syndrome. Administration: administered as 35 mg tablets for young children in powdered form or 70-140 mg capsules for older children; dosing is adjusted by age: 1 tablet (capsule) 2-3-4 times daily for up to 3 months.

S-adenosyl-L-methionine (SAMe)

SAMe is a naturally occurring compound involved in metabolic processes and hepatic detoxification. It is a precursor of glutathione, one of the most important antioxidants in the body, and participates in the synthesis of phospholipids, essential components of hepatocyte membranes. Mechanism of action: SAMe supports hepatocyte regeneration, protects the liver from oxidative stress, reduces inflammation, and contributes to glutathione synthesis. Indications: cytolysis syndrome induced by chronic liver diseases, toxic hepatitis, alcoholic hepatitis, and hepatic involvement in metabolic disorders. Administration: administered orally or intravenously,

with careful monitoring of treatment response. (Not recommended in children under 18 years.)

Essential Phospholipids (Essentiale)

Administration: Essentiale may be administered intravenously, diluted in 5-10 % glucose solution as a slow infusion at doses of 3-10 ml for a period of 5-10 days. Oral administration depends on age: children aged 3-5 years typically receive half a capsule twice daily, children aged 5-10 years receive one capsule twice daily, and children older than 10 years receive one capsule three times daily after meals. The recommended duration of therapy is approximately 3 months. Essentiale is contraindicated in children under 3 years of age.

Etiologic treatment

Etiotropic treatment represents the therapeutic approach aimed at eliminating the primary cause of a disease that manifests with cytolysis syndrome, by acting directly on the responsible pathogen, mechanism, or etiologic factor. Over the past five years, advances in medical science have enabled the development of more effective and targeted therapies for a wide spectrum of conditions, including viral and non-viral liver diseases, metabolic disorders, autoimmune diseases, and infectious processes. The use of etiotropic treatment not only alleviates symptoms but also prevents complications and disease progression.

Recent guidelines emphasize the importance of a personalized etiotropic approach, tailored to the specific characteristics of each pathology. For example, in infectious diseases, the administration of antiviral, antibacterial, or antiparasitic agents depending on the identified pathogen is essential for eliminating the infectious agent and preventing further organ damage. In autoimmune diseases, etiotropic treatment includes immunosuppressive and immunomodulatory therapies that target inflammatory and autoimmune mechanisms responsible for tissue destruction, as seen in autoimmune hepatitis or primary sclerosing cholangitis.

Another important example involves etiotropic therapies in metabolic diseases, where interventions aim to correct the underlying genetic or metabolic abnormalities. In Wilson disease, copper chelation

with agents such as D-penicillamine or trientine is crucial to prevent toxic copper accumulation in the liver and other organs. Likewise, in hemochromatosis, regular phlebotomy and iron chelation therapy prevent excessive iron deposition, thereby protecting the liver and other vital organs.

In oncology, etiotropic treatments have advanced considerably, with the introduction of targeted therapies such as tyrosine kinase inhibitors (for example, sorafenib for hepatocellular carcinoma), which selectively target tumor cells while minimizing injury to healthy tissue. This approach, combined with the use of surgical methods according to clinical protocols, including surgical resection, has significantly improved prognosis in cases of hepatic tumors and other neoplasms.

Table 14

Therapeutic Approaches in Selected Infectious and Non-Infectious Liver Diseases

Disease	Treatment
Acute Viral Hepatitis A	Supportive treatment: hydration, dietary regimen. No specific antiviral therapy. Preventive vaccination.
Chronic Hepatitis B	Antivirals: Tenofovir (age >12 years), Entecavir (age >2 years) for chronic hepatitis B. Pegylated interferon (PEG-IFN-α) in selected cases when direct antiviral administration is possible. HepB vaccination according to national immunization schedule.
Chronic Hepatitis C	Direct-acting antivirals (age >3 years): sofosbuvir, ledipasvir, velpatasvir. Anti-HCV vaccine is not available.
Chronic Hepatitis D	Supportive treatment: hydration, correction of electrolyte imbalances. Antiviral therapy with PEG-IFN-α. No specific antiviral therapy available beyond this.
Hepatitis associated with Cytomegalovirus infection	Supportive treatment. Antiviral therapy in severe or generalized disease: ganciclovir, valganciclovir, to prevent viral replication.
Galactosemia	Strict galactose-free diet (elimination of foods containing galactose/lactose, including milk and dairy products).
Alpha-1 Antitrypsin Deficiency	Liver or lung transplantation as indicated; the only curative option for hepatic and pulmonary disease. Life-long alpha-1 antitrypsin replacement therapy in eligible patients; no proven efficacy for pulmonary forms in children.
Hereditary Hemochromatosis	Regular phlebotomies (to eliminate excess iron). Iron chelators: deferoxamine, deferiprone, deferasirox (in severe cases when phlebotomy is not tolerated).
Wilson Disease	Copper chelators: penicillamine, trientine (for elimination of excess copper). Zinc: inhibits intestinal absorption of copper. Liver transplantation in severe hepatic failure or non-responsive forms.
Toxic Liver Injury	Removal of exposure to toxins (alcohol, hepatotoxic medications). N-acetylcysteine antidote in cases of acute paracetamol toxicity. Extracorporeal detoxification, liver transplantation when indicated.
Autoimmune Hepatitis (AIH)	Corticosteroids (prednisone) to reduce autoimmune inflammation. Immunosuppressants: azathioprine, mycophenolate mofetil, tacrolimus.
Primary Sclerosing Cholangitis (PSC)	Ursodeoxycholic acid to improve bile flow. Endoscopic dilation of strictures or stenting in advanced biliary disease. Liver transplantation in advanced fibrosis or liver failure.
Neoplasms (Liver Tumors)	Surgical resection or liver transplantation in resectable hepatic tumors. Targeted therapy: sorafenib for hepatocellular carcinoma. Chemotherapy or radiotherapy for advanced tumors.
Cryptogenic Hepatitis	Supportive liver care (hepatoprotective therapy, nutritional support). Liver transplantation in cases of advanced or irreversible liver failure.

Etiotropic treatment in acute and chronic liver diseases requires a thorough understanding of the underlying cause and the individual patient's response. Therefore, recent guidelines emphasize the necessity of precise diagnosis and continuous monitoring in order to adjust the therapeutic strategy according to the disease evolution and the patient's reaction to therapy.

Etiologic therapy for hepatic and extrahepatic diseases that present with hepatocellular injury represents the cornerstone of modern management, allowing targeted interventions that address the underlying causes and reduce long-term risks. Recent advances in the development of targeted therapies, antiviral agents, and immunosuppressive treatments offer new perspectives for patients with complex diseases, significantly improving prognosis and quality of life.

Detoxification therapy. In addition to etiologic treatment targeting the underlying cause, detoxification therapy is essential for facilitating the elimination of harmful substances from the body and for reducing hepatic stress, thereby supporting liver regeneration. Detoxification therapy is a multidimensional approach that includes pharmacologic treatment, nutritional support, and measures aimed at sustaining hepatic function. Recent guidelines and literature emphasize the importance of this therapeutic component in improving the prognosis of children with hepatic and extrahepatic diseases that manifest with hepatocellular injury, especially in cases of toxic or metabolic liver damage.

Mechanisms of hepatic detoxification. The liver plays a central role in detoxification by metabolizing and eliminating toxins and metabolic by-products from the body. In hepatocellular injury, the liver's ability to perform these functions may be compromised, leading to the accumulation of toxic metabolites. Detoxification therapy aims to reduce the liver's toxic load, improve bile flow for effective toxin elimination through the biliary system, and support hepatocyte regeneration by decreasing inflammation and oxidative stress.

METHODS AND STRATEGIES FOR DETOXIFICATION IN HEPATOCELLULAR INJURY

N-acetylcysteine (NAC). Indications: primarily administered in cases of acetaminophen (paracetamol) intoxication and other toxic hepatic injuries. Mechanism of action: NAC restores glutathione levels, an essential antioxidant for hepatic detoxification, thereby reducing oxidative stress and preventing hepatocyte necrosis. Administration: intravenous or oral administration depending on the severity of intoxication and the degree of hepatic impairment.

Lactulose. Indications: used to treat and prevent hepatic encephalopathy in cases of hepatic failure. Mechanism of action: reduces the production and absorption of ammonia by increasing its elimination in the intestine. Ammonia is a toxic metabolite that accumulates in significant hepatic impairment. Administration: oral or rectal (enemas), adjusted according to symptom severity and serum ammonia levels.

Nutritional support for hepatic detoxification. An essential component of detoxification therapy in hepatocellular injury is providing adequate nutritional support. Children with hepatic cytolysis require a diet that supports liver function and promotes hepatocyte regeneration. High-quality proteins: in cases of hepatic failure with moderate encephalopathy, protein intake must be reduced or moderated to prevent ammonia accumulation. In severe cases, low-protein diets may be necessary. Vitamins: fat-soluble vitamins (A, D, E, K) are essential in cholestatic liver diseases to correct malabsorption. Vitamin C and vitamin E exert antioxidant effects and support hepatic function. Omega-3 fatty acids: may have anti-inflammatory properties and help reduce hepatic inflammation.

Hydration and supportive therapy. Adequate hydration is crucial for efficient toxin elimination through the kidneys. In severe hepatic impairment or hepatic failure, it may be necessary to provide: intravenous fluid administration to maintain hydration and prevent dehydration; correction of electrolyte imbalances and acid-base disturbances, which are frequently encountered in acute and severe chronic liver diseases.

PREVENTIVE MEASURES FOR CYTOLYSIS SYNDROME IN CHILDREN

Prevention and prophylaxis in cytolysis syndrome in children are essential for reducing the risk of liver injury and preventing progression toward severe complications such as cirrhosis and hepatic failure. The preventive approach must be multidisciplinary, incorporating measures adapted to the underlying causes of cytolysis infectious, toxic, metabolic, or autoimmune.

Vaccination.

Vaccination is one of the most important pillars in preventing infectious liver diseases that may lead to cytolysis syndrome. International guidelines recommend specific vaccination against hepatitis B as part of national immunization schedules.

According to the World Health Organization (WHO) and international guidelines, hepatitis B vaccination is mandatory starting from the neonatal period and continued throughout the first year of life. The first dose (HepB1) is administered within the first 24 hours after birth to all infants without increased risk. Newborns of HBV-positive mothers must receive both HepB vaccine and hepatitis B immunoglobulin (HBIG) at birth to provide immediate passive protection. Completion of the 4-dose schedule (0, 1-2 months, 6 months, 12 months) is essential for developing long-term protective immunity. Hepatitis A vaccination is recommended for children living in hyperendemic areas or for those with chronic liver diseases.

Avoidance of toxic substances.

Toxic liver injury is a major cause of hepatocellular cytolysis; prevention relies on reducing exposure to hepatotoxic agents. *Hepatotoxic medications:* Parents must be educated on the correct use of drugs such as paracetamol and NSAIDs. Overdosing must be avoided to prevent acute liver toxicity. *Toxic chemicals:* Children must be shielded from exposure to hazardous household chemicals, pesticides, and heavy metals.

PREVENTION OF VIRAL TRANSMISSION.

Personal and public hygiene: Prevention of hepatitis A and E requires proper hand hygiene, safe water, and safe food consumption. Avoiding exposure to infected bodily fluids is important for preventing hepatitis B and C. *Vertical transmission:* HBV-positive pregnant women must be monitored and treated to reduce mother-to-child transmission. Newborns of infected mothers require both HepB vaccine and HBIG.

Prophylaxis of metabolic diseases. In metabolic disorders such as Wilson disease, hemochromatosis, or alpha-1 antitrypsin deficiency, prevention focuses on early detection and timely intervention. *Genetic screening and monitoring:* Families with known risk should undergo genetic testing and regular assessment of hepatic markers (copper, iron). *Preventive therapy:* In Wilson disease, early administration of copper chelators and periodic monitoring significantly decrease the risk of cytolysis.

Education on lifestyle and nutrition. A balanced diet: Essential for all children, especially those at risk for MASLD. Diet should be rich in fruits, vegetables, lean proteins, and healthy fats, while limiting sugars and saturated fats. *Avoidance of alcohol exposure:* Children and adolescents must be educated about the dangers of alcohol ingestion and accidental exposure. *Nutritional supplements:* Children with cholestasis or fat-soluble vitamin malabsorption require supplementation with vitamins A, D, E, and K.

Long-term monitoring and surveillance.

Children at increased risk for cytolysis (e.g., those with chronic diseases or prolonged medication use) must undergo regular follow-up. International guidelines recommend: periodic laboratory evaluation of liver function (ALT, AST, bilirubin, PT/INR); abdominal ultrasound or elastography every 6-12 months to monitor hepatic structure and fibrosis progression.

Prevention of hepatic complications.

Prevention and early management of ascites and portal hypertension are crucial in at-risk children (particularly those with cirrhosis). Diuretics and specific interventions may be required. Monitoring for hepatocellular

carcinoma (HCC) is essential in children with chronic hepatitis B or C, autoimmune liver disease, or cirrhosis performed by abdominal ultrasound and alpha-fetoprotein (AFP) every 6 months.

Psychological support and family education.

Psychological care is vital for children living with chronic liver disease and their families. Counseling helps manage stress, anxiety, and treatment adherence. Family education regarding disease management, recognizing complications, and maintaining close collaboration with healthcare providers is critical for long-term outcomes.

In summary, prevention of cytolysis syndrome in children is fundamental to reducing the risk of liver damage and avoiding severe complications. Preventive measures must be individualized and guided by the underlying cause infectious, toxic, metabolic, or autoimmune while integrating vaccination, lifestyle education, avoidance of toxic exposures, and continuous medical monitoring.

CONCLUSIONS

In conclusion, the diagnosis of cytolysis syndrome and the identification of its etiological cause represent a complex, stepwise process that requires careful evaluation of clinical symptoms, laboratory findings, and relevant patient history. A well-defined diagnostic algorithm for children presenting with cytolysis syndrome enables clinicians to accurately determine the underlying cause, assess the severity of liver involvement, and establish an individualized and effective management plan tailored to each patient. Laboratory investigations including hepatic transaminases, bilirubin levels, LDH, and other biochemical parameters are essential for assessing hepatic function and determining the degree of cytolysis. In addition, specific immunoserological markers may provide important information regarding the possible etiologic mechanisms involved.

Instrumental diagnostic methods, both non-invasive and invasive, play a crucial role in the initial assessment and ongoing monitoring of cytolysis syndrome. Ultrasonography, abdominal CT, and MRI offer detailed structural visualization of the liver and digestive organs, while liver

biopsy, elastography, and other invasive techniques can provide comprehensive information on the macroscopic and microscopic morphofunctional characteristics of hepatic tissue. Importantly, establishing the precise etiology of cytolysis syndrome requires a comprehensive and multidisciplinary approach involving collaboration among specialists, including gastroenterologists, hepatologists, pediatricians, nephrologists, cardiologists, radiologists, intensivists, and others.

A thorough and accurate clinical evaluation, combined with careful interpretation of laboratory and instrumental results, is essential for establishing an early and correct diagnosis and for formulating an individualized, effective, and stepwise therapeutic strategy.

RECOMMENDATIONS

1. Initial evaluation for early detection of potential liver disease should include serum total and fractionated bilirubin, ALT, AST, total protein, albumin, ALP, γ-GGT, and a complete blood count if these tests have not been performed within the last 12 months (Level 2b, Grade B).
2. Further specialized evidence is needed to determine the cost-effectiveness of cytolysis screening in children at high risk for Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) before routine screening can be recommended (Level 5, Grade D).
3. Abnormal liver blood tests (elevated ALT/AST) must always be interpreted in the context of previous laboratory values, past medical history, and current clinical findings (Level 5, Grade D).
4. The degree of liver test abnormality (ALT and AST outside age-specific reference ranges) does not establish a diagnosis and requires assessment by an experienced clinician who interprets results within the complete clinical and paraclinical context (Level 5, Grade D).
5. Children with cytolysis syndrome and abnormal liver blood tests should undergo additional investigations, including etiological

screening tests, regardless of the degree or duration of cytolysis (Level 2b, Grade B).

6. In adults, standard liver screening should also include abdominal ultrasonography, HBsAg with acute/chronic HBV markers, anti-HCV testing, and when indicated, HBV DNA or HCV RNA PCR testing. Autoimmune antibody screening (AMA, ASMA, ANA), serum immunoglobulins, ferritin, and transferrin saturation should also be performed (Level 2b, Grade C).
7. In children, the autoimmune panel should additionally include anti-LKM antibodies, liver-specific autoantibodies, and celiac-specific antibodies. Serum alpha-1 antitrypsin and ceruloplasmin should be measured in children over 3 years of age, with referral to pediatric hepatology/metabolic disease specialists when needed (Level 2b, Grade C).
8. Risk stratification for MASLD in older children and adults should include first-line fibrosis assessment using FIB-4 or the NAFLD Fibrosis Score (NFS). These tools should be integrated into healthcare information systems across all levels of care (Level 5, Grade D).
9. Second-line instrumental evaluation of cytolysis should include quantitative assessment of hepatic fibrosis using ELF serum tests or elastographic modalities such as Transient Elastography (FibroScan), Real-Time Tissue Elastography, or ARFI elastography (Level 2b, Grade B).
10. Pediatric gastroenterology and hepatology specialists should advocate at the national level for implementing strategies to address pediatric liver disease and ensure that these recommendations are acknowledged by key healthcare decision-makers.

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