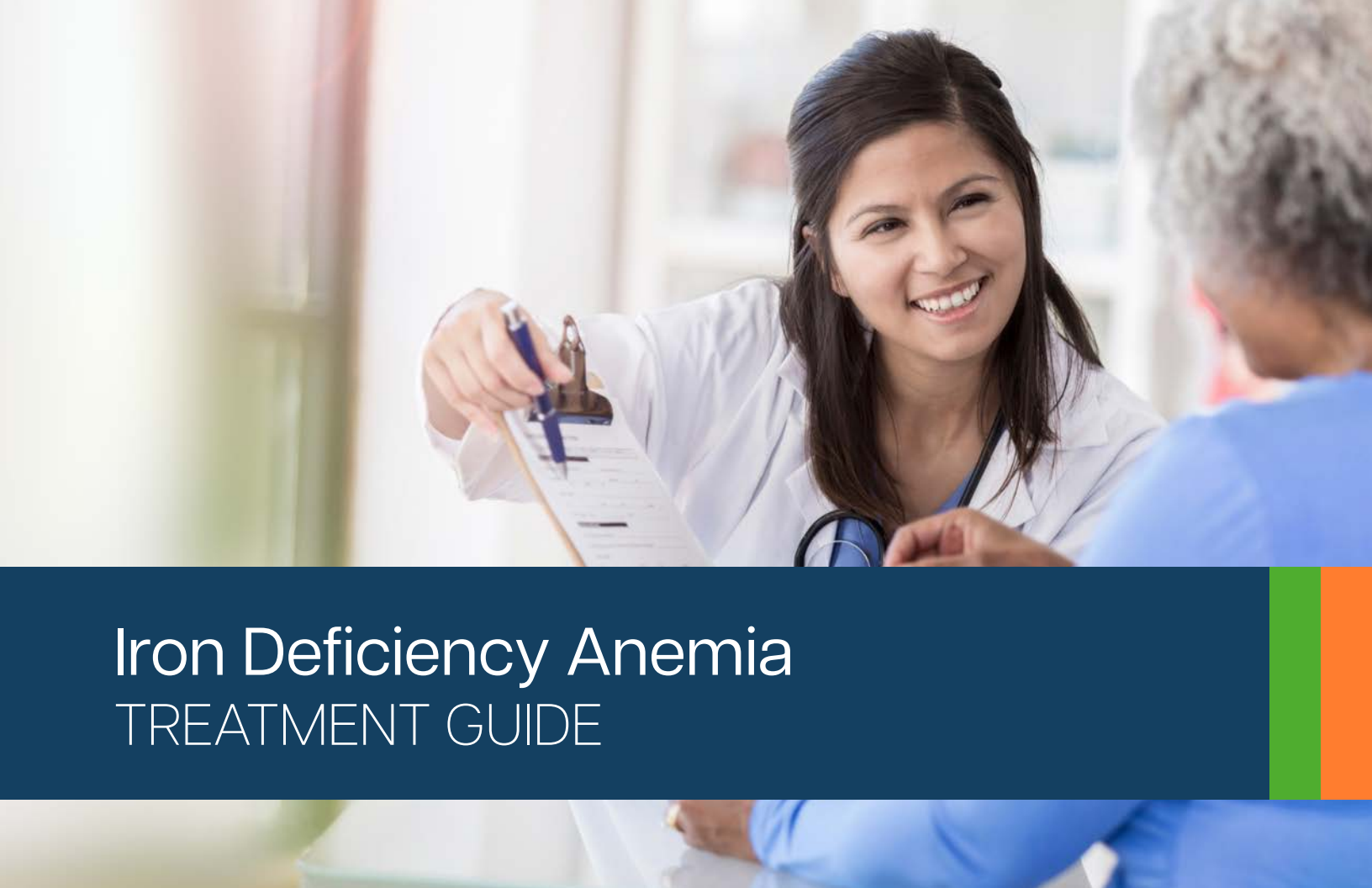

Iron Deficiency Anemia
TREATMENT GUIDE

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Recognition of Iron Deficiency in Clinical Practice[1,2]

Screening for iron deficiency is currently not recommended in the general population. High-risk patients should be identified and screened as appropriate.

INCREASED IRON NEEDED

Physiologic State:

- Menstruation
- Rapid growth spurts (infants, children, adolescents)
- Pregnancy (2nd/3rd trimester)
- Lactation

Blood Loss:

- GI bleeding (GI cancer, hemorrhoids, peptic ulcer disease, IBD, angiodysplasia, chronic/ high dose use of salicylates or NSAIDs, etc.)
- Genitourinary (menorrhagia, hematuria)
- Intravascular hemolysis
- Regular blood donation
- Post-operative patients with significant blood loss
- Endurance athletes

DECREASED IRON AVAILABILITY

Decreased Intake:

- Low socioeconomic status
- Diet (vegetarian/vegan, iron poor, malnutrition)
- Eating disorder
- Alcohol use disorder
- Age above 65 years old

Decreased Absorption:

- Diet (carbonated drinks, coffee, etc.)
- Upper GI pathology (chronic gastritis, gastric lymphoma, celiac disease)
- Medications that decrease gastric acidity or bind iron (e.g. antiacids/PPIs)
- Gastrectomy or duodenal bypass
- Bariatric surgery
- Chronic renal failure
- Pediatric short bowel syndrome

Typically, iron deficiency is indicative of an underlying etiology of a decrease in iron availability or an increase in iron need (negative iron balance)

GI: gastrointestinal; IBD: inflammatory bowel disease; NSAID: non-steroidal anti-inflammatory drugs; PPI: proton pump inhibitors.

Recognition of Iron Deficiency in Clinical Practice[1,2]

Early-stage iron deficiency can present as non-hematological symptoms due to insufficient levels of iron-containing cellular enzymes and unsaturated myoglobin, and should be monitored accordingly.

COMMON SIGNS AND SYMPTOMS OF IRON DEFICIENCY IN ADULTS INCLUDE:

SYMPTOMS


Fatigue/shortness of breath


Irritability/ depression


Light-headedness


Headaches


Cold intolerance


Decreased exercise performance, or difficulty in daily regular activities


Hair loss


Chest pain


Pica/pagophagia (ice craving)

SIGNS


Nail changes (e.g. koilonychia [spoon nails])


Angular cheilitis*


Atrophic glossitis (loss of tongue papillae)


Restless leg syndrome


Blue sclerae


Adverse pregnancy outcome


Impaired immune function

- The earliest clinical clue is the symptom of chronic fatigue & decreased exercise tolerance
- Iron deficiency should always be included in differential diagnosis

*Angular cheilitis is a condition that causes red, swollen patches in the corners of mouth where lips meet and make an angle. It often causes painful, cracked sores which may be confused with cold sores; however, unlike cold sores, angular cheilitis is not contagious.

Clinical Evaluation of IDA[1]

Once iron deficiency has been diagnosed, clinical evaluation of the etiology should be performed based on the patient's history, symptom review and physical examination, and should include:

- Nutrition and physical activity history
- Pregnancy status and number of pregnancies
- History of blood loss, including GI bleeding, hematuria, menorrhagia and blood donation
- History of AUB in pre- and post-menopausal women
- GI symptoms including changes in bowel habits, abdominal pain, dyspepsia, presence of fresh blood in the stool and dark stool
- Unexplained weight loss
- Family history of GI malignancies including colorectal cancer

Investigating the underlying cause of IDA is as important as treating the IDA.

Etiology Considerations

- Menorrhagia is the most frequent cause of iron deficiency among women
- For adult men, post-menopausal women and pre-menopausal women without menorrhagia, iron deficiency is likely to have serious underlying causes of blood loss, including malignancy
- Additional investigation for overt and occult GI and GU bleeding is strongly recommended

AUB: abnormal uterine bleeding; CBC: complete blood count; GI: gastrointestinal.

Testing for Iron Deficiency[1,2]

For patients suspected of iron deficiency, initial testing includes serum ferritin and complete blood count.

SERUM FERRITIN*	CUT-OFF VALUES
Male	<30 µg/L
Female	<30 µg/L
Children (under 12 years old)	<10 µg/L
COMPLETE BLOOD COUNT (CBC)	**CUT-OFF VALUES****
Mean Corpuscular Volume (MCV)	<75 fl
Hemoglobin (Hb)	
Male (above 14 years old)	<135 g/L
Female (above 14 years old)	<120 g/L
Male (12-14 years old)	<115 g/L
Female (12-14 years old)	<125 g/L
Male & female (>12 years old)	<115 g/L

*There is considerable variation in serum ferritin cut-offs recommended by different expert groups to diagnose iron deficiency and IDA. Also, the diagnosis of iron deficiency anemia in the context of inflammation requires significantly higher threshold levels for ferritin to define iron deficiency anemia.
**Cut-off values vary by labs and references used. These are suggested cut-offs only, and clinical interpretation is also required.

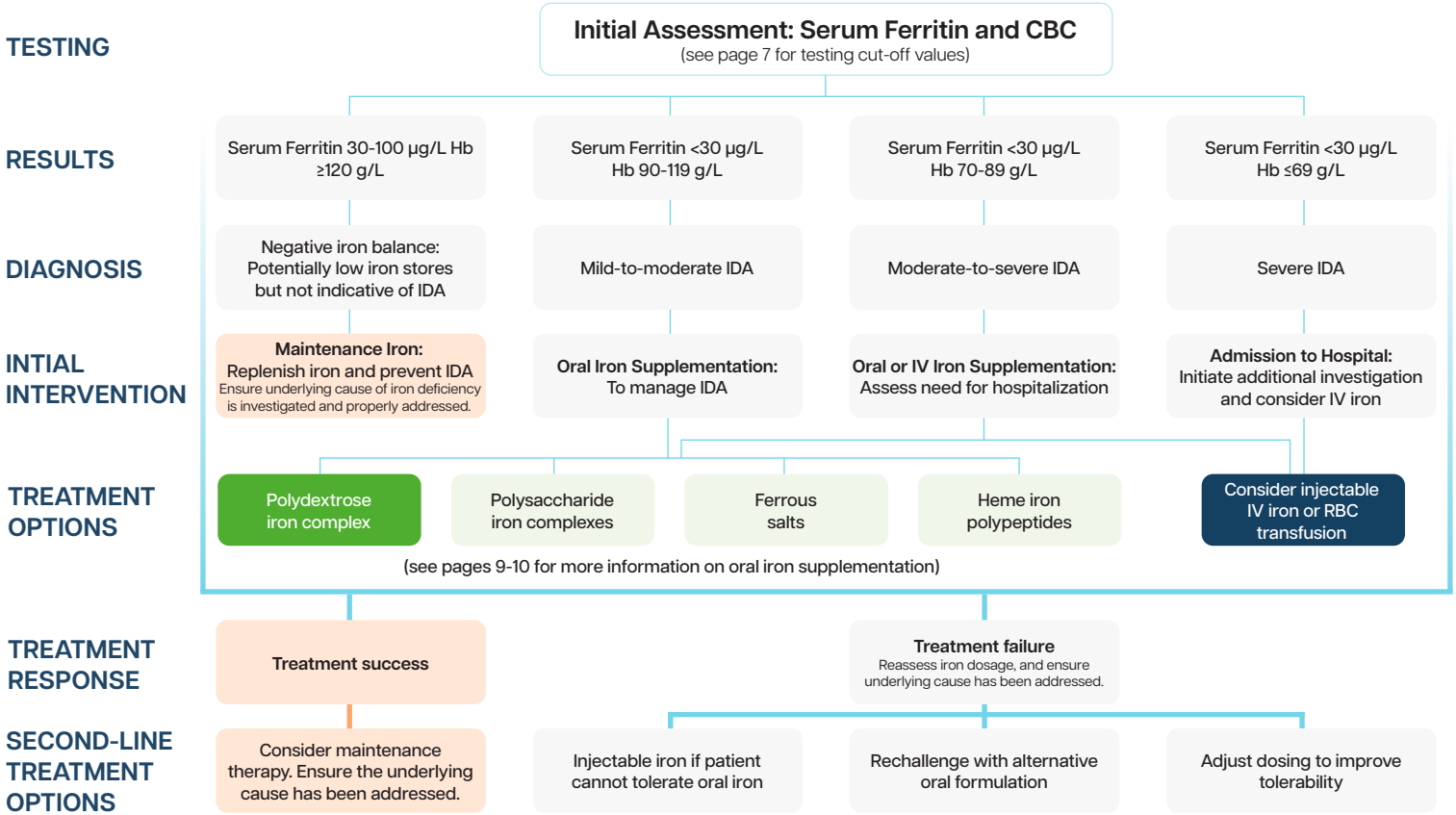
Serum ferritin is the diagnostic test of choice for iron deficiency as it gives an indication of total body iron stores.

CBC may suggest iron deficiency; however, patients with IDA may present with normal MCV and therefore measuring serum ferritin is required.

Although the commonly reported threshold of 15 µg/L is likely specific, it can miss many cases of iron deficiency. Using a cut-off of 30 improves sensitivity from 25 to 92 percent, when specificity remains high at 98 percent.[3]

- Iron replacement therapy should begin as soon as iron deficiency is detected (Ferritin 30-100 ug/L), whether or not anemia is also present.
- Consider iron supplementation primarily to increase stores to protect against future losses.

Suspected Iron Deficiency Treatment Algorithm[1,2]



CBC: complete blood count; IDA: iron deficiency anemia; IV: intravenous; Hb: hemoglobin.

Adult Oral Iron Formulations

Common oral iron formulations along with their dosing recommendations and precautions.

PRODUCT INFORMATION	FORMULATION	ELEMENTAL IRON (PER UNIT)	DOSE	DOSING CONSIDERATIONS AND PRECAUTIONS
Polydextrose iron complex (FeraMAX® Pd products)	Chewable tablet (FeraMAX® Pd Maintenance 45)	45 mg	1 tablet QD	**Benefits:** • No aftertaste or staining of teeth • FeraMAX® Pd Maintenance 45 chewable tablets contain vitamin B12 (1,000 mcg) and vitamin C (75 mg) • FeraMAX® Pd Therapeutic 150 capsules may be opened and sprinkled over food **Precautions:** • Take a few hours before or after other medications or NHPs
	Capsule (FeraMAX® Pd Therapeutic 150)	150 mg	1 capsule QD	
Ferrous sulfate	Tablet 300 mg	60 mg	1 tablet TID	**Benefits:** • Least expensive • RCTs suggest: • Every-other-day dosing of ferrous sulfate may increase iron absorption **Precautions:** • Avoid enteric coated or sustained-release products which may result in reduced iron intake • Similar rates of adverse effects between ferrous salts when equivalent doses of elemental iron provided
Ferrous gluconate	Tablet 300 mg	35 mg	2 tablets TID	
Ferrous fumarate	Tablet 300 mg	100 mg	1 tablet BID	
Heme iron polypeptide	Tablet 11 mg	11 mg as heme iron	1 tablet TID	**Precautions:** • Not suitable for vegetarians – made from animal product

GI: gastrointestinal; NHP: natural health product; RCT: randomized clinical trial; QD: once daily; TID: three times daily; BID: Two times daily.

Monitoring

- Reassess patients by testing CBC as early as 2-4 weeks post-treatment initiation
- Hemoglobin should increase by 10-20 g/L after 4 weeks
- If hemoglobin does not increase, patient should be reassessed (refer to treatment failure)

Pediatric and Adolescent Oral Iron Formulations

PRODUCT INFORMATION	FORMULATION	ELEMENTAL IRON	DOSE	DOSING CONSIDERATIONS AND PRECAUTIONS
FeraMAX® Pd Powder 15	Powder	15 mg (per ¼ tsp – 1 scoop as supplied)	**Infants and children (3 years or younger):** • Take ¼ to ½ tsp (15-30 mg of elemental iron) 1 time per day. Dosing by weight of the child (3-6 mg/kg of body weight) and degree of iron deficiency, or as directed by a health care practitioner. **Children (4-13 years):** • Take ¼ to ½ tsp (15-30 mg of elemental iron), 1 time per day. Dosing by weight of the child (3-6 mg/kg of body weight) and degree of iron deficiency, or as directed by a health care practitioner.	**Benefits:** • No aftertaste or staining of teeth • FeraMAX® Pd Powder 15 can be mixed in soft foods, powdered **Precautions:** • Take a few hours before or after other medications or NHPs
FeraMAX® Pd Maintenance 45	Chewable Tablet	45 mg	**Not recommended for infants and children** **Adolescents above 14 years old:** • Take 1 chewable tablet QD	**Benefits:** • No aftertaste or staining of teeth • FeraMAX® Pd Maintenance 45 chewable tablets contain vitamin B12 (1,000 mcg) and vitamin C (75 mg) **Precautions:** • Take with food a few hours before or after taking other medications or natural health products
Ferrous sulfate	Suspension 30 mg/mL	6 mg/mL	Based on weight and age	**Benefits:** • Least expensive • RCTs suggest: • Every-other-day dosing of ferrous sulfate may increase iron absorption **Precautions:** • Liquid stains teeth • Similar rates of adverse effects between ferrous salts when equivalent doses of elemental iron provided
	Drops 75 mg/mL	15 mg/mL	Based on weight and age	
Ferrous fumarate	Suspension 300 mg/5 mL	20 mg/mL	Based on weight and age	

GI: gastrointestinal; NHP: natural health product; QD: once daily; RCT: randomized clinical trial.

IV Iron Formulations[2,5-7]

Common IV iron formulations along with their dosing considerations and precautions.

Usual dose:

- Calculate: 'Iron Deficit' (total dose needed) using hemoglobin deficit equation
  - *Total iron deficit [mg] = body weight [kg] x (target Hb-actual Hb) [g/dl] x 2.4 + depot iron [mg]**
- Divide 'Iron Deficit' into appropriate individual doses
- Administer doses 1-2 times weekly until total dose complete (interval varies by product, check product monograph)

IRON TYPE	DOSE	CONSIDERATIONS
Iron sucrose	Iron sucrose 20 mg/mL e.g. Total Iron Deficit 1000 mg, consider: 200 mg IV x 5 doses	• Each single use 5 mL vial contains 100 mg of elemental iron • It may be administered undiluted as a 100 mg slow IV injection over 2-5 minutes, or as an infusion of 100 mg diluted in a maximum of 100 mL of 0.9% NaCl over a period of at least 15 minutes for a total cumulative dose of 1000 mg on different sessions within a 14-28 day period • Patients weighing less than 70 kg may require a longer infusion time • Dosages >300 mg are associated with increased risk of adverse reaction due to iron overload
Ferric gluconate complex	Ferric gluconate 12.5 mg/mL e.g. Total Iron Deficit 1000 mg consider: 125 mg IV x 8 doses	• Each single use 5 mL vial contains 62.5 mg of elemental iron • It may be diluted in 100 mL of 0.9% NaCl for injection, administered by IV infusion over 1 hour • It may also be administered undiluted as a slow IV injection (at a rate of up to 12.5 mg/min)
Ferric derisomaltose	Ferric derisomaltose 100 mg/mL e.g. Total Iron Deficit 1000 mg, consider: 100 mg IV x 10 doses	• Each single use 5 mL vial contains 100 mg elemental iron/mL • It may be administered as an IV bolus injection up to 500 mg up to once a week at an administration rate of up to 250 mg iron/minute • It may be administered undiluted or diluted in a maximum of 20 mL sterile 0.9% NaCl • For stability reasons, it should not be diluted to concentrations less than 1 mg iron/mL (not including the volume of the ferric derisomaltose solution) and never diluted in more than 500 mL of sterile 0.9% NaCl

*The factor 2.4 is derived from the following assumptions: a) Blood volume 70 ml/kg of body weight ~7% of body weight b) Iron content of hemoglobin 0.34% Factor 2.4 = 0.0034 x 0.07 x 10000 (conversion for g/dL).
Hb: hemoblogin; IV: intravenous; NaCl: sodium chloride.

Use of Maintenance Iron Dosing[1,2]

Many people may have a low-negative iron balance, even after treatment of iron deficiency anemia, and may still benefit from maintenance iron dosing to ensure iron sufficiency.

Individuals with borderline (normal) Hb and low ferritin

Medical conditions requiring ongoing need for iron supplementation (e.g. patients with IBD, GI blood loss, patients experiencing iron malabsorption, unresolved underlying cause of ID)

Individuals with increased iron demand such as periods of rapid growth, menorrhagia, and pregnancy

Daily maintenance iron can help correct an early negative iron balance and support iron sufficiency

GI: gastrointestinal; Hb: hemoglobin; IBD: inflammatory bowel disease; ID: iron deficiency.

Improving Oral Iron Tolerability[1,2]

Tolerability of oral iron supplementation can be increased by employing the following strategies:

- Start at a lower dose and titrate up slowly (every 4-5 days) until target dose achieved
- Use of divided doses
- Take supplements with meals (iron absorption is enhanced when supplements are taken on an empty stomach; however, tolerance and adherence may be improved when iron is taken with meals)
- Use of a different iron preparation
- Use of alternative dosing schedules such as every other day dosing (resolution of symptoms and replenishment of iron stores may take longer)

Considerations for Special Populations

Please select your special population of interest:

PREGNANT WOMEN
(pg. 15)

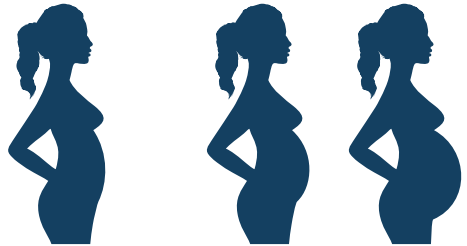
PEDIATRIC PATIENTS
(pg. 16)

ADOLESCENT PATIENTS
(pg. 17)

ELDERLY PATIENTS
(pg. 18)

Special Patient Population: Pregnant Women[1,2]

For female patients, consider inquiring into pregnancy status to determine potential need for supplemental iron.



Trimester	1st	2nd	3rd
IDA	Hb <110 g/L	Hb <105 g/L	

Iron supplementation should be considered to increase iron stores and protect against future losses during pregnancy

IV iron is not recommended during the first trimester due to lack of available safety data

FERRITIN FUNCTIONALLY DECREASES BY ~30% IN ALL PREGNANT WOMEN BY THE SECOND TRIMESTER AND THEREFORE IS NOT INDICATIVE OF IRON DEFICIENCY

An increase in oral iron consumption of 15-30 mg elemental iron/day is recommended for non-anemic women

Hb: hemoglobin; IDA: iron deficiency anemia; IV: intravenous.

Special Patient Population: Pediatric Patients[1]

ID in infants may present as poor feeding, lethargy, failure to thrive or tachypnea.

Serum ferritin concentrations <12 µg/L is indicative of ID in pediatrics, while ferritin levels of 12-20 µg/L is a possible ID.

TREATMENT:
Important to specify the strength and dosing instructions to parents/legal guardians to prevent dosing errors

Liquid formulation are recommended for infants and toddlers with ID

Age	Elemental Iron (per kg bodyweight/day)
<12 months old	3 mg
≥12 months old	3-6 mg

For non-responders, consider additional testing such as electrophoresis, vitamin B12 and folate levels

ID: iron deficiency.

Special Patient Population: Adolescent Patients[1,8]

No indication for population-based general screening.
A case-finding approach to identify individuals at risk of iron deficiency is recommended.

TREATMENT:

- Oral iron therapy in conjunction with dietary counselling is recommended in adolescents
- 60-130 mg elemental iron per day
- Important to specify the strength and dosing instructions to parents/legal guardians to prevent dosing errors
- It is recommended to start at lower end of dosing range as larger doses may lead to intolerance

ADDITIONAL TESTING:

- For non-responders, consider additional testing such as electrophoresis, vitamin B12 and folate levels
- For adolescents who are iron deficient but not anemic, conduct follow up testing of ferritin and CBC 3 months after the course of iron supplementation
- Normalization of serum ferritin indicates treatment success

MAINTENANCE:

- Using a daily maintenance iron supplement is encouraged in adolescents to ensure iron sufficiency and avoidance of negative iron balance due to the increased physiologic needs caused by rapid growth

CBC: complete blood count.

Special Patient Population: Elderly Patients[1,2,7]

Ferritin below 50 µg/L should be investigated for iron deficiency in the elderly, though cut-offs between 30 and 100 mg/L have been proposed.

IV iron may be favoured in elderly individuals due to poor tolerability of oral formulations

Dosing should be no more frequent than once daily to improve tolerability. Low dose iron therapy (15-45 mg elemental iron per day) may be an effective option

Iron supplementation associated with fewer side effects (e.g. polydextrose iron complex) may be preferred

Older individuals may have higher intolerance to oral therapies due to reduced absorption from antacid use or impaired gastric acid production

IV: intravenous.

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