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# Evidence-based Egyptian clinical practice guidelines: for the prevention and management of iron deficiency and iron deficiency anemia in infants, children and adolescents

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## Abstract

**Background** Iron deficiency (ID) is the most common nutritional disorder affecting all age groups. Infants and young children are vulnerable to anemia especially iron deficiency anemia (IDA), which represents a public health problem with defined impacts on the health of communities. IDA, however, is a preventable and treatable condition; therefore, early diagnosis represents the cornerstone in protection from its adverse consequences and combating its contributing factors. Several international guidelines for the management of ID/IDA are available, however national guidelines that can be implemented and suits our local needs are lacking.

**Objective** To adapt the pre-existing high-quality practice guidelines for the screening, prevention and management of ID/IDA in different pediatric age groups, to be available for the national use by general practitioners, pediatricians, and other health care professionals.

**Results** The adaptation group for this guideline included key leaders from different Egyptian institutions. The panel used the ADAPTE methodology for adaptation of guidelines. 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 the target context of use. The guideline covered all important aspects of detection, identification of infants, children, and adolescents at high risk of developing ID/IDA, proper management, and prevention. The final version of the adapted clinical practice guideline has been made after thorough review of an external review panel and was guided by their official recommendations and modifications. Implementation tools included algorithms, tables, and flow charts to aid decision making in practice, as well as patient-directed information in the Arabic language.

**Conclusions** This adapted guideline serves as a tool for the screening, prevention and management of ID/IDA in different pediatric age groups.

**Keywords** Anemia, Iron-deficiency, Pediatrics

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## Background

Iron deficiency anemia (IDA), the most prevalent single nutrient deficiency in the world, is recognized by world health organization (WHO) as one of 10 greatest global health risks in existence today (Low et al. 2013).

There are three peak times for the risk of developing ID in early life, based on the balance of iron supply and demand, which are perinatal, toddlerhood, and adolescence, with the latter being particularly in females. Unfortunately, several human infant studies have demonstrated that the effects of “early” ID on biological neural functioning are potentially irreversible (Georgieff 2008).

Globally, iron deficiency anemia ranks number 9 among 26 risk factors included in the Global Burden of Disease (GBD) 2000, and accounts for 841,000 deaths and 35,057,000 disability-adjusted life years lost (WHO 2011; Stoltzfus 2003). In 2021, the global prevalence of anaemia across all ages was 24.3% corresponding to 1.92 billion (1.89–1.95) prevalent cases, compared with a prevalence of 28.2% and 1.50 billion (1.48–1.52) prevalent cases in 1990. Dietary iron deficiency was reported as one of the most common causes of anaemia years lived with disability (YLDs) in 2021 (GBD 2023).

The prevalence of anemia, mainly IDA, in developing countries is three to four times higher than that for developed countries (ACC/SCN 2000). Africa and parts of Asia bear 71% of the global mortality burden and 65% of the disability-adjusted life years lost (WHO 2011; Stoltzfus 2003).

In Egypt, previous studies have indicated that anemia is a major public health problem affecting 30–40% of children, especially school children. IDA was found to be the most common cause of anemia, affecting 43% of Egyptian infants 6 to 24 months of low socioeconomic standard. In children aged less than 5 years, IDA affects more than 40%. Among children 6–12 years of age, reported IDA prevalence was 12%, 26.6%, 29% in Qena governorate, Beni-suef and Elmenofya governorates, respectively (Mabrouk et al. 2022; El-Asheer et al. 2021). Other studies reported variable prevalence of anemia, with the 55.7% recorded among schoolchildren in Lower Egypt, 54.1% among preschool children and 52% among adolescents (Data and on Iron Deficiency Anemia in Egypt 2010).

Screening of infants with one or more risk factors for ID would allow treatment of ID in the pre-anemic stage, thereby preventing its associated mental, motor, and behavior effects (Baker and Greer 2010). Prevention and control strategies against IDA are mainly dependent on the timing of diagnosis and start of treatment. The WHO ‘Global Strategy for Infant and Young Child Feeding’ was developed as guidance to the prevention of micronutrient

deficiencies including ID and IDA (World Health Organization 2003).

The purpose of developing the Egyptian guidelines was to identify strategies and comprehensive actions needed to eliminate anemia as a major public health problem among infants, young children and adolescents based on the available evidence.

## Methods

The scope of this guideline is ID and IDA in infants, children, and adolescents. The objectives are early detection, identification of infants, children, and adolescents at high risk of developing ID/IDA, proper management, and prevention. The population targeted are infants, children, and adolescents less than 18 years, of both genders, with or at risk of ID and IDA, and with no comorbidities. The panel chose not to address non-nutritional causes of iron deficiency as in cases of parasitic infestations, bleeding disorders, inflammatory disorders, and diseases where anemia is multifactorial and requires specific lines of treatment other than iron. The target users include primary health care physicians at Ministry of Health (MOH), general practitioners, family medicine specialists, pediatricians, neonatologists and specialists from related disciplines, nurses and rural social health workers, medical students, dentists, pharmacists, parents, and caregivers. Primary and secondary governmental, non-governmental and private sectors are targeted. The aim is to decrease prevalence of ID and IDA through early detection, treatment, and prevention of complications. Health questions were constructed to fulfill this aim.

The adaptation group for this guideline was chosen from various Egyptian Universities and the national research center. The panel used the ADAPTE methodology for adaptation of guidelines (ADAPTE Resource Toolkit versions 2.0 2009; Yasser Sami Amer et al. 2015).

The ADAPTE process consists of three phases, nine modules and 24 steps (Adaptation Working Group 2015; Fervers et al. 2006, 2011; Harrison et al. 2009). The process utilizes the AGREE II Instrument, that is both valid and reliable, consists of 23 items/questions that are organized into six quality domains. Each item of the 23 assesses a different aspect of the quality of the clinical practice guideline (CPG). The six domains include (1) scope and purpose; (2) stakeholder involvement; (3) rigor of development; (4) clarity of presentation; (5) applicability; and (6) editorial independence. The AGREE II also includes two final overall assessment items (AGREE Website by Minervation <http://www.minervation.com/aboutus/contact/>; Cluzeau and The AGREE Collaboration 2003; Alonso-Coello et al. 2010; The AGREE Collaboration 2003; Burgers et al. 2003a, b; The AGREE Collaboration Writing Group 2000; Brouwers et al.

2010). A shorter tool, the AGREE II-Global Rating Scale Instrument (AGREE II-GRS Instrument), with only 5 items has been developed and evaluated (The AGREE II-GRS Instrument 2015). The My AGREE PLUS is a user-friendly online platform to facilitate and support the completion, calculation, and coordination of multi-rater AGREE II appraisal groups. It can be used free of charge upon registration (My AGREE PLUS Platform 2015).

The search in literature was done using PubMed and google scholar portals. Searches were conducted from February 2019 to March 2019. The ID Egyptian pediatric clinical practice guidelines (EPG) committee studied several guidelines addressing diagnosis, management & prevention of ID/IDA. Critical appraisal was done by AGREE II (Appraisal of Guidelines, Research and Evaluation) (ADAPTE Resource Toolkit versions 2.0 2009; Yasser Sami Amer et al. 2015), to rate and select the appropriate guidelines. The final decision was to adapt:

- WHO Guideline: Daily iron supplementation in adult women and adolescent girls. Geneva: World Health Organization (2016).
- WHO Guideline: Daily iron supplementation in infants and children. Geneva: World Health Organization (2016).
- The National Blood Authority's Patient Blood Management Guidelines: Module 6—Neonatal and Paediatrics, which is licensed under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Australia licence. (NBA) (2016).

The source guidelines representatives were approached via e-mails and approval for adaptation was obtained. The ID EPG committee suggested different health questions to be answered from the chosen guidelines. The search for answer to each question was assigned to different members of ID EPG committee. The members met 7 times, face-to-face meetings, throughout the development of these guidelines to discuss and finalize the recommendations. Implementation tools were developed and revised by the ID EPG group to be used by health care professions and families for education and awareness.

Generally, the panel has chosen the recommendations with clearly presented evidence that were common in the three source guidelines and those that represent the current acceptable and applicable practice. Health questions, for which no answers were found in the chosen guidelines' committee, with one exception that was answered from US Preventive Services Task Force (USPSTF) 2006 recommendation on screening for iron deficiency anemia, agreed upon from the guideline committee (Siu and

US Preventive Services Task Force 2015). The grading of recommendations was taken from the source guidelines. WHO guidelines utilized The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (GRADE Working Group 2015), while the NBA utilized National Health and Medical Research Council (NHMRC) grades for recommendations (2009).

The final version of the adapted CPG has been made after thorough review from the external review panel of the first draft adapted CPG and was guided by their official recommendations and modifications. Implementation tools included algorithms, tables, and flow charts to aid decision making in practice, as well as patient-directed information in the Arabic language.

The panel has decided to review the adapted guideline for updates after 5 years from its publication date (2019), which should be in (2024), after checking for updates in the source guidelines, consultation of expert opinion on the changes needed for updating according to the newest evidence and recommendations published in this area and the clinical audit and feedback from implementation efforts in local healthcare settings, except if any breakthrough evidence-based recommendations is published before that date.

## Results

### Health Questions used to develop this Adapted guideline

#### Questions 1–2: Clinical screening

1. Does clinical screening for symptoms and signs of iron deficiency anemia in infants and children done by the primary health care professional/pediatrician in primary health care setting/ out-patient clinic (OPC), improve the early detection of IDA and the neurodevelopmental outcome?
2. Does clinical screening for symptoms and signs of iron deficiency anemia in adolescent females at yearly school visit, done by the primary health care professional/pediatrician in primary health care setting/ OPC, improve the early detection of IDA?

#### Question 3: Dietary screening

3. Does routine dietary history checklist for iron containing food in infants, children, and adolescents, done by the primary health care professional/ pediatrician in primary health care setting/ OPC, help identify dietetic problems, improve the early detection of ID/IDA and neurodevelopmental outcome?

**Questions 4–5: Laboratory screening**

4. Is there a non-invasive, simple, safe, precise screening test for ID/IDA in infants, children, and adolescents?
5. Does routine basic laboratory screening for ID/IDA in infants, children, and adolescents, in primary health care setting or OPC improve the early detection of ID/IDA and the neurodevelopmental outcome?

**Questions 6: Diagnosis**

6. What are the laboratory tests with the cut-off levels for diagnosis of IDA in infants, children, and adolescents, in primary health care setting or OPC?

**Questions 7–8: Treatment and monitoring response**

7. What is the best treatment, dose, and duration for treatment of ID and IDA in infants, school children and adolescents done in primary health care setting or general pediatric department to ensure successful treatment of ID and IDA?
8. What is the most cost-effective plan to monitor response to treatment of infants, school children and adolescents with identified ID and IDA, in primary health care setting or general pediatric department, to ensure successful treatment of ID and IDA?

**Questions 9–10: Referral / Other non-dietetic etiologies**

9. Does history taking about symptoms suggestive of possible gastrointestinal malabsorption, losses or inflammatory conditions in patients identified with IDA with no obvious dietetic problem help in diagnosing underlying undiagnosed etiology compared to simple dietetic history taking?
10. When to consider referral to hematologist/ gastroenterologist / gynecologist, in infants, school children and adolescents

with ID and IDA, in primary health care setting or general pediatric department?

**Questions 11–12: Prevention by supplementation and diet**

11. Does routine iron supplementation help in preventing development of ID and IDA in infants, children and adolescent females in primary health care setting or general pediatric department?
12. Does routine dietary modification with high iron containing food help in preventing development of ID and IDA in infants, children and adolescent females in primary health care setting or general pediatric department?

**Summary of key recommendations**

Health question number	CPGL Source	Recommendation	Grade of evidence
<i>Screening</i>			
1	Guideline's expert opinion	Clinical screening for symptoms and signs of iron deficiency anemia, in infants and children, done by the primary health care professional/ pediatricians in primary health care setting/ OPC, improves the early detection of IDA and the neurodevelopmental outcome	GEOP*
2	Guideline's expert opinion	Clinical screening for symptoms and signs of iron deficiency anemia, in adolescent females, at yearly school visit, done by the primary health care professional/pediatrician in primary health care setting/OPC, improves the early detection of IDA	GEOP*

Health question number	CPGL Source	Recommendation	Grade of evidence	Health question number	CPGL Source	Recommendation	Grade of evidence
3	Guideline's expert opinion	Routine dietary history checklist, for iron containing food in infants, children and adolescents, without non-iron related comorbidities, done by the primary health care professional/ pediatrician in primary health care setting/OPC, helps identify dietetic problems, improve the early detection of ID/IDA and neurodevelopmental outcome	GEOP*	6	WHO 2016	Iron deficiency is considered if serum ferritin level is below 12 ug/L in all age groups in the absence of infection/ inflammation	D
4	Guideline's expert opinion	There is no one test considered gold standard for diagnosing iron deficiency or IDA, so official recommendations vary There is no sufficient evidence to recommend specific screen tests for IDA No studies evaluating the benefits or harms of screening programs for asymptomatic children	GEOP*	6	WHO 2016	Iron deficiency is considered if serum ferritin level is below 30 ug/L in all age groups in the presence of infection/ inflammation	D
5	US Taskforce	Laboratory screening of the general population for ID/IDA is not recommended Laboratory testing of infants, children, and adolescents at high risk (identified by clinical screening i.e., symptoms and signs) is recommended		<i>Treatment</i> 7, 8	NBA 2016	Oral iron therapy: Dose: 3–6 mg/kg/day for all ages Forms: syrup; tablets (each preparation contains different elemental iron dose) (not exceed maximum dose) Time: 1h before or 2 h after meals with Vitamin C at daytime Monitoring: after one month by CBC and reticulocytic count, then at 3, 6 months If no response after one month: revise dose, compliance, tolerability, type of formula and consider change of formula for another month Duration: for 3 months after recovery of hemoglobin Tips for Oral iron intake Lower and intermittent dose may be as effective and better tolerated To avoid gastric upset, can be taken at night, and increasing dose gradually Teeth staining can be avoided by brushing teeth and taking with water	EOP***
<i>Diagnosis**</i>				6	WHO 2016	Anemia is diagnosed if hemoglobin level is below the cut-off level for age and sex	C
6	WHO 2016	Microcytosis is diagnosed if mean corpuscular volume is below – 2 SD for age related reference range	D				

Health question number	CPGL Source	Recommendation	Grade of evidence	Health question number	CPGL Source	Recommendation	Grade of evidence
7, 8	NBA 2016	If oral iron is ineffective or is not tolerated, consider other causes of anemia, and refer to Hematologist (avoid parenteral iron therapy) Packed RBCs should be considered after Hematologist opinion	EOP***	11	WHO 2016	Daily iron supplementation of 30 mg elemental iron daily (Drops/syrups/tablets) for three consecutive months is recommended as a public health intervention in preschool children aged 24 to 59 months, living in settings where anemia is highly prevalent****	B
7, 8	NBA 2016	Nutritional support with iron rich formulas, solid food, and oral iron support 1–2 mg/kg/day elemental iron should be used to treat asymptomatic iron deficiency anemia in infants	EOP***	11	WHO 2016	Daily iron supplementation of 30–60 mg elemental iron daily (Drops/syrups/tablets) for three consecutive months is recommended as a public health intervention in school aged children aged 5–12 years, living in settings where anemia is highly prevalent***** Daily iron supplementation 30–60 mg elemental iron daily (Tablets), for three consecutive months in a year, is recommended as a public health intervention in menstruating adult women and adolescent girls, living in settings where anemia is highly prevalent*****, for the prevention of anemia and iron deficiency	A
<i>Referral</i> 9, 10	Guideline's expert opinion	Referral to hematologist should be considered in cases of severe anemia, history of recurrent bleeding or with failure of increase in the hemoglobin concentration after proper iron dose and proper way of administration	GEOP*				
<i>Prevention of ID and IDA</i> 11	WHO 2016	Daily iron supplementation of 10–12.5 mg elemental iron daily (Drops/syrups) for three consecutive months is recommended as a public health intervention in infants and young children aged 6–23 months, living in settings where anemia is highly prevalent****	B				

Health question number	CPGL Source	Recommendation	Grade of evidence
12	WHO 2009 NBA 2016	Dietary prevention Start complementary feeding with iron rich food Avoid cow milk, goat milk, soy to infants under 12 months of age From 12 months, cow milk should not exceed 500 ml per day For non-breast-fed infants, iron fortified formula can play a role in prevention and treatment of IDA	

\*Guideline's expert opinion point

\*\*Diagnosis of IDA should include the presence of anemia, microcytosis and iron deficiency

\*\*\*NBA Expert Opinion Point

\*\*\*\*The prevalence of anemia among children less than 5 years (% of children under 5) in Egypt was 31.70 in 2016 (<https://www.who.int/data/gho>)

\*\*\*\*\*Girls aged 5–19 years were somewhat more likely than boys in the same age group to be anemic (21% and 18%, respectively) (Ministry of Health and Population [Egypt], El-Zanaty and Associates [Egypt], and ICF International 2015)

## Discussion

Clinical practice guidelines (CPGs) are statements that include recommendations for improving patient care. High-quality evidence-based CPGs are of value to support the clinical decisions of relevant healthcare providers and to improve patient outcomes (Djulgovic et al. 2019; Liu et al. 2021).

As defined by the Guidelines International Network (GIN) (and the former ADAPTE Collaboration), adaptation is “the systematic approach to the modification of a guideline(s) or recommendation(s) produced in one cultural and organizational setting for application in a different context. Adaptation may be used as an alternative to de novo guideline development (e.g., for customizing (an) existing guideline/s to suit the local context)” (Fervers et al. 2011; The ADAPTE Collaboration 2009).

The EPG committee marks the first national and collaborative initiative for the generation of Pediatric CPGs using an evidence-based methodology in Egypt.

The EPG committee decided to use the CPG adaptation methodology, specifically the ‘Adapted ADAPTE’ methodological framework, because it is clearly structured and easy to follow with a set of tools to support the process (Abdel Baky et al. 2023).

Given the lack of relevant high-quality systematic reviews and randomized controlled trials from the Egyptian context, the adaptation of CPG recommendations is a good and valid alternative to developing de-novo CPG for children with ID/IDA. The ID/IDA guideline adaptation project marks the first for the EPG Hematology Group as part of the first wave of the EPG (Abdel Baky et al. 2023).

The strategic plan for national pediatric evidence-based CPGs includes identifying the national health-care priorities (high-priority health topics for CPGs) in the field of pediatrics and child health. ID, and specifically IDA, remains one of the most severe and important nutritional deficiencies in the world today. Every age group is vulnerable. Iron deficiency impairs the cognitive development of children from infancy to adolescence. It damages immune mechanisms and is associated with increased morbidity rates (Georgieff 2011).

Generally, the panel has chosen the recommendations with clearly presented evidence that were common in the three source guidelines and that represent the current acceptable and applicable practice of primary health care physicians at MOH, general practitioners, family medicine specialists, pediatricians, neonatologists and specialists from related disciplines, nurses and rural social health workers, medical students, dentists, pharmacists, parents, and caregivers.

This CPG is not intended to be explained or to serve as a standard of medical care. Adherence to the CPG recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgment regarding a particular clinical procedure or treatment plan must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgment should only be arrived following discussion of the options with the patient/caregiver, in light of the diagnostic and treatment choices available. However, it is advised that significant departures from the national CPG or any local CPGs derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

With the establishment of the Egyptian Health Council (2023), the authors hope the EPG CPGs in general and the EPG Hematology Group CPGs in particular will be properly disseminated, implemented, and audited throughout different sectors of the Egyptian health system that provide healthcare services for children with hematological diseases and disorders to improve quality and safety.

The ID/IDA EPG group included a comprehensive implementation tools set (e.g. tables for cut-off values for hemoglobin, microcytosis, dietary reference for adequate iron intake, factors that increase or decrease iron absorption, etc....) to facilitate successful uptake of the adapted recommendations (Additional file 1).

Barriers to implement the guidelines could be lack of awareness of the magnitude of this national health problem which necessitates further efforts to shed light on it through campaigns, media, schools and health care centers. Another barrier could be shortage of heme-iron rich diet which could be solved by mixing several iron containing plants and cereals. Nutritional advice to improve bioavailability should include avoidance of excess milk, tea, coffee and fast foods. Moreover, availability of iron supplements in different forms and concentrations and with minimal side effects should be a master key in treating iron deficiency anemia.

There are several limitations to the application of this CPG. The panel chose not to discuss the issue of delayed cord clamping in neonates, as this may vary in different institutions according to the local practice guidelines. The chosen adapted guidelines did not differentiate between doses of iron supplementation in preterm and term infants. The current CPG focused on dietary ID/IDA, and excluded patients with comorbidities like parasitic infestations, inflammatory conditions, chronic kidney disease and other conditions that have multiple pathogenetic mechanisms with specific modes of treatment. However, with future revisions, these objectives could be revisited, and other objectives may be sought in view of the most recent evidence in the coming years.

## Conclusions

This CPG intended to assist the practitioners (Primary and secondary health care practitioners working in governmental, non-governmental and private sectors) to apply the best available research evidence to clinical decisions about the prevention and management of iron deficiency and iron deficiency anemia in infants, children and adolescents.

## Abbreviations

AFCM	Armed Forces College of Medicine
AGREE II-GRS Instrument	AGREE II-Global Rating Scale Instrument
CPG	Clinical practice guideline
EOP	Expert opinion point
EPG	Egyptian pediatric clinical practice guidelines
GBD	Global Burden of Disease
GEOP	Guideline's expert opinion point
GIN	Guidelines International Network
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ID	Iron deficiency
IDA	Iron deficiency anemia

MOH  
NBA  
NHMRC  
OPC  
USPSTF  
WHO  
YLDs

Ministry of Health  
National Blood Authority  
National Health and Medical Research Council  
Outpatient clinic  
US Preventive Services Task Force  
World health organization  
Years lived with disability

## Supplementary Information

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**Additional file 1.** Implementation Tools.

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## Author contributions

AA and TO supervised the adaptation methodology. GM, AY, EE, ER, IY, IR, LS, MF, MH, NS, RA, SS, SH, and YG searched for existing guidelines, prioritized the health questions and recommendations according to their importance for clinicians and patients. GM, AY, AA, EE, ER, IY, IR, LS, MF, MH, NS, RA, SS, SH, TO, and YG revised and approved the submitted manuscript.

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## Availability of data and materials

Not applicable.

## 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.

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