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Diagnosis, management and prevention of Pediatric Acute Hemolytic Anemia: Egyptian adapted evidence-based clinical practice guidelines

Galila Mokhtar[1], Ashraf Abdel Baky[2], Ilham Youssry[3], Iman Ragab[1], Laila Sherief[4], Marwa Zakaria[4], Mervat Hesham[4], Nouran Salah[5], Rasha Abdel-Raouf[3,5], Sara Makkeyah[1], Sherein Shalaby[6], Sonia Adolf Habib[7], Tarek Omar[8], Yasser Amer[9,10,11] and Niveen M. Salama[3*]

Abstract

Background Acute hemolytic anemia (AHA) is a common emergency in pediatric emergency departments, hence the need to adapt pre-existing high-quality practice guidelines for the diagnosis, management, and prevention of AHA to be available for national use.

Methods The guideline panel used the adapted ADAPTE methodology. The panel prioritized the health questions and recommendations according to their importance for clinicians and patients. The procedure included searching for existing guidelines, quality appraisal, and adaptation of the recommendations to be used in low-resource countries.

Results The guideline provided approach to a child with AHA: laboratory diagnosis of glucose-6-phosphate dehydrogenase (G6PD) deficiency, autoimmune hemolytic anemia (AIHA), and hemolytic uremic syndrome (HUS); treatment of AHA including indications for red cell transfusion, medical treatment, plasma exchange, and indications of antibiotic in HUS; how to avoid further episodes of hemolysis; and when to refer to a hematologist. Implementation tools included a checklist for history and examination, lists of differential diagnoses, flow charts for the diagnosis of AHA, and a list of medications and food to be avoided in patients with G6PD deficiency.

Conclusion This adapted guideline will aid decision-making related to the diagnosis, management, and prevention of AHA.

Keywords Guideline adaptation, Acute hemolytic anemia, Autoimmune hemolytic anemia, Glucose-6-phosphate dehydrogenase deficiency, Hemolytic uremic syndrome

*Correspondence:
Niveen M. Salama
niveensab@yahoo.com
Full list of author information is available at the end of the article

Background

Acute hemolytic anemia is one of the most pressing concerns for emergency physicians as it represents 9–14% of all patients visiting the emergency department (ED) [1] and it may result in immediate, life-threatening complications [2]. The most common causes of acute hemolytic anemia, where early treatment can reduce the risk or extent of end-organ failure, are glucose-6-phosphate-dehydrogenase (G6PD) deficiency, autoimmune hemolytic anemia (AIHA), and hemolytic uremic syndrome (HUS) [3–6]. Other less common causes include microangiopathies as thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulopathy (DIC), infection, malaria, toxins such as lead or copper poisoning, and drugs such as penicillins, ceftriaxone, quinine, and methyldopa [7].

Glucose-6-phosphate-dehydrogenase deficiency is a congenital X-linked disease caused by mutations in the G6PD gene, located on the long arm of the X chromosome. The prevalence of G6PD deficiency among Egyptian neonates is 8.9% [8], while worldwide, it affects more than 400 million people [7]. A deficiency of the enzyme causes insufficient reduced glutathione (GSH) production, which makes RBCs more susceptible to oxidant stress. Exposure to oxidants results in damage of critical erythrocyte proteins, production of methemoglobin, and intracellular precipitates of Hb known as Heinz bodies and can result in episodic hemolytic anemia [7–9].

Patients who are usually males presented to the ED with acute onset of pallor, fever, abdominal pain with jaundice, and abdominal pain after consumption of oxidant [7]. The initial management of acute hemolysis caused by exposure to oxidant is red blood cell (RBC) transfusion based on the severity of hemolysis [8].

Autoimmune hemolytic anemia (AIHA) is a medical condition in which the body produces antibodies that attack and hemolyze self-RBCs [9, 10]. The annual incidence of AIHA is approximately 0.8 per 10,000 [11]. AIHA can be idiopathic or secondary to some drug intake or systemic diseases [12]. Depending on the type and the thermal activity of the antibodies, AIHA can be classified into warm antibody hemolysis, cold antibody hemolysis, or mixed hemolysis [10, 12]. Warm antibody hemolysis is the most common in pediatrics, associated with an IgG antibody, and causes extravascular hemolysis, while cold antibody hemolysis is more common in adults, associated with IgM antibody, and leads to both extravascular and intravascular hemolysis [7]. The primary management of AIHA depends on the severity of hemolysis [4]. As with any unstable patient, unstable vital signs should be first managed. RBC transfusion should be limited only to cases with life-threatening anemia [6, 8, 12]. This is because it might be difficult to find an accurate crossmatch, and transfusions can result in more autoantibody production [12]. Corticosteroids slow the rate of hemolysis and are considered a first-line therapy that should be started as soon as possible [10, 12, 13].

Hemolytic uremic syndrome (HUS) is an uncommon disorder with an annual incidence of 0.66 per 100,000 people, but it can have significant consequences on the individual affected [14], as it is one of the common causes of renal failure in less than 5-year-old children [7]. HUS is a clinical syndrome characterized by progressive impairment of the kidney function, associated with microangiopathic hemolysis of the RBCs and platelet with the resultant triade of acute renal failure, anemia, and thrombocytopenia [1]. Typical HUS is caused by Shiga toxin produced by *Shigella dysenteriae* or Shiga-like toxin produced by *Escherichia coli* and should be suspected in any child that presents with a previously mentioned triade of acute onset in the presence of a history of bloody diarrhea [15, 16]. Atypical HUS should be suspected in patients with similar symptoms, but with no history of acute diarrheal illness [16]; it is usually associated with other infections (such as *Clostridium difficile*, *Streptococcus pneumoniae*, influenza A virus, coxsackievirus, HIV, or histoplasmosis), medications (as cyclosporine, quinine, mitomycin C, or cocaine), or immune-associated processes that lead to endothelial damage [7]. Atypical familial HUS is a rare subtype due to inherited variants of the complement pathway that lead to endothelial damage [7, 16]. The initial management of typical HUS is supportive and if indicated renal dialysis [17].

Aim of work

The purpose of developing the Egyptian guidelines is to assist the practitioners (primary and secondary health care practitioners working in governmental, non-governmental, and private sectors) to apply the best available evidence to clinical decisions about the diagnosis, management, and prevention of acute hemolytic anemia with the following objective in mind: putting a differential diagnosis and approach to the diagnosis and proper management of acute hemolytic anemia in infants, children, and adolescents; identification of infants, children, and adolescents at high risk of developing acute hemolysis; prevention of recurrence of hemolysis in the targeted population.

Study design

The study design is an adapted evidence-based clinical practice guideline.

Methods

A pediatric hematology work group (PHWG) panel was initiated containing representatives of the major universities in Egypt (namely Cairo, Ain Shamas, Zagazig, Armed Forces, and Helwan universities) as well as the National Research Center. All the participants declared no conflict of interest.

During 2019–2020, the panel reviewed all pediatric guidelines related to our topics that were published during the previous 10 years in order to select those suitable to our society.

The collected guidelines were evaluated using the AGREE II (2017) [18] (an international assessment tool for guideline evaluation), and any guideline that scored more than 70% overall assessment was approved for adaptation. The PHWG applied the adapted ADAPTE methodology [19] on all the chosen guidelines.

The following guidelines were adapted: laboratory diagnosis of G6PD deficiency, a British Society for Haematology Guideline (BSH, 2020) [20]; diagnosis and management of G6PD deficiency, American Family Physician (AFP 2005) [21]; the diagnosis and management of primary autoimmune hemolytic anemia (BSH, 2017) [22]; diagnosis and management of newly diagnosed childhood autoimmune hemolytic anemia, recommendations from the Red Cell Study Group of the Paediatric Haemato-Oncology Italian Association (AIEOP 2017) [23]; 2017 Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea (IDSA, 2017) [24]; hemolytic uremic syndrome in a developing country: consensus guidelines, Pediatr Nephrol (2019) [25].

The health questions were presented in the PIPOH model (Fig. 1) [19], and the clinical questions (Table 1) were formulated in PIPOH format (Patient, Intervention, Professionals, Outcomes, Healthcare settings).

Recommendations were formulated by the PHWG and then reviewed by both national and international reviewers. The final version of the guideline was modified based upon the reviewers' comments, the available resources and facilities, the applicability of the clinical practice guideline (CPG) recommendations, and the acceptability in the local settings.

Levels of evidence and grades of recommendation

Rating the level of evidence, the panel used the original grading system of the reference guidelines after their permission. Code A represents a high quality of evidence, B represents a moderate quality of evidence, C represents a low quality of evidence, and D represents a very low quality of evidence, while number 1 stands for a strong level of recommendations and number 2 stands for a weak level of recommendations.

The guidelines were adopted in 2021, with a proposed update in 2026 except if any breakthrough evidence-based recommendations were published before that date. An update will be carried on after checking for updates in the source guidelines, consultation for expert opinion on the changes needed, and taking into consideration the clinical audit and feedback from implementation efforts in local healthcare settings.

Results

The key recommendations (diagnosis, management, and prevention) are as follows.

Diagnosis recommendations

What is the initial laboratory panel for infants, children, and adolescents presenting with AHA?

First-level testing includes hemoglobin level, red cell indices, and morphology on peripheral smear; reticulocyte count; WBC and platelet count; indices of hemolysis (indirect bilirubin, LDH); urine analysis; direct and indirect antibody tests (Coombs's test); and blood group (D) (AIEOP 2017) [23]. The panel should also include liver transaminases and kidney function: blood urea and serum creatinine (2C) (BSH 2017) [22].

What is the best timing and test to diagnose G6PD deficiency in infants, children, and adolescents presenting with AHA?

If the G6PD assay was done during a hemolytic episode of unknown cause, a re-assay is warranted to ensure the diagnosis of G6PD deficiency is not missed (1C). G6PD enzyme assay should be tested after complete recovery of the hemolytic attack and patient discharge (D) (BSH 2020) [20]. A normal G6PD activity during a hemolytic episode should be repeated after 2 months in the absence of clinical and laboratory evidence of hemolysis (D) [26].

G6PD can be diagnosed with a quantitative spectrophotometric analysis or, more commonly, by a rapid fluorescent spot test (1C). A quantitative assay must be carried out if the screening test is abnormal or borderline (1C). Do not rely on screening tests for female patients (1C) (BSH 2020) [20].

The final G6PD activity should be interpreted in the light of the reticulocyte count measured on the same sample (1C). Samples with very low mean corpuscular hemoglobin (MCH) may give G6PD activity levels above the expected value (1D) (BSH 2020) [20].

What are the indications of G6PD testing?

The indications of G6PD testing are as follows: favism (hemolysis with fava beans intake); hemolysis associated with "oxidant" drugs (Table 3) or infection; red-cell morphology suggestive of oxidant damage (blister cells/positive Heinz body stain); hemoglobinuria; hemolysis with

Fig. 1 The PIPOH model of the health questions. *G6PD* glucose-6-phosphate dehydrogenase, *MOH* Ministry of Health

previous history of neonatal pallor/jaundice (D) (BSH 2020) [20].

What is the best test to diagnose AIHA in infants, children, and adolescents presenting with AHA?

At a minimum, the direct antibody test (DAT) should include monospecific anti-IgG and anti-C3d (1C) (BSH 2017) [22].

Investigation of DAT-negative hemolysis is as follows: in patients with unexplained hemolysis and a negative screening DAT, retest with a column agglutination DAT method that includes monospecific anti-IgG, anti-IgA, and anti-C3d (1B). If also negative, consider preparing and investigating a red cell eluate (2C) (BSH 2017) [22].

What are the additional tests to be done before starting treatment in patients with AIHA?

The additional tests to be done before starting treatment in patients with AIHA are as follows: immunological markers: ANA, anti-DNA, C3, antiphospholipid, total serum immunoglobulins, CD markers, and double-negative α/β T cells if hepatosplenomegaly exists (1A) (BSH 2017) [22].

Bone marrow aspiration is only recommended in the presence of another associated cytopenia or persistent reticulocytopenia or on suspicion of neoplasia or myelodysplasia (D) (AIEOP 2017) [23].

Table 1 Health questions used to develop this adapted clinical practice guideline

Diagnosis	*History and clinical examination*: (see Figs. 2 and 3) *Laboratory diagnosis*: 1. What is the initial laboratory panel for infants, children, and adolescents presenting with AHA? 2. What is the best timing and test to diagnose G6PD deficiency in infants, children, and adolescents presenting with AHA? 3. What are the indications of G6PD testing? 4. What is the best test to diagnose AIHA in infants, children, and adolescents presenting with AHA? 5. What are the additional immunological tests before starting treatment in patients with AIHA? 6. What is the initial laboratory panel for patients with suspected post diarrheal hemolytic uremic syndrome?
Management	*Emergency management*: 1. What is the emergency treatment for infants, children, and adolescents presenting with AHA? 2. When are packed red cells indicated? Sub-question: are volume/precautions needed? *Medical pharmacological treatment*: 3. What is the medical treatment in infants, children, and adolescents with AIHA? What are the criteria of adequate/good response to treatment in infants, children, and adolescents with AIHA? *Monitoring and follow-up* 4. For follow-up after discharge, what are the laboratory tests needed in patients with G6PD and AIHA?
Prevention	1. What are the drugs to be avoided and the dietary modifications required to prevent the occurrence of AHA in patients with G6PD deficiency? 2. For prevention of HUS, when is empiric antibacterial treatment indicated for children with bloody diarrhea?

AHA acute hemolytic anemia, *G6PD* glucose-6-phosphate dehydrogenase, *AIHA* autoimmune hemolytic anemia, *HUS* hemolytic uremic syndrome

What is the initial laboratory panel for patients with suspected post diarrheal hemolytic uremic syndrome?

The initial laboratory panel for patients with suspected post diarrheal hemolytic uremic syndrome is as follows: complete blood count (hemoglobin < 10 g/dl, hematocrit < 30%, platelet count < 150,000/μl), peripheral smear (fragmented red cells – schistocytes ≥ 2%), lactate dehydrogenase (LDH > 450 IU/l), haptoglobin (undetectable), and kidney function tests (increased serum creatinine by 50% over baseline level) (D) [25].

Management recommendations

What is the emergency treatment for AHA?

If anemia is life-threatening, transfuse with ABO, Rh, and K-matched red cells (1C) (BSH 2017) [22].

When are packed red cells indicated in AHA? volume/precautions needed?

Transfusion can be avoided in hemodynamically stable patients with regular monitoring until no evidence of hemolysis (2C) (BSH 2017) [20]. Transfuse if the Hb < 5 g/dl (2C) (BSH 2017) [22]; however, based on local settings, transfuse if the Hb is < 7 g/dl with cardiac decompensation (expert opinion).

Consider the use of a blood warmer for transfusion in patients with cold AIHA (2C) (BSH 2017) [22].

Dose: 3–5 ml/kg of packed RBCs fully compatible ABO, Rh, K, and leuco-depleted and filtered blood. Transfuse slowly over 4 h (D) (AIEOP 2017) [23].

What is the medical treatment, and what are the criteria of adequate/good response to treatment in infants, children, and adolescents with AIHA?

The first-line therapy is prednisolone 1–2 mg/kg/day (1B) (BSH 2017) [22].

The second-line therapy (should be considered if no response to steroids after 3 weeks, or relapse during or after steroid reduction): consider IVIg or plasma exchange for severe or life-threatening anemia (2C) (BSH 2017) [22] and refer to the hematologist.

Patients with AIHA should receive folic acid supplementation (1C) (BSH 2017) [22].

All patients should receive oral calcium and vitamin D supplements while taking corticosteroids (typically 1200–1500 mg of calcium and 800–1000 units of vitamin D) (1A) (BSH 2017) [22].

For follow-up after discharge, what are the laboratory tests needed in patients with G6PD and AIHA?

The laboratory tests needed in patients with G6PD and AIHA are follow-up by CBC and reticulocyte count every 2–4 weeks when indicated by the treating physician (1C) (BSH 2020) [20].

Prevention recommendations

What are the drugs to be avoided and the dietary modifications required to prevent the occurrence of AHA in patients with G6PD deficiency?

Patients with G6PD deficiency should avoid exposure to oxidant drugs and ingestion of fava beans (C) (AFP 2005) [21].

Patients with suspected G6PD deficiency should avoid exposure to oxidant drugs and ingestion of fava beans till diagnosis (C) (AFP 2005) [21].

For prevention of HUS, when is empiric antibacterial treatment indicated for children with bloody diarrhea?

Antimicrobial therapy should be avoided in children with infections attributed to a certain strain of Shiga toxin-producing *Escherichia coli* that produce Shiga toxin 2 (or if the toxin genotype is unknown) (1B) (IDSA 2017) [24].

In immunocompetent children, empiric antimicrobial therapy for bloody diarrhea while waiting for results of investigations is not recommended, except for infants < 3 months of age with suspicion of a bacterial etiology (1C) (IDSA 2017) [24], ill immunocompetent children with fever, abdominal pain, bloody diarrhea, and bacillary dysentery presumptively due to *Shigella* (1C) (IDSA 2017) [24], and people who have recently traveled internationally with body temperatures ≥ 38.5 °C and/or signs of sepsis (2C) (IDSA 2017) [24].

This CPG includes a set of implementation tools: Table 2 (lists of differential diagnoses), Table 3 (list of medications and food to be avoided in patients with G6PD deficiency), Fig. 2 (algorism with a checklist for history and examination), and Fig. 3 (flow charts for the diagnosis of AHA).

Table 2 Differential diagnosis of AIHA [23]

Congenital forms	Spherocytosis and other defects of the erythrocyte membrane proteins; erythrocyte enzyme deficiency; dyserythropoietic anemia; hemoglobinopathies; Wilson's disease
Hemolytic anemia from mechanical causes	Synthetic heart valves; march hemoglobinuria; cardiopulmonary bypass
Hemolytic anemia due to vascular injury	Microangiopathic anemia; thrombotic thrombocytopenic purpura; hemolytic-uremic syndrome; disseminated intravascular coagulation; arterio-venous malformations
Hemolytic anemia due to thermal damage	Extensive burns
Hemolytic anemia from chemical causes	Chemicals: solvents; methyl chloride; lead; arsenic and hydrogen; snake venom
Hemolytic anemia due to infectious agents	Bacteria (*Mycoplasma pneumoniae*, *Clostridium welchii*); viruses (cytomegalovirus, herpes virus); protozoa (*Plasmodium* spp.)

Table 3 Common drugs that patients with G6PD deficiency should avoid or use with caution [27, 28]

Generic name	Risk level	Generic name	Risk level
Acetaminophen	Low	Moxifloxacin	High
Acetylsalicylic acid	Variable[a]	Naphthalene	High
Ascorbic acid (vitamin C)	High with high dose	Nitric oxide	High
Chloramphenicol	High	Nitrofurantoin	High
Ciprofloxacin	High	Nitroglycerin	High
Colchicine	Low	Phenazopyridine (Pyridium)	High
Dapsone	High	Primaquine	High[b]
Diphenhydramine	Low	Probenecid	High
Glimepiride	High	Rasburicase	High[c]
Glipizide	High	Sodium nitroprusside	High
Glyburide	Use with caution	Streptomycin	Low
Hydroxychloroquine	High	Sulfacetamide	High
Isoniazid	Low	Sulfamethoxazole	High[d]
Levofloxacin	High	Trimethoprim	Low[d]
Methylene blue	High	Vitamin K	Low to high[e]

[a] Risk level low to none, use with caution

[b] Reduce dose with medical therapy if required

[c] Prescribing modification required

[d] Also, when in combination with the other drug

[e] High with vitamin K3 (menadione), low with vitamin K1 (phytomenadione)

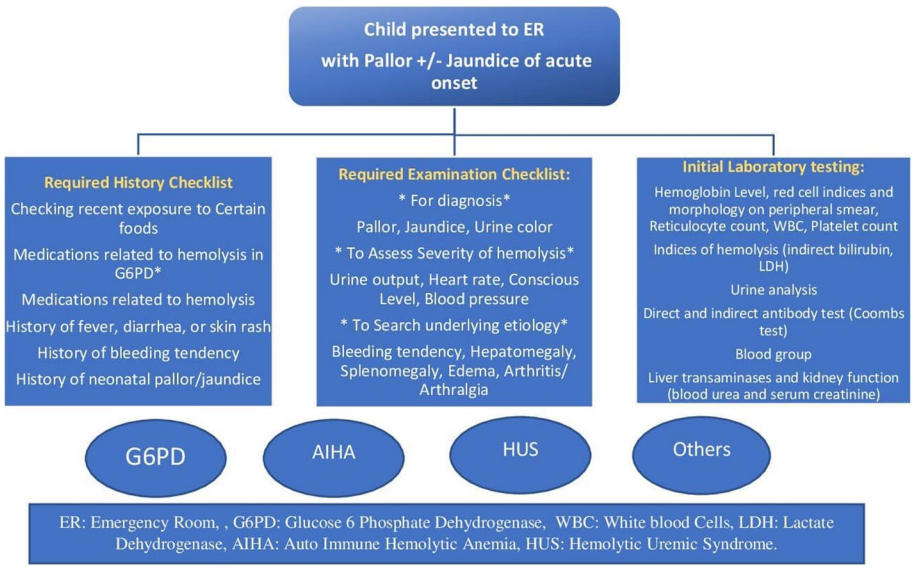

Fig. 2 Diagnostic approach to the child presenting to the ER with acute pallor +/– jaundice

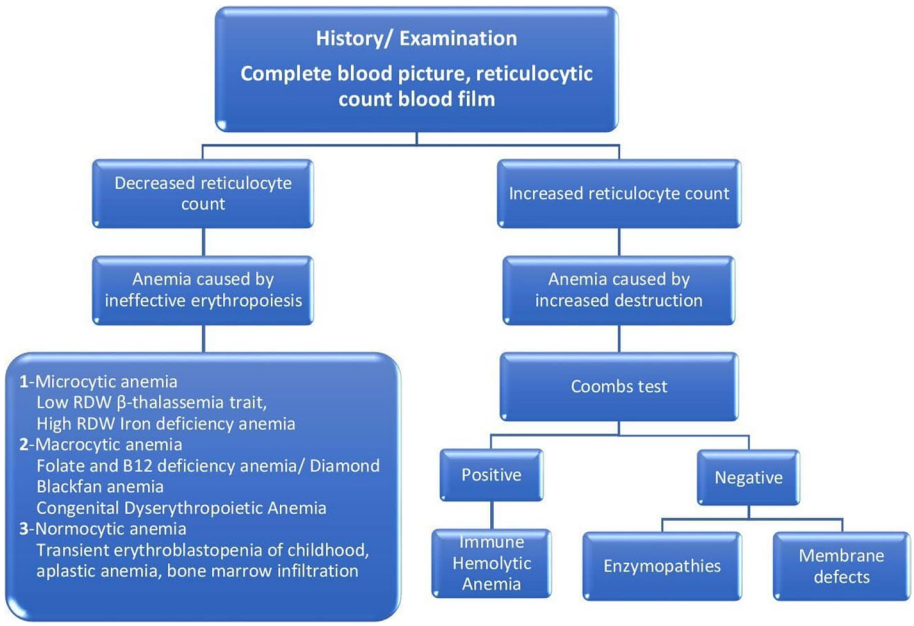

Fig. 3 Diagnostic approach to the child with acute pallor +/– jaundice according to the reticulocyte count

Discussion

These clinical practice guidelines (CPGs) were systematically developed recommendations in order to assist healthcare professionals and patients in medical decision-making for AHA. CPGs intended to optimize patient care that is informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options, but are in no way a substitute for a medical professional's independent judgment and should not be considered medical advice. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied. This adapted guideline will aid decision-making related to the diagnosis, management, and prevention of AHA.

Conclusion

Diagnosis and prevention show strong recommendations, while management plans depend on patient assessment. Referral to a pediatric hematologist is recommended in complicated cases.

Abbreviations

AHA	Acute hemolytic anemia
AKI	Acute kidney injury
AEA	Anti-erythrocyte autoantibodies
AIHA	Autoimmune hemolytic anemia
AFP	American Family Physician
AIEOP	Italian Association of Paediatric Onco-Haematology
BSH	British Society of Haematology
C3	Complement 3
CPG	Clinical practice guidelines
DAT	Direct antiglobulin test
G6PD	Glucose-6-phosphate dehydrogenase deficiency
GL	Guideline
GSH	Reduced glutathione
Hb	Hemoglobin
HUS	Hemolytic uremic syndrome
IDSA	Infectious Diseases Society of America
PCH	Paroxysmal cold hemoglobinuria
PHWG	Pediatric hematology work group
PIPOH	Patient, Intervention, Professionals, Outcomes, Healthcare settings
RBC	Red blood cell
STEC	Shiga toxin-producing *Escherichia coli*

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Authors' contributions

GM: selection of the topics and reference guidelines, revise checklists for scoping. AB: member of The Egyptian Pediatric Clinical Guidelines Committee (EPCGC) that approved the submitted version statements after local and international peer reviewing for validation. IY: searched and extracted the recommendations for prevention. IR: searched and extracted the recommendations for diagnosis. LS: searched and extracted the recommendations for diagnosis. MZ: searched and extracted the recommendations for diagnosis and author of the "Methods" section and figures. MH: searched and extracted the recommendations for diagnosis. NS: searched and extracted the recommendations for prevention. RR: searched and extracted the recommendations for prevention. SM: searched and extracted the recommendations for diagnosis and author of the "Abstract." SS: searched and extracted the recommendations for treatment. SAH: searched and extracted the recommendations for diagnosis. TO: member of EPCGC that approved the submitted version statements after local and international peer reviewing for validation. YA: member of EPCGC that approved the submitted version statements after local and international peer reviewing for validation. NMS: searched and extracted the recommendations for prevention, principal and corresponding author. All authors participated in the selection and appraisal of the guidelines. All have read and approved the manuscript and have given rights to the corresponding author to make necessary changes requested by the journal on behalf of all authors.

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Availability of data and materials

All Egyptian Practice Guidelines CPG summaries and related documents can be freely accessed from the official website: http://epg.edu.eg/.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Pediatrics, Pediatric Hematology, Oncology and BMT Unit, Ain Shams University, Cairo, Egypt. [2]Department of Pediatrics, Pediatric Allergy and Immunology, Ain Shams University, Cairo, Egypt. [3]Department of Pediatrics, Pediatric Hematology and BMT Unit, Cairo University, Cairo, Egypt. [4]Department of Pediatrics, Pediatric Hematology and Oncology Unit, Zagazig University, Zagazig, Egypt. [5]Armed Forces College of Medicine, Cairo, Egypt. [6]Department of Pediatrics, Helwan University, Cairo, Egypt. [7]Department of Pediatrics, National Research Institute, Cairo, Egypt. [8]Department of Pediatrics, Pediatric Neurology, Alexandria University, Alexandria, Egypt. [9]Pediatrics Department, Clinical Practice Guidelines & Quality Research Unit, Quality Management Department, and Research Chair for Evidence-Based Health Care and Knowledge Translation, King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia. [10]Egyptian Pediatric Clinical Practice Guidelines Committee (EPG), Cairo, Egypt. [11]Adaptation Working Group, Guidelines International Network, Perth, Scotland.

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