frontiers in Hematology

TYPE Case Report
PUBLISHED 26 August 2026
DOI 10.3389/frhem.2026.1858024

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OPEN ACCESS

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RECEIVED 16 April 2026
REVISED 20 July 2026
ACCEPTED 27 July 2026
PUBLISHED 26 August 2026

CITATION
Fantasia M, Faraguna MC, Pagani R, Catalano A, Colombo D, Paredi M, Guerra F, Ferrari GM and Corti P (2026) Case Report: A diagnostic algorithm for pediatric cholelithiasis: recognizing underlying hemolytic anemia through a case of hereditary spherocytosis. *Front. Hematol.* 5:1858024. doi: 10.3389/frhem.2026.1858024

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Case Report: A diagnostic algorithm for pediatric cholelithiasis: recognizing underlying hemolytic anemia through a case of hereditary spherocytosis

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Pediatric cholelithiasis is increasingly encountered in clinical practice, largely driven by the rising prevalence of obesity. However, chronic hemolytic disorders remain a significant and potentially underrecognized cause, particularly when presenting with mild or compensated forms. In such cases, gallstones may represent the first manifestation of an underlying hematologic condition, posing a diagnostic challenge. We report the case of a 7-year-old girl presenting with abdominal pain, vomiting, and jaundice. Abdominal ultrasound revealed gallbladder distension, biliary sludge, and a gallstone associated with splenomegaly. Within 48 hours, the clinical course rapidly progressed to biliary pancreatitis, requiring endoscopic retrograde cholangiopancreatography with sphincterotomy and stone extraction, followed by elective cholecystectomy three days later. The coexistence of cholelithiasis and splenomegaly raised suspicion of hemolysis, and subsequent investigations led to the diagnosis of hereditary spherocytosis. This case highlights the risk of underdiagnosing congenital hemolytic anemias—particularly in mild or compensated forms—in children presenting with biliary disease, as standard laboratory tests may be misleading. It underscores that pediatric cholelithiasis may represent the initial manifestation of otherwise unrecognized hemolytic disorders. We further propose a practical diagnostic flowchart to facilitate early identification and prompt hematologic referral. The algorithm was produced entirely by us. Early recognition is crucial to prevent complications and optimize long-term outcomes.

KEYWORDS
cholelithiasis, chronic hemolysis, gallstones, hemoglobinopathies, hemolytic anemia

Introduction

Over the past two decades, the incidence of pediatric cholelithiasis has increased, largely driven by the rising prevalence of obesity (1). In contrast, gallstones secondary to hematologic disorders have remained relatively stable, accounting for less than 20% of cases. In children, cholelithiasis may represent the first clinical manifestation of an underlying chronic hematologic condition. Early recognition of anamnestic, clinical, and biochemical "red flags" is therefore essential to ensure timely referral to a pediatric hematologist when appropriate.

In this brief report, we describe a pediatric patient presenting with cholelithiasis and acute cholestasis secondary to chronic hemolysis. We also propose a diagnostic flowchart summarizing the principal hematologic disorders associated with pediatric cholelithiasis, with the aim of providing practical guidance for pediatricians and general practitioners regarding indications for hematologic referral.

Clinical case

A 7-year-old girl with a normal body mass index presented with acute abdominal pain, vomiting, and jaundice. Her medical history was notable for neonatal hemolytic jaundice, while no family history of hematologic disorders was reported. Furthermore, there was no history of recent travel to endemic areas for parasitic infections, no chronic medication use, and no antibiotic therapy, including ceftriaxone, in the preceding weeks. Physical examination revealed jaundice, tenderness in the right upper quadrant, and mild splenomegaly. Laboratory evaluation showed nearly normal blood counts, elevated indirect bilirubin and transaminases, mild elevation of pancreatic enzymes, and cola-colored urine (Table 1). Abdominal ultrasound demonstrated a distended gallbladder containing biliary sludge and a 5 × 5 mm gallstone, with normal bile ducts and associated splenomegaly. Based on these findings, a diagnosis of obstructive choledocholithiasis with biliary pancreatitis and splenomegaly was established.

Within 48 hours, the patient's clinical condition progressed to biliary pancreatitis. Laboratory tests showed a further increase in transaminases, pancreatic enzymes, and total bilirubin, predominantly due to an elevation in the direct bilirubin fraction (Table 1). Repeat ultrasonography revealed obstruction of the distal common bile duct at the level of the pancreatic duct confluence. The gallbladder was moderately distended, with a thin wall and hyperechoic intraluminal material consistent with biliary sludge. Endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy and stone extraction was therefore performed.

Three days later, elective laparoscopic cholecystectomy was undertaken following magnetic resonance cholangiopancreatography (MRCP), to allow adequate delineation of the biliary tree.

Given the coexistence of cholelithiasis, splenomegaly, and laboratory evidence of hemolysis, the patient was referred for hematologic evaluation. Further investigations confirmed markers of chronic hemolysis, including elevated indirect bilirubin and lactate dehydrogenase (LDH) levels and decreased haptoglobin (Tables 2a, b). Peripheral blood smear revealed anisopoikilocytosis with spherocytes and occasional elliptocytes, together with increased red cell distribution width and reticulocytosis. Immune-mediated hemolysis, hemoglobinopathies, and red blood cell enzymatic defects were excluded. Functional testing of red blood cell membrane integrity, including the eosin-5-maleimide (EMA) binding test and osmotic fragility testing, confirmed the diagnosis of hereditary spherocytosis (2). Subsequent red blood cell membrane protein analysis demonstrated spectrin deficiency. As neither parent showed clinical or laboratory evidence of hereditary spherocytosis, the patient's disease was considered most likely to represent a *de novo* occurrence.

Discussion

The incidence of cholelithiasis in children has increased over the past two decades (1, 3), paralleling a rise in pediatric cholecystectomies (4). This trend is largely attributed to the increasing prevalence of obesity (5) and the widespread use of abdominal ultrasonography (1), which may incidentally detect asymptomatic gallstones. Hematologic causes, including chronic hemolytic anemias, have remained relatively stable and account for approximately 5–20% of pediatric cases (6, 7).

The detection of gallstones, even in asymptomatic patients, warrants gastroenterological or surgical evaluation. Diagnosis is based on a combination of clinical manifestations—such as jaundice, colicky right upper quadrant or epigastric pain, nausea, and vomiting—and laboratory abnormalities, including hyperbilirubinemia and elevated levels of transaminases, γ-glutamyl transferase, amylase, and lipase. In cases of intravascular hemolysis, patients may also present with dark or "cola-colored" urine, reflecting hemoglobinuria secondary to increased circulating free hemoglobin.

Abdominal ultrasonography (8) represents the first-line imaging modality, whereas additional investigations, such as magnetic resonance cholangiopancreatography (MRCP), may be selectively indicated in cases with inconclusive findings (9). MRCP also plays a key role not only in equivocal cases of suspected biliary pathology, but also in the assessment of complications, in differentiating choledocholithiasis from congenital biliary anomalies such as choledochal cysts, and in identifying underlying causes of cholangitis when the etiology is not immediately evident (4).

Urgent surgical consultation may be required in patients presenting with acute biliary colic. Complicated gallstone disease in children, including choledocholithiasis and biliary pancreatitis, represents a medical emergency that requires a coordinated multidisciplinary approach. Optimal management relies on close collaboration among pediatric gastroenterologists, surgeons, and hematologists, particularly when an underlying hemolytic disorder is present, in order to ensure timely diagnosis, appropriate intervention, and prevention of recurrence. Longitudinal follow-up is typically

Abbreviations: MRCP, magnetic resonance cholangiopancreatography; ERCP, endoscopic retrograde cholangiopancreatography; LDH, lactate dehydrogenase levels; EMA, eosin-5-maleimide binding test.

TABLE 1 Laboratory parameters at presentation in the emergency department and maximum values during hospital stay.

Hematological and biochemical laboratory parameters	Value at emergency department	Value during hospitalization	Unit	Range
White blood cell (WBC)	11.36		$\times 10^9$/L	5.00-14.00
Red blood cell (RBC)	3.76		$\times 10^{12}$/L	4.00-5.00
Hemoglobin (Hb)	12.3		g/dL	12.0-16.0
Hematocrit (Ht)	35.0		%	35.0-45.0
Mean Corpuscular Volume (MCV)	87.0		fL	77.0-95.0
Mean Corpuscular Hemoglobin (MCH)	32.4		pg	25.0-33.0
Mean Corpuscular Hemoglobin Concentration (MCHC)	34.3		g/dL	31.0-37.0
Platelets (PLT)	292		$\times 10^9$/L	140-440
Reticulocyte count	n.a.	5.93	%	0.5-2.0
Alanine aminotransferase (ALT)	213	309	U/L	<33
Aspartate aminotransferase (AST)	134	234	U/L	<32
Gamma-glutamyl transferase (GGT)	181	328	U/L	<40
Total bilirubin	7.9	19.6	mg/dL	0.2-1.2
Direct bilirubin	2.0	16.1	mg/dL	<0.9
Amylase	292	633	U/L	28-100
Lipase	175	520	U/L	13-60
Lactate dehydrogenase (LDH)	315	480	U/L	120-300
Haptoglobin	n.a.	0.2	g/L	0.3-2.0
Triglycerides	n.a.	157	mg/dL	<150
Cholesterol	n.a.	115	mg/dL	<190

n.a, not available.

managed by pediatricians or internists, who play a pivotal role in identifying patients who may require hematological referral (4).

Chronic hemolysis results in increased bilirubin turnover, promoting the precipitation of calcium bilirubinate and subsequent formation of pigment gallstones (7). Chronic hemolytic anemia usually manifests in early childhood with recurrent hemolytic episodes, anemia of variable severity, jaundice, and splenomegaly (8). Hemoglobinopathies, such as thalassemia and sickle cell disease (9), although not clinically apparent at birth, generally become evident within the first year of life or early childhood (7).

Disorders with a milder phenotype—such as certain forms of non–transfusion dependent thalassemia, compound heterozygosity (e.g., alpha-globin gene triplications or quadruplications associated with beta-globin mutations), sickle cell disease in compound heterozygosity with other hemoglobin variants, or homozygosity for hemoglobin C or E—may remain undiagnosed until adulthood and may initially present with biliary colic, thereby complicating recognition.

Failure to identify chronic hemolytic anemia—even in mild phenotypes—may result in complications, undertreatment, inadequate monitoring, and potential reproductive risks. Standard hematologic parameters may appear normal on cursory evaluation (Table 1); therefore, careful attention to subtle clinical and laboratory warning signs is essential (Tables 2a, b).

To assist clinicians, we propose a two-section flowchart (Figure 1). The first section provides a diagnostic algorithm for general practitioners aimed at identifying mild congenital hemolytic anemias that may present with acute gallbladder pathology. The second section outlines the hematologist's diagnostic pathway. The direct antiglobulin test (DAT) is included among first-line investigations to promptly distinguish immune-mediated from congenital hemolytic anemias. Although autoimmune hemolytic anemia only rarely presents with gallstone disease as the initial manifestation, DAT represents a standard component of the initial diagnostic work-up of hemolysis and should therefore be performed early in the evaluation. Bone marrow assessment is reserved for rare conditions, such as congenital dyserythropoietic anemias, as well as for cases of diagnostic uncertainty or involvement of multiple hematopoietic lineages.

Beyond its illustrative purpose, the proposed flowchart represents one of the main strengths of this report, as it provides a practical and structured diagnostic tool applicable to daily clinical practice. From a clinical perspective, the algorithm may assist pediatricians and surgeons in recognizing early warning signs of underlying hemolytic disorders and in determining the appropriate timing for hematological referral in children presenting with gallstone disease, particularly in complicated cases. From a hematological standpoint, it offers a stepwise diagnostic approach

TABLE 2 Complete blood count values with red blood cell indices (a), and hemolysis markers (b) of the same patient at steady state, following resolution of the acute episode.

a Hematological and biochemical laboratory parameters	Value	Unit	Range
White blood cell (WBC)	7.76	$\times 10^9$/L	5.00-14.00
Red blood cell (RBC)	3.82	$\times 10^{12}$/L	4.00-5.00
Hemoglobin (Hb)	12	g/dL	12.0-16.0
Hematocrit (Ht)	34.0	%	35.0-45.0
Mean Corpuscular Volume (MCV)	89.0	fL	77.0-95.0
Mean Corpuscular Hemoglobin (MCH)	31.4	pg	25.0-33.0
Mean Corpuscular Hemoglobin Concentration (MCHC)	35.3	g/dL	31.0-37.0
Red Cell Distribution Width (RDW)	22.2	%	10.0-16.0
Mean Platelet Volume (MPV)	9	fL	9-13
Platelets (PLT)	312	$\times 10^9$/L	140-440
Absolute erythroblasts	0.0	$\times 10^9$/L	absent
Reticulocyte count	5.93	%	0.5-2.0
Absolute reticulocyte count	226.52	$\times 10^9$/L	
b			
Total bilirubin	2.9	mg/dL	0.2-1.2
Direct bilirubin	0.6	mg/dL	<0.9
Lactate dehydrogenase (LDH)	450	U/L	120-300
Haptoglobin	0.2	g/L	0.3-2.0

Indices highlighted in gray indicate those requiring particular attention in the diagnostic workup of chronic hemolytic anemias.

distinguishing first-, second-, and third-level investigations. It encompasses the initial evaluation of the most common forms of chronic hemolytic anemia, such as hereditary spherocytosis, while also extending to rarer and more complex conditions requiring a comprehensive diagnostic work-up. In these cases, accurate diagnosis relies on an integrated interpretation of clinical findings, hematochemical parameters, red blood cell indices, peripheral blood smear morphology, functional assays of red blood cell membrane integrity, and, when indicated, molecular genetic testing. This structured approach may therefore facilitate a more efficient and systematic diagnostic work-up across the full spectrum of congenital hemolytic anemias.

Surgical intervention is clearly indicated in symptomatic cholelithiasis (10) and in the presence of obstructive or infectious complications. Conversely, the management of asymptomatic cholelithiasis remains controversial (11) in both pediatric and adult populations, and decisions regarding prophylactic cholecystectomy should be individualized according to the underlying disease, patient-related risk factors, and the likelihood of future biliary complications. Although many gallstones remain clinically silent for prolonged periods, some patients may subsequently develop biliary complications. Our patient presented with rapid progression to obstructive cholestasis and acute biliary pancreatitis requiring urgent ERCP with sphincterotomy (12).

The management of cholelithiasis in children with hematologic disorders generally follows the same principles applied to otherwise healthy pediatric patients. Current guidelines support concomitant cholecystectomy in patients with chronic hemolytic anemia undergoing elective splenectomy when gallstones are present, including asymptomatic stones (10, 13). Outside this specific clinical setting, the management of asymptomatic cholelithiasis should be individualized according to the patient's clinical characteristics and underlying disease. In sickle cell disease, perioperative management should be individualized. Preoperative transfusion support, including simple transfusion or red blood cell exchange transfusion when indicated, together with appropriate perioperative care (antibiotic and antithrombotic prophylaxis when indicated, early mobilization, and respiratory physiotherapy), may reduce perioperative complications (9).

Early cholestasis in congenital hemolytic anemias may be misinterpreted as baseline chronic hemolysis. Prompt recognition of acute cholestasis -which may progress rapidly- allows close clinical and laboratory monitoring, appropriate imaging (including ultrasonography and MRCP when indicated), and timely surgical evaluation.

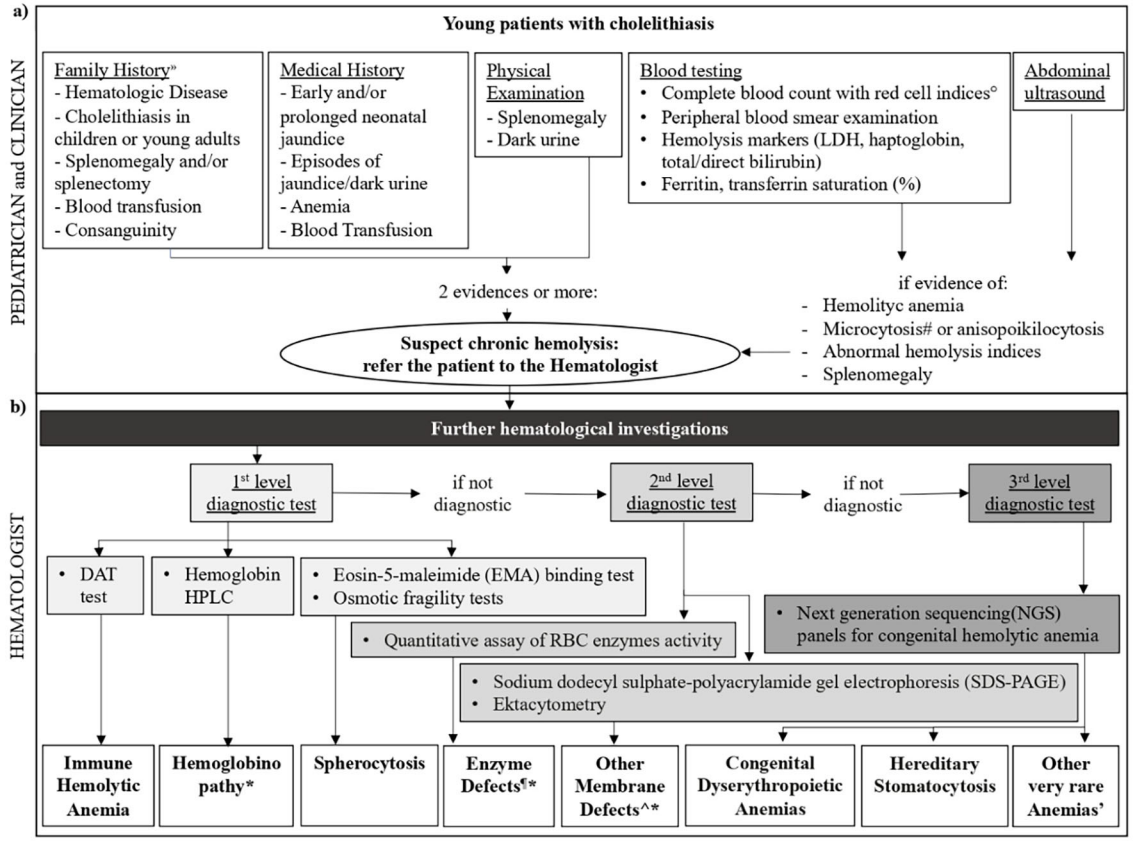


FIGURE 1
Flow-chart for pediatricians and clinicians for the management of a young patient with cholelithiasis: **(a)** criteria for referral to the hematologist, and **(b)** first-, second-, and thrird-level diagnostic hematological tests. *when collecting the family medical history, review the parents' complete blood count, if available; °red indices: MCV, RDW, reiculocytes; # with non depleted iron stores; ¶ Pyruvate Kinase decifiency, rare Glucose-6-Phosphate Dehydrogenase deficiency conditioning chronic hemolyic anemia, Glucose Phosphate Isomerase deficiency; *molecular testing is always required; ^hereditary ovalocytosis, hereditary elliptocytosis; ' Sideroblastic anemia, paroxysmal nocturnal hemoglobinuria and others.

Conclusion

Chronic hemolysis accounts for less than 20% of pediatric cholelithiasis cases and has remained relatively stable over recent decades, in contrast to the increasing prevalence of metabolic causes. Pediatricians, general physicians, and pediatric surgeons should therefore recognize patients with potential underlying hematologic disorders. A detailed family and medical history, thorough physical examination, and careful assessment of basic laboratory parameters—including complete blood count with red blood cell indices, reticulocyte count, hepatic and renal function parameters, and markers of hemolysis (LDH and haptoglobin)—are essential.

To support clinical decision-making, we propose a diagnostic flowchart designed to help clinicians recognize warning signs and determine the need for hematologic referral.

Importantly, pediatricians and surgeons should perform early and systematic hematological screening —including complete blood count with red blood cell indices, reticulocyte count, peripheral blood smear, lactate dehydrogenase, haptoglobin, bilirubin, and the direct antiglobulin test—at the initial assessment of gallstone disease, particularly in complicated cases. This approach enables prompt identification of underlying hemolytic disorders and facilitates timely referral to a hematologist.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Fondazione IRCCS San Gerardo dei Tintori. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

MFan: Writing – review & editing, Writing – original draft. MFar: Writing – original draft. RP: Writing – original draft. AC: Writing – original draft. DC: Writing – original draft. MP: Writing – original draft. FG: Writing – review & editing, Supervision. GF: Supervision, Writing – review & editing. PC: Writing – review & editing, Validation, Conceptualization, Supervision.

Funding

The author(s) declared that financial support was received for this work and/or its publication. This paper has been partially supported by the Italian Ministry of Health, within "Ricerca Corrente Program".

Acknowledgments

This paper has been partially supported by the Italian Ministry of Health, within "Ricerca Corrente Program".

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/frhem.2026.1858024/full#supplementary-material

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