Management of iron deficiency in children, adults, and pregnant individuals: evidence-based and expert consensus recommendations

Ashley E Benson, Jamie O Lo*, Maureen O Achebe, Jorgeane S Aslan, Michael Auerbach, Bethany T Samuelson Bannow, Marie J Boller, Thomas G Deloughery, Jacquelin Dingman, Layla Van Doren, Geolani W Dy, Patricia A Ford, Jason A Freed, Michael K Georgieff, Kristina M Haley, Chloe I Han, Adam K Lewkowitz, Kylee L Martens, Robert T Means Jr, Elizabeta Nemeth, Sven R Olson, Jacquelyn M Powers, Kristin C Prewitt, Toby Richards, Don C Rockey, Eric J Roeland, Kimberly S Ryan, Hanny Al-Samkari, Michelle Sholzberg, Methodius G Tuuli, Angela C Weyand, Michelle P Zeller, Annette M Totten, Ilya Ivlev†, Joseph J Shatzel†, on behalf of the Iron Consortium at Oregon Health & Science University*

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*Authors contributed equally

†Authors contributed equally

Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Oregon Health & Science University, Portland, OR, USA (A E Benson MD, J O Lo MD, M J Boller MD, K C Prewitt MD, K S Ryan MD); **Department of Urology, Oregon Health & Science University, Portland, OR, USA** (J O Lo, G J Dy MD); **Division of Hematology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA** (M O Achebe MD); **Division of Hematology and Medical Oncology, Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA** (J S Aslan MS, B T Samuelson Bannow MD, T G Deloughery MD, K L Martens MD, J J Shatzel MD); **Department of Medicine, Georgetown University School of Medicine, Washington, DC, USA** (M Auerbach MD); **Knight Cancer Institute** (J Dingman BA, S R Olson MD, E J Roeland MD) **and Pacific Northwest Evidence-based Practice Center** (A M Totten PhD, I Ivlev MD), **Oregon Health & Science University, Portland, OR, USA; Section of Hematology, Department of Medicine, Yale School of Medicine, New Haven, CT, USA** (L Van Doren MD); **Abramson Cancer Center, Pennsylvania Hospital of the University of Pennsylvania, Philadelphia, PA, USA** (P A Ford MD); **Division of Hematology and Hematologic Malignancies, Beth Israel Deaconess Medical Center, Boston, MA, USA** (J A Freed MD); **Division of Neonatology, Department of Pediatrics, University of**

Iron deficiency is the most common micronutrient deficiency worldwide. Oral iron is often recommended as first-line treatment, but there is no consensus on the optimal formulation, dosing strategy, or which patients should be treated preferentially with intravenous iron. To address these challenges, the Iron Consortium at Oregon Health & Science University (OHSU) convened an international panel of 26 experts in haematology, primary care, paediatrics, obstetrics, gastroenterology, cancer, and patient advocacy among its members. This panel was supplemented by insights from a four-person patient focus group to develop current recommendations using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology. The panel developed clinically relevant questions in five priority topic areas, a systematic literature search was performed, and studies meeting a priori criteria were included to generate evidence tables for recommendation development. Evidence-based and expert opinion-based recommendations were made through a structured anonymous consensus voting process at an in-person meeting in Portland, OR, USA, hosted by OHSU on Feb 16–17, 2024. The expert panel made seven evidence-based recommendations for three demographic groups with iron deficiency: non-pregnant adults, pregnant individuals, and infants, children, and adolescents. Expert opinions supported the recommendations on 21 aspects of care for which there is insufficient evidence. This Review provides evidence-based recommendations and expert consensus on the diagnosis, treatment, and management of iron deficiency, detailing best practices for oral and intravenous iron repletion across diverse patient populations.

Introduction

Iron deficiency is the most prevalent micronutrient deficiency globally, affecting people of all ages, including adults, pregnant individuals, and children;[1,2] characterised by depleted iron stores, it leads to symptoms such as fatigue, cognitive impairment, and adverse maternal and offspring health outcomes.[3] If untreated, iron deficiency can progress to anaemia, which can intensify symptoms and necessitate a blood transfusion.[4]

Despite its high prevalence, iron deficiency often remains undiagnosed and untreated due to the gradual onset of its non-specific symptoms, inconsistent screening practices, and the absence of a universally accepted diagnostic threshold.[5,6] This lack of consensus substantially contributes to its public health burden.

To address these issues, an international panel of experts has developed clinical practice recommendations for managing iron deficiency, both with and without anaemia. These recommendations are advisory, aiming to support clinicians and patients by providing a framework that considers various clinical situations and patient needs. Additionally, the panel addressed important contextual questions that fall outside the main scope of these recommendations—such as the identification and management of iron deficiency in specific populations and clinical conditions—but for which practitioners could welcome additional guidance (panel; appendix pp 6–13).

Methods

The Iron Consortium at OHSU convened an international expert panel from among its members (appendix pp 2–5). This panel was established in the autumn of 2023, and included 26 international experts (23 voting members: AEB, JOL, MOA, MA, BTSB, TGD, LVD, PAF, JAF, MKG, KMH, KLM, RTM, EN, SRO, JMP, TR, DCR, EJR, MGT, ACW, MPZ, and JJS; and three non-voting members: MS, HA-S, and AKL), primarily from North America, spanning diverse medical and research disciplines, including haematology, primary care, paediatrics, obstetrics, gastroenterology, cancer, and patient advocacy, supplemented by insights from a four-person patient focus group. A strict conflict of interest policy was implemented, with resultant statements detailed in the appendix (pp 2–5). With the exception of the methodologists and organisers, participants were reimbursed for attending the development meeting in Portland, OR, USA, and received honoraria from OHSU.

We followed the Institute of Medicine standards for developing clinical guidelines,[7] the Guidelines International Network Public Toolkit for patient engagement,[8] and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.[9]

Panel: **Abbreviated answers for contextual questions**

Current practices for identification of iron deficiency

- Several guidelines and professional groups recommend against using haemoglobin or haematocrit alone to evaluate susceptible patients for iron deficiency
- Assessment of ferritin for identification of iron deficiency is encouraged on the basis of its superior diagnostic performance. However, there is no consensus on diagnostic cutoff levels, and ferritin concentrations can be affected by several factors, including inflammation and aging. As a result, combining different biomarkers could provide a better assessment than ferritin alone. When tests cannot be conclusive, a time-limited trial of iron could be useful
- Suggested ferritin values that might be considered as a starting point for iron deficiency are <50 ng/mL for adults, although a lower concentration could be used for screening. However, the appropriate cutoff is not possible to identify on the basis of current evidence; and in adults with cancer, a higher serum ferritin cutoff of <100 ng/mL is considered diagnostic of absolute iron deficiency. Less data is available on children, so a cutoff is more difficult to establish. Pregnant individuals with ferritin above 70 ng/mL do not develop iron deficiency or iron deficiency anaemia throughout gestation
- Epidemiological studies suggest that WHO cutoffs for ferritin levels to detect iron deficiency of <12 ng/mL for children aged younger than 5 years and <15 ng/mL for children aged 5 years and older are likely too low, and a threshold of 20 ng/mL identifies iron deficient erythropoiesis

Current iron deficiency management approaches for specific situations

Gastrointestinal evaluation:

- All adult men and postmenopausal women with iron deficiency anaemia should undergo bidirectional endoscopy to identify putative gastrointestinal tract lesions that could cause occult bleeding. Whether this group of patients with iron deficiency alone should undergo endoscopy is unclear. Ultimately, the decision should be made on the basis of an assessment and discussion with the patient about risks and benefits. The benefits are likely to be lower in younger patients. If bidirectional endoscopy does not identify a lesion, a trial of iron therapy is recommended before small bowel evaluation

Inflammatory bowel disease:

- Patients with inflammatory bowel disease often have inflammation-related intestinal malabsorption of iron. Although treating inflammation and gastrointestinal blood loss can improve iron deficiency in patients with inflammatory bowel disease, if iron is needed, strong consideration should be given to intravenous iron as first-line therapy

Bariatric surgery:

- Many patients who have had bariatric surgery also have impaired absorption of iron, decreased tolerance of iron-rich foods, and bleeding from ulcers. Iron deficiency following surgery is more prevalent in female patients with the Roux-en-Y gastric bypass. Intravenous iron could be considered earlier and more often in treating iron deficiency associated with bariatric surgery

Heavy menstrual bleeding:

- Heavy menstrual bleeding is difficult to define as can be subjective and influenced by many factors, therefore, if a person reports excessive menstrual blood loss that interferes with quality of life and occurs with other symptoms, it is appropriate to consider preventing or treating iron deficiency. As iron deficiency could reoccur with menstruation, treatment might need to include both iron supplementation and menstrual management strategies

The protocol for systematic review was registered at PROSPERO (CRD42023490379), and the Iron Consortium at Oregon Health & Science University (OHSU) plan to reassess the emerging evidence every 3 years.

Patient and public involvement

To inform the recommendations in this Review, we conducted a 90-minute focus group with four patients aged 30–40 years (randomly selected from patients who had received intravenous iron during their pregnancy and had delivered within the past year) to discuss iron deficiency care experiences (appendix pp 115–120). These patients also reviewed the recommendations draft.

External peer review

Two independent experts (Dr Chika Arinze [a physician] and Dr Curtis Harrod, both with expertise in systematic reviews and guideline development) provided peer review comments before submission of the Review.

Recommendation development

During Feb 16–17, 2024, the expert panel met at OHSU to develop recommendations using the GRADE approach. Panellists assessed net benefits that included patient preferences, resource implications, and equity to develop evidence-based recommendations. In cases of limited evidence, expert opinions were formulated following the Institute of Medicine's standards and Guidelines International Network guidance.[7,8] Recommendations were voted on anonymously, requiring 87% (20 of 23) agreement of voting members (tables 1–3); if consensus was not reached, the panel revised the recommendation statement and re-voted until consensus or concluded no statement could be made.

Minnesota, Minneapolis, MN, USA (M K Georgieff MD); **Division of Pediatric Hematology and Oncology** (K M Haley MD) **and Division of Pediatric Critical Care** (C I Han NP), **Department of Pediatrics, Oregon Health & Science University, Portland, OR, USA; Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Brown University Warren Alpert Medical School, Providence, RI, USA** (A K Lewkowitz MD, M G Tuuli MD); **Departments of Internal Medicine, Medical Education, and Pathology, James H Quillen College of Medicine, East Tennessee State University, Johnson City, TN, USA** (R T Means Jr MD); **Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, CA, USA** (E Nemeth PhD); **Division of Hematology/Oncology, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA** (J M Powers MD); **Institute of Clinical Trials and Methodology, University College London, London, UK** (T Richards MD); **Medical University of South Carolina Digestive Disease Research Center, Medical University of South Carolina, Charleston, SC, USA** (D C Rockey MD); **Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA** (H Al-Samkari MD); **Departments of Medicine, and Laboratory Medicine & Pathobiology, St. Michael's Hospital, Li Ka Shing Knowledge Institute, University of Toronto, Toronto, ON, Canada** (M Sholzberg MD); **Department of Pediatrics, University of Michigan Medical School, Ann Arbor, MI, USA** (A C Weyand MD); **Michael G DeGroote Centre for Transfusion Research, Department of Medicine, McMaster University, Hamilton, ON Canada** (M P Zeller MD); **Canadian Blood Services, Hamilton, ON, Canada** (M P Zeller MD)

Correspondence to:
Jamie Lo, Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Oregon Health & Science University, Portland, OR 97239, USA
loj@ohsu.edu

See Online for appendix

	Recommendation, as agreed by the expert panel	Basis of the recommendation	Strength of the recommendation	Consensus (percentage of 23 voting members)
1	For non-pregnant adults with iron deficiency and without conditions affecting absorption, we recommend oral iron once daily to improve fatigue levels, ferritin and haemoglobin concentrations	Evidence-based	Strong: very low-certainty evidence, but benefits outweigh risks	100%
1.1	There is insufficient evidence to support a specific oral iron formulation over another. It is reasonable to start with an iron salt (eg, ferrous sulphate, gluconate, fumarate) with 60–110 mg of elemental iron per day	Expert opinion	NA	100%
1.2	We do not support enteric-coated iron or timed, slow, controlled release formulations for treating iron deficiency	Expert opinion	NA	100%
1.3	We do not support diet modifications alone for the treatment of iron deficiency or alternative approaches to iron supplementation such as iron ingots, patches, or sprays	Expert opinion	NA	100%
1.4	We support providing information on best practices for taking oral iron	Expert opinion	NA	100%
1.5	We support using IV iron over oral iron for treating iron deficiency in individuals who require rapid correction of iron deficiency, who are unlikely to respond to oral iron, individuals with insufficient response to oral iron by ferritin or haemoglobin concentrations (ie, insufficient rise* in 4–12 weeks), and individuals who cannot tolerate oral iron due to side effects	Expert opinion	NA	100%
2	For adults with iron deficiency and without conditions impacting iron absorption, we suggest alternate-day oral iron dosing if daily dosing is not well tolerated (eg, due to gastrointestinal side effects)	Evidence-based	Weak: very low-certainty evidence, but benefits slightly outweigh risks	100%
2.1	For adults with iron deficiency, we recommend against more than once daily oral iron	Expert opinion	NA	100%
3	For adults with iron deficiency, we recommend using IV iron when indicated (eg, patients who do not respond to or are intolerant of oral iron, those with malabsorptive conditions, or those requiring rapid correction) given the low risk of serious adverse events	Evidence-based	Moderate: low-certainty evidence, but some benefits outweigh risks	100%
3.1	For individuals receiving IV iron therapy, we suggest a total dose infusion instead of multiple-dose treatment	Expert opinion	NA	100%
3.2	For adults with iron deficiency, we do not support the routine use of pre-medication with intravenous iron	Expert opinion	NA	100%
3.3	For individuals with a history of infusion reactions to IV iron, we support considering an alternative IV iron formulation, a slower infusion rate, or both	Expert opinion	NA	100%
3.4	For individuals with multiple severe drug allergies or inflammatory arthritis, we support considering a slower infusion rate, premedication, or both	Expert opinion	NA	100%
3.5	We support reassessing individuals for treatment response to intravenous iron no sooner than 4 weeks after infusion	Expert opinion	NA	100%
3.6	For individuals who require IV iron, we support the development of long-term monitoring and management plans	Expert opinion	NA	96%
4	For treatment-naive adults with iron deficiency, we do not provide guidance about which iron formulation (oral or IV) to use as the first-line therapy	Evidence-based	Weak: very low-certainty evidence, and no clear benefits between treatments	91%

NA=not applicable. IV=intravenous. *Individuals with insufficient response to oral iron by the rise in ferritin or haemoglobin concentrations (eg, some experts consider a haemoglobin concentration increase of <1 g/dL or not reaching a ferritin concentration of 30–50 ng/mL within 4–12 weeks as insufficient response to oral iron).

Table 1: **Treatment recommendations for non-pregnant adults with iron deficiency**

Recommendations

These recommendations are intended to provide guidance for managing iron deficiency; they are not prescriptive, but aim to support clinicians and patients by providing a framework that considers various clinical situations and patient needs. The recommendations within this Review are designed to promote favorable patient outcomes but do not guarantee specific results, and do not cover all possible patient care nuances or uncertainties. As medical knowledge, technology, and practices evolve, these recommendations are subject to review and update. These recommendations are not meant to dictate insurance or payment decisions or promote specific drug formularies. References to these recommendations should clearly state their advisory nature.

Treatment of non-pregnant adults with iron deficiency

Based on three key questions (appendix pp 31–77), the expert panel developed 4 evidence-based recommendations and 12 accompanying expert opinion

	Recommendation, as agreed by the expert panel	Basis of the recommendation	Strength of the recommendation	Consensus (percentage of 23 voting members)
5	For pregnant individuals with iron deficiency anaemia in the second and third trimesters, we suggest offering intravenous iron over oral iron treatment to improve maternal outcomes	Evidence-based	Weak: low-certainty evidence, but benefits slightly outweigh risks	100%
6	For pregnant individuals diagnosed with iron deficiency anaemia, we do not provide guidance about which iron formulation (oral or IV) to use for neonatal benefit	Evidence-based	Insufficient evidence	100%
6.1	For pregnant individuals with anaemia, we support laboratory confirmation of iron deficiency as the aetiology	Expert opinion	NA	100%
6.2	For individuals planning pregnancy and pregnant individuals with confirmed iron deficiency with or without anaemia, we support the treatment of iron deficiency to prevent the adverse effects of iron deficiency anaemia in pregnancy	Expert opinion	NA	100%
6.3	For pregnant individuals with confirmed iron deficiency with or without anaemia and in the first trimester, we support oral iron for treatment	Expert opinion	NA	100%
6.4	For pregnant individuals with confirmed iron deficiency anaemia who receive IV iron, we support assessing haemoglobin response around 4 weeks after iron initiation. If there is a lack of response to iron, consider confirming an adequate dose or broader workup for the aetiology of anaemia if not already performed	Expert opinion	NA	96%
6.5	In pregnant individuals with confirmed iron deficiency anaemia who receive oral iron, we support assessing tolerability and haemoglobin response approximately 4 weeks after initiation. If there is insufficient response or intolerability to oral iron, IV iron is indicated in the second or third trimester	Expert opinion	NA	96%

NA=not applicable. IV=intravenous.

Table 2: **Treatment recommendations for pregnant individuals with iron deficiency**

	Recommendation, as agreed by the expert panel	Basis of the recommendation	Strength of the recommendation	Consensus (percentage of 23 voting members)
7	For infants, children, and adolescents diagnosed with iron deficiency with or without anaemia, we suggest oral iron treatment	Evidence-based	Weak: very low-certainty evidence, but benefits outweigh harms	100%
7.1	For infants, children, and adolescents diagnosed with iron deficiency with or without anaemia, we support identifying and addressing aetiology in addition to iron supplementation	Expert opinion	NA	96%
7.2	For infants, children, and adolescents who started oral iron therapy for iron deficiency anaemia, we support assessing haemoglobin response at approximately 4 weeks. For infants, children, and adolescents who started oral iron therapy for iron deficiency without anaemia, we also support assessing ferritin concentrations within 12 weeks of treatment initiation	Expert opinion	NA	87%
7.3	For infants, children, and adolescents with iron deficiency with or without anaemia who demonstrate insufficient response, inability to take, or intolerance to oral iron, we support offering IV iron	Expert opinion	NA	100%

NA=not applicable. IV=intravenous.

Table 3: **Treatment recommendations for infants, children, and adolescents with iron deficiency**

recommendations for treating non-pregnant adults (table 1). The overall evidence included 7 systematic reviews with 68 RCTs, supplemented by 8 additional RCTs not included in the systematic reviews (appendix pp 31–77).

Evidence-based recommendation 1

Recommendation: for non-pregnant adults with iron deficiency and without conditions affecting absorption, we recommend oral iron once daily to improve fatigue levels and ferritin and haemoglobin concentrations.

Strength of the recommendation: strong. Consensus: 100% of 23 votes supported this recommendation.

Very low-certainty evidence from two systematic reviews and one additional RCT supports the effectiveness of oral iron in individuals without anaemia to reduce fatigue and improve haemoglobin concentration outcomes, despite mild to moderate adverse side-effects.

One systematic review (18 RCTs and two companion papers, n [total participants]=1170) found improvements with oral iron in fatigue levels and ferritin concentrations, with moderate evidence strength for ferritin concentration and low for other outcomes.[10] Another systematic review (3 RCTs, n=284) and an RCT (n=87) found some improvements with oral iron in haemoglobin and ferritin concentrations in specific populations, including those with chronic heart failure; however, the evidence was limited by methodological issues.[11,12]

The strong recommendation for daily oral iron is based on the clear outweighing of benefits over harms, tolerability, patient acceptability, and additional factors such as low cost, when compared with other iron repletion protocols.

Accompanying expert opinion recommendations for recommendation 1

Recommendation 1.1: there is insufficient evidence to support a specific oral iron formulation over another; it is reasonable to start treatment of iron deficiency with an iron salt (eg, ferrous sulphate, gluconate, or fumarate) with 60–110 mg of elemental iron per day.

Consensus: 100%.

The toxicity and efficacy of oral iron formulations can depend more on the elemental iron dose than the type of iron preparation.[6] Therefore, selecting from several widely available and affordable iron salts is reasonable, ensuring that the dose is adequate for treating iron deficiency. None of the evidence supported the use of more expensive oral formulations over iron salts. Clinicians and patients should accurately identify the amount of elemental iron contained in a selected supplement to ensure it effectively addresses the deficiency.

Recommendation 1.2: we do not support enteric-coated iron or timed, slow, or controlled release formulations for treating iron deficiency.

Consensus: 100%.

These formulations often result in lower absorption because enteric coatings render iron inaccessible in the proximal small intestine, where it is best absorbed, and delay the release to less optimal absorption sites.[13,14] Although designed to minimise gastrointestinal side effects, these formulations are less effective and are more expensive than non-enteric-coated formulations. Moreover, the lack of stringent US Food and Drug Administration (FDA) regulations on these products allows for potentially misleading claims.

Recommendation 1.3: we do not support diet modifications alone to treat iron deficiency, or alternative approaches to iron supplementation such as iron ingots, patches, or sprays.

Consensus: 100%.

These approaches often do not deliver the necessary amounts of elemental iron to effectively treat iron deficiency. Even with tools such as cast iron cookware or iron fish, dietary changes typically cannot match the 60–110 mg of elemental iron provided by a single oral supplement.[15] Topical applications (eg, patches and sprays) are ineffective for increasing iron levels due to minimal absorption, and their safety is unknown.

Recommendation 1.4: we support the provision of information to patients on best practices for taking oral iron.

Consensus: 100%.

It is important to optimise the timing of oral iron intake to enhance treatment efficacy and adherence. Taking iron with water at bedtime minimises interference from dietary inhibitors such as dairy, phytates, caffeinated drinks, common breakfast beverages such as coffee and tea, and calcium-rich juices, and its interaction with various medications underscores the importance of careful timing.[16,17] Guidance on these practices is available from the Red Cross.[18]

Recommendation 1.5: we support the use of intravenous iron over oral iron for treating iron deficiency in individuals who require rapid correction of iron deficiency, who are unlikely to respond to oral iron, who have insufficient response to oral iron as assessed by measurement of ferritin or haemoglobin concentrations (ie, insufficient rise in 4–12 weeks), and who cannot tolerate oral iron due to side-effects.

Consensus: 100%.

Intravenous iron is the preferred initial therapy for conditions such as inflammatory bowel disease, celiac disease, chronic gastrointestinal bleeding, post-bariatric surgery, bleeding disorders, and chronic kidney disease, in which oral iron is often ineffective or could exacerbate the condition.[19–21]

Evidence-based recommendation 2

Recommendation: for adults with iron deficiency without conditions affecting iron absorption, we suggest alternate-day dosing of oral iron when daily dosing is not well tolerated (eg, due to gastrointestinal side-effects).

Strength of the recommendation: weak. Consensus: 100% of 23 votes supported this recommendation.

This recommendation is based on very low-certainty evidence from three RCTs, one of which did not present a haemoglobin outcome, and the other two showing no significant difference in haemoglobin concentrations between daily and alternate-day dosing of iron.[22–24] One of these RCTs (n=200) reported no difference in haemoglobin concentrations between daily and alternate-day dosing over 8 weeks.[22] The other two RCTs (n=40[23] and n=62[24]) echoing this finding also observed no difference in haemoglobin concentrations over 3 weeks between the dosing schedules.[23,24] One RCT found a more rapid improvement in anaemia with twice-daily dosing and a higher risk of nausea compared with alternate-day dosing of iron.[24]

The expert panel judged that the benefits of alternate-day dosing, such as reduced gastrointestinal side-effects, slightly outweigh the harms of undertreating patients

who cannot tolerate daily dosing. In our experience, patients generally prefer a dosing schedule that minimises side-effects while maintaining efficacy, with the final treatment protocol made in decision partnership with the health-care provider and patient. Alternate-day dosing could improve adherence and be more acceptable for those with side-effects from daily dosing. This approach balances tolerability with efficacy, making it a suitable option for management of iron deficiency.

Accompanying expert opinion recommendation for recommendation 2

Recommendation 2.1: for adults with iron deficiency, we do not support oral iron dosing more than once daily.

Consensus: 100%.

The expert panel recommended against more frequent dosing, judging that gastrointestinal side-effects outweigh the slight benefits of faster iron repletion. Clinical experience and available data[25] suggest that more frequent doses of oral iron prolong hepcidin induction, reducing iron absorption and diminishing potential clinical benefit. Furthermore, several studies have shown dose-dependent toxicity with oral iron dosed more than once daily,[22] which has meant this no longer commonly practiced.

Evidence-based recommendation 3

Recommendation: for adults with iron deficiency, we recommend using intravenous iron in patients without an adequate response to, or who are intolerant of, oral iron, those with malabsorptive conditions, or those requiring rapid correction, given the low risk of serious adverse events.

Strength of the recommendation: moderate. Consensus: 100% of 23 votes supported this recommendation.

This recommendation is based on low-certainty evidence across key clinical outcomes from two systematic reviews[26,27] and one additional RCT.[28] Evidence across key clinical outcomes suggests that intravenous iron increases haemoglobin concentrations to a greater extent than placebo (mean difference [MD] 4·65 g/L, 95% CI 2·53–678) in a systematic review[26] including 15 RCTs (n=1675), and MD 5·7 g/L, 95% CI 4·3–7·2 in an RCT[28] (n=505). Results were mixed for the association of intravenous iron and functional status, with the systematic review[26] (n=814) suggesting a reduction in the fatigue score (standardised mean difference –0·3, 95% CI –0·52 to –0·09), whereas the RCT[28] (n=505) showed no difference using the multidimensional fatigue symptom inventory assessment. Both the systematic review[26] (n=1,030, 12 week follow-up) and the RCT[28] (n=505; 6–8 week follow-up) found no association between intravenous iron and quality of life (standardised mean difference 0·15; 95% CI, –0·01 to 0·31 in the systematic review,[26] and MD –0·1, 95% CI –0·3 to 0·1 in the RCT)[28], using the EQ-5D questionnaire. Furthermore, intravenous iron was not associated with severe adverse events (10 RCTs in the systematic review,[26] n=1182, risk difference 00·00, 95% CI 0·01–0·01).

Despite mixed evidence on functional status improvements, and no significant quality of life benefit, the effectiveness of intravenous iron in raising haemoglobin concentrations and its favourable safety profile are considered to outweigh the harms in this population. The expert panel unanimously agreed that the potential benefits, including avoiding preventable transfusions and associated risks, justify intravenous iron even with low-certainty evidence. Although intravenous iron is recommended for its effectiveness and safety, iron selection can be influenced by resource availability, feasibility, and patient preferences.

Accompanying expert opinion recommendations for recommendation 3

Recommendation 3.1: for individuals receiving intravenous iron therapy, we support a total dose infusion instead of multiple-dose treatment.

Consensus: 100%.

This suggestion is based on evidence that most intravenous iron products have similar efficacy and safety.[29] Total dose infusion refers to formulations intended to be administered in 1–2 sessions. These formulations are preferred over regimens requiring 3 or more sessions. Total dose infusions are generally more cost-effective than multiple-dose treatments, reduce the time burden on patients, and replenish iron stores more rapidly.[30]

Recommendation 3.2: for adults with iron deficiency, we do not support the routine use of pre-medication with intravenous iron.

Consensus: 100%.

The expert panel recommends that routine use of test doses or pre-medication for prophylaxis of the rare risk of severe reactions to intravenous iron therapy is unnecessary with current available intravenous iron formulations and is of unclear benefit.[31,32] Further research is needed to optimise the prevention and management of infusion-related reactions.[33]

Recommendation 3.3: for individuals with a history of infusion reactions to intravenous iron, we support consideration of an alternative intravenous iron formulation, a slower infusion rate, or both.

Consensus: 100%.

Specific management strategies for patients who have had infusion reactions are understudied. The expert panel's viewpoint is based on its collective clinical experience, evidence from large cohort studies,[31] and the belief that decreasing the risk of recurring reactions will enhance the likelihood of iron repletion and patient adherence to treatment.[32]

Recommendation 3.4: for individuals with multiple severe drug allergies or inflammatory arthritis, we support consideration of a slower infusion rate, premedication, or both.

Consensus: 100%.

Although infusion reactions are uncommon, they can occur in some patients (eg, multiple severe drug allergies or inflammatory arthritis). Pre-medicating with corticosteroids has shown promising results in the management of these reactions despite a paucity of high-quality evidence supporting their routine use.[31] For patients with persistent infusion reactions, seeking guidance from an allergist can help optimise the safety and effectiveness of intravenous iron therapy.

Recommendation 3.5: we support the reassessment of individuals for treatment response to intravenous iron no sooner than 4 weeks after infusion.

Consensus: 100%.

There is considerable practice variability in the evaluation of the effectiveness of intravenous iron. Assessing iron indices too soon after infusion (ie, within the first 4 weeks) might not accurately reflect true iron stores because iron parameters could transiently increase after intravenous iron administration. Data from clinical trials,[34] which tracked iron metrics weekly, support this observation. Therefore, we support follow-up testing of haemoglobin and iron indices no sooner than 4 weeks post-infusion to obtain a reliable assessment.

Recommendation 3.6: for individuals who require intravenous iron, we support the development of long-term monitoring and management plans.

Consensus: 96%.

Patients receiving intravenous iron, particularly those with ongoing health concerns (eg, chronic blood loss or malabsorption of iron), require a structured approach to treatment monitoring. Without a systematic plan to assess and manage iron levels over time, there is a risk of ineffective treatment and recurrent deficiency.

Evidence-based recommendation 4

Recommendation: for treatment-naive adults with iron deficiency, we do not provide guidance about which iron preparation (oral or intravenous) to use as the first-line therapy.

Strength of the recommendation: weak. Consensus: 91% of 23 votes supported this recommendation.

Very low-certainty evidence from three systematic reviews[35–37] and one RCT[38] indicated no clear advantage of intravenous iron over oral iron as initial therapy. This data reflects the very low certainty regarding critical outcomes, with no clear preference for one form of iron over another. Additionally, patient preferences, resource availability, insurance coverage, higher costs associated with some treatments, and the need to administer intravenous iron in a health-care setting contribute to this non-preferential stance. Costs and availability can vary substantially across settings and countries, but a detailed discussion of these factors is beyond the scope of this work.[39–41] These considerations allow us to conclude that no universal treatment modality (oral or intravenous iron) can be recommended as the preferred initial treatment for all individuals. Ferric carboxymaltose, although effective in repleting iron stores, has been associated with high rates (~50–75%) of treatment-emergent hypophosphataemia in individuals receiving a standard two-dose infusion series.[29] Phosphate concentrations typically nadir approximately 2 weeks after the initial ferric carboxymaltose infusion. As indicated in the FDA prescribing information, monitoring of serum phosphate concentrations is necessary for patients at high risk for hypophosphataemia.[42] Although the clinical significance of isolated, mild biochemical hypophosphataemia is uncertain, ferric carboxymaltose is the only formulation associated with severe (<1·0 mg/dL) and prolonged hypophosphatemia, persisting for weeks to several months. Notably, pregnant individuals receiving this formulation do not appear to be at risk for hypophosphatemia.[43]

For individuals requiring repeated episodes of intravenous iron repletion, ferric carboxymaltose should be avoided due to the potential for chronic complications of treatment-emergent hypophosphataemia, such as osteomalacia and pseudofractures. Although the exact number of repeated doses when this risk emerges remains uncertain, alternative intravenous iron formulations should be considered for individuals who might require repeated courses of intravenous iron (eg, due to chronic bleeding).

Treatment of pregnant individuals with iron deficiency

Based on two key questions (KQ4 and 4a; appendix pp 77–100), the expert panel developed three evidence-based and five accompanying expert opinion recommendations (table 2). The overall evidence included two systematic reviews, supplemented by two RCTs (appendix pp 83–97).

Evidence-based recommendation 5

Recommendation: for pregnant individuals with iron deficiency anaemia in the second trimester, we recommend intravenous iron where possible and acceptable to the patient, and in the third trimester, we suggest offering intravenous iron to patients over oral iron treatment to improve maternal outcomes.

Strength of the recommendation: weak. Consensus: 100% of 23 votes supporting this recommendation.

This recommendation is based on low-certainty evidence among key clinical outcomes from one systematic review[44] (12 RCTs) and two additional RCTs.[45,46] The evidence (one RCT[45], n=182) found a greater short-term fatigue benefit (measured by the Functional Assessment of Chronic Illness Therapy fatigue scale) of single-dose intravenous ferric derisomaltose compared with daily oral ferrous fumarate at up to 6 weeks follow-up (low strength of evidence), and a lower risk of blood transfusion among those who used intravenous iron at up to 15 weeks (odds ratio [OR] 0·19, 95% 0·05–0·78, I^2=0%). There was no difference in fatigue between 12 weeks and 18 weeks and in rates of serious adverse events between iron formulations (relative risk 0·93,

95% CI 0·69–1·27).[45] The recommendation for intravenous iron in pregnant individuals is primarily supported by the systematic review[44] and one RCT,[45] showing a lower risk for blood transfusions and transient improvement in fatigue at 3 weeks and 6 weeks after intravenous versus oral iron treatment, respectively. Evidence[44–47] favoured intravenous over oral iron in improving important but non-critical outcomes of maternal haemoglobin and iron stores (ferritin).

The weak recommendation for intravenous iron in this population is based on very low certainty in the evidence about its potential benefits (eg, reduced fatigue and lower transfusion rates), which slightly outweigh the risks.[48] Challenges such as higher costs than oral iron, variable insurance coverage, and limited availability, especially in rural areas and low-income or middle-income countries, also contributed to the weak recommendation. These challenges underscore the importance of shared decision making to ensure treatment aligns with individual patient circumstances and preferences.

Evidence-based recommendation 6

Recommendation: for pregnant individuals diagnosed with iron deficiency anaemia, we do not provide guidance about which iron formulation (oral or intravenous) to use for neonatal benefit.

Strength of the recommendation: insufficient evidence. Consensus: 100% of 23 votes supporting this recommendation.

Very low-certainty evidence based on one systematic review[44] and two additional RCTs[45,46] found no difference in effect between between oral and intravenous formulations on neonatal haemoglobin and ferritin concentrations when the maternal iron deficiency was treated. We found no trials presenting harms data in the literature. The systematic review[44] (6 RCTs, n=849) indicated a non-significant improvement in ferritin concentrations at delivery among neonates whose parent received intravenous iron compared with oral iron (MD 11·2 µg/L, 95% CI –1·6 to 24·1). This systematic review also found no association between the type of iron formulation (intravenous *vs* oral) and neonatal haemoglobin level (MD –1·0; 95% CI –4·7 to 2·8). Both additional RCTs (n=205) showed findings consistent with the review.

The inability of the expert panel to recommend one iron formulation over another for neonatal benefit is due to the inability to define the net benefit. However, the expert panel agreed that adequate neonatal iron stores protect against postnatal iron deficiency. The expert panel also acknowledges preclinical studies that suggest that fetal iron delivery is modulated by maternal hepcidin levels, which could be differently affected by the route of iron supplementation, although this is poorly understood.[49] Ferric gluconate contains benzyl alcohol, which linked to neonatal gasping syndrome; the FDA recommends considering alternative iron therapies without benzyl alcohol in pregnancy.[50] With insufficient data on placental transfer, and no human studies to assess risks, it is reasonable to consider alternatives to ferric gluconate until more safety data are available. Other factors contributing to uncertainty include resource utilisation, inconsistent insurance coverage for intravenous iron, higher costs than oral iron, and the need for clinical settings for intravenous administration.

Accompanying expert opinion recommendations for recommendation 6

Recommendation 6.1: for pregnant individuals with anaemia, we support laboratory confirmation of iron deficiency as the cause.

Consensus: 100%.

Although iron deficiency is a common cause of anaemia during pregnancy, prompt and accurate diagnosis is necessary through red blood cell indices, serum iron concentrations, and ferritin concentrations. This approach ensures timely treatment to reduce the risk of adverse maternal–fetal outcomes associated with iron deficiency versus other potential causes of anaemia in pregnancy.

Recommendation 6.2: for individuals planning pregnancy and pregnant individuals with confirmed iron deficiency with or without anaemia, we support the treatment of iron deficiency to prevent the adverse effects of iron deficiency anaemia in pregnancy.

Consensus: 100%.

Addressing iron deficiency helps treat symptoms of fatigue and depression and reduces the risk of maternal complications (eg, preterm labour or postpartum haemorrhage),[3] and also decreases the likelihood of adverse infant outcomes (eg, low birth weight or neurocognitive issues) that can persist into adolescence.[3]

Recommendation 6.3: for pregnant individuals with confirmed iron deficiency with or without anaemia in the first trimester, we support oral iron for treatment.

Consensus: 100%.

A trial of oral iron can mitigate iron deficiency risks during early pregnancy. Intravenous iron is not recommended in the first trimester due to insufficient safety data on fetal development. The evidence supporting intravenous iron at this stage is insufficient, marked by research inconsistencies and feasibility.

Recommendation 6.4: for pregnant individuals with confirmed iron deficiency anaemia who receive intravenous iron, we support the assessment of haemoglobin response at approximately 4 weeks after iron initiation. If there is insufficient response to iron, consider confirming an adequate dose or conducting a broader workup for the cause of anaemia, if not already performed.

Consensus: 96%.

Patients without evidence of alternative causes of anaemia, other than iron deficiency, and who receive adequate iron therapy should undergo monitoring for an appropriate increase in haemoglobin and haematocrit concentrations in subsequent weeks. The expert panel agrees that the absence of a sufficient response should prompt further investigation into other potential causes (eg, incorrect diagnosis, inadequate treatment, or coexisting conditions such as gastrointestinal bleeding).

Recommendation 6.5: in pregnant individuals with confirmed iron deficiency anaemia who receive oral iron, we support the assessment of tolerability and haemoglobin response approximately 4 weeks after initiation. If there is an insufficient response or intolerability to oral iron, intravenous iron is indicated in the second or third trimester.

Consensus: 96%.

Haemoglobin concentrations typically respond to effective iron therapy within 2–3 weeks. Testing at 4 weeks could ensure timely adjustment if the treatment is ineffective. Oral iron is preferred in the first trimester due to insufficient safety data for intravenous iron during this period. However, due to common gastrointestinal side-effects from oral iron, which can affect patient adherence to treatment, it is important to assess treatment efficacy and tolerability. If oral iron is ineffective, intravenous iron in the second and third trimesters is suggested to prevent adverse outcomes for the pregnant individual and infant.

Treatment of infants, children, and adolescents with iron deficiency

Based on one key question (KQ 5), appendix pp 101–13), the panel developed one evidence-based and three accompanying expert opinion recommendations (table 3). The overall evidence included two SRs (appendix pp 105–109).

Evidence-based Recommendation 7

Recommendation: for infants, children, and adolescents diagnosed with iron deficiency, with or without anaemia, we suggest oral iron treatment.

Strength of the recommendation: weak. Consensus: 100% of 23 votes supported this recommendation.

Very low-certainty evidence from two systematic reviews indicated some benefit of oral iron for those aged 4–23 months[43] and 6–12 years,[51] with no gastrointestinal adverse reactions for younger patients. Harms in the 6–12-year-old population were not studied. Among key clinical outcomes, a systematic review[43] found very low-certainty evidence of an association between iron supplementation and improved ferritin concentrations (MD 30·65 ng/mL, 95% CI 3·79–57·51) at 12 weeks, improvement one aspect of neurocognition (Bayley Scales of Infant and Toddler Development [BSID] mental development index, MD 5·90, 95% CI 1·81–10·00) but not another (BSID psychomotor index, MD 3·76, 95% CI −3·14 to 10·66). Trials found no association between oral iron and haemoglobin concentrations, diarrhoea, and transferrin concentrations for children aged 4–23 months. For the older group (8–12 years),[51] low and very low-certainty evidence existed for all critical outcomes; oral iron was associated with increased haemoglobin (MD 1·08 g/L; 95% CI 0·68–1·49) compared to placebo, but no difference was seen in neurocognitive development (Raven's Color Progressive Matrices and IQ score). Oral iron did not affect serum ferritin or transferrin in all age groups. We did not find any evidence existing for adolescents.

Despite very low-certainty evidence, the benefits of oral iron outweigh the risk of non-serious harms. Parents generally prioritise treating nutritional deficiencies, further supporting oral iron use. Challenges include access to supplements, insurance coverage, costs, and varying parental preferences. Given these considerations, oral iron is recommended for managing iron deficiency in this age group, with similar benefits expected for adolescents.

Accompanying expert opinion recommendations for recommendation 7

Recommendation 7.1: for infants, children, and adolescents diagnosed with iron deficiency, with or without anaemia, we support identification and addressing of cause in addition to iron supplementation.

Consensus: 96%.

Iron deficiency exists in children due to many underlying causes that must ultimately be treated. Causes to consider include inadequate iron stores at birth due to intrauterine growth restriction and prematurity, inadequate diet in young children, menstrual blood loss, disordered eating, blood donation in adolescents, or gastrointestinal conditions.

Recommendation 7.2: for infants, children, and adolescents who started oral iron therapy for iron deficiency anaemia, we support assessing haemoglobin response at approximately 4 weeks. For infants, children, and adolescents who started oral iron therapy for iron deficiency without anaemia, we also support assessing ferritin response within 12 weeks of treatment initiation.

Consensus: 87%.

Patients receiving iron therapy should show a haemoglobin increase of ≥1 g/dL within 4 weeks. At least 12 weeks are required to observe ferritin concentration changes.

Recommendation 7.3: for infants, children, and adolescents with iron deficiency with or without anaemia who show a lack of response, inability to take, or intolerability to oral iron, we support offering intravenous iron.

Consensus: 100%.

All children with iron deficiency should receive iron therapy. For children who cannot tolerate oral nutrition or medications, intravenous iron therapy should be

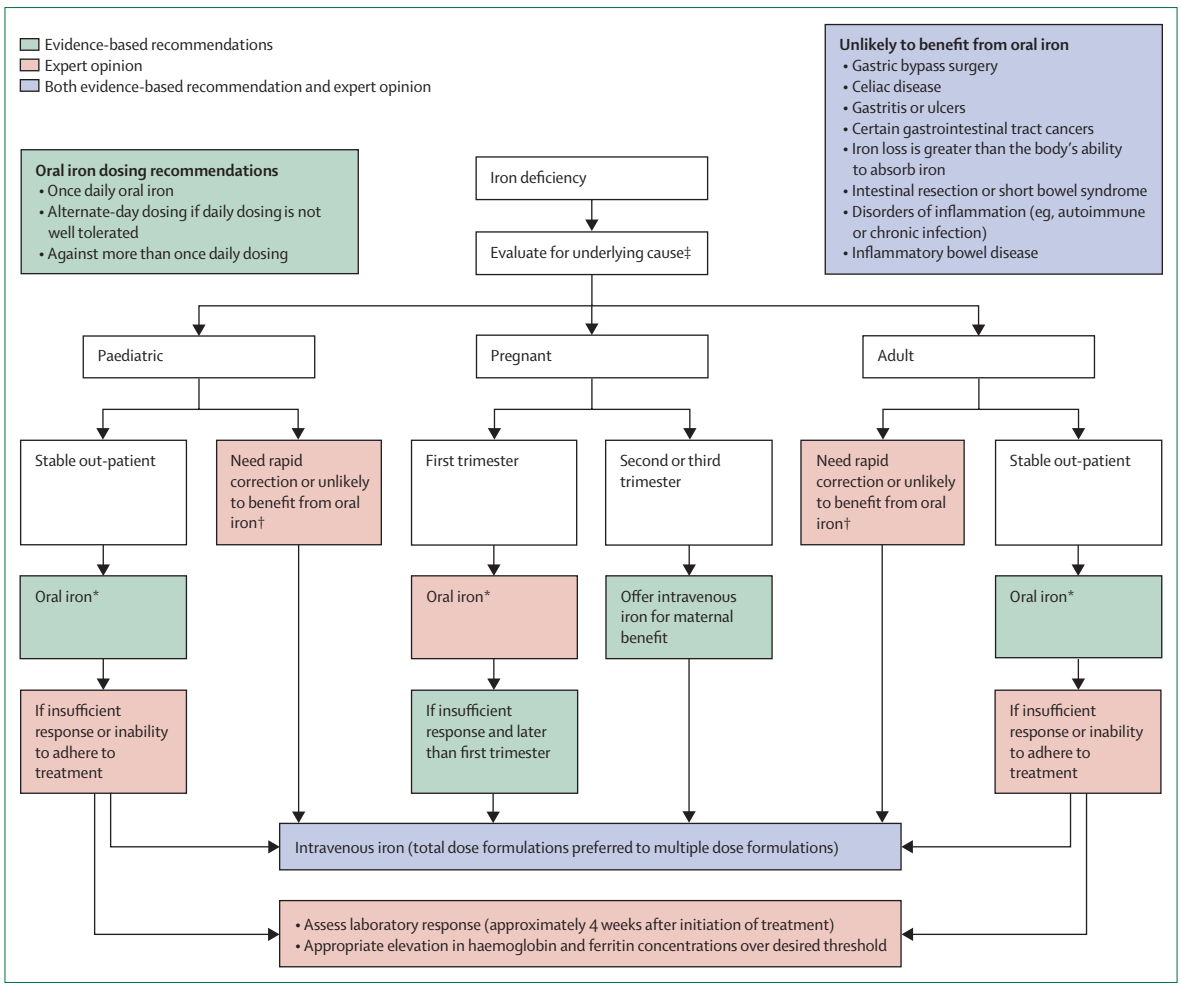

***Figure*: Recommendations for treatment of iron deficiency with or without anaemia**
*Refer to details in the box Oral iron dosing recommendations. †Refer to details in the box Unlikely to benefit from oral iron. ‡The recommendations in this Review focus only on the treatment, not diagnosis, of confirmed iron deficiency.

considered as an alternative option. Patients most likely to benefit include paediatric patients with oral aversions, those requiring parenteral nutrition, and those with gastrointestinal conditions, active gastrointestinal inflammation, and poor iron absorption.

Recommendations of other organisations

The United States Preventive Services Task Force (USPSTF) recommended against routine screening and supplementation for iron deficiency in asymptomatic pregnant women.[52] The USPSTF acknowledged that prenatal iron supplementation might improve maternal haematological indices and reduce the incidence of iron deficiency and anaemia during pregnancy; however, evidence regarding its effect on maternal and infant health is scarce or inconclusive. Routine iron supplementation was not associated with serious maternal harms.[52] The British Society of Gastroenterology recommended iron replacement therapy tailored to patient-specific factors, starting with oral supplements (eg, ferrous sulphate, fumarate, or gluconate).[53] However, if oral iron is contraindicated, ineffective, or not tolerated, intravenous iron therapy should be considered, particularly in cases where the need for correction of iron deficiency is urgent. Additionally, the British Society of Gastroenterology guidelines stress the importance of monitoring patients' response to treatment, with regular assessment of haemoglobin levels and iron status to ensure adequate repletion of iron stores. In cases in which iron deficiency recurs or persists despite treatment, further investigation and management strategies, including long-term iron replacement therapy, could be warranted. Overall, the guidelines emphasise the need for regular monitoring and further investigation if iron deficiency persists or recurs.[53] Lastly, a 2021 systematic review by Syed Numan and Karolina Kaluza[54] examined current guidelines for the treatment of iron deficiency anaemia using intravenous iron across different medical specialties, which identified 35 relevant guidelines for inclusion.[54]

Search strategy and selection criteria

Searches were conducted in Ovid MEDLINE(R) ALL until Jan 4, 2024 for systematic reviews published from database inception to Jan 4, 2024 and randomised clinical trials (RCTs) published between Jan 1, 2018 and Jan 2, 2024. We included systematic reviews that searched multiple databases and provided quantitative estimates, and randomised controlled trials (RCTs) relevant to the topic (appendix pp 23–26). The literature review on oral and intravenous iron treatment efficacy and safety was based on five key questions from the panel about benefits and harms. We also considered seven contextual questions regarding special populations and diagnostic uncertainties, which were not systematically reviewed (panel; appendix pp 6–13).

These guidelines generally recommend the use of intravenous iron in managing iron deficiency anaemia; however, a substantial proportion of the guidelines were outdated, failing to reflect current evidence on the safety and efficacy of intravenous iron.[54] A review by Don C Rockey and colleagues considered special populations and diagnostic uncertainties (panel; appendix pp 6–17) not systematically reviewed and did not focus on the evaluation of iron deficiency given existing published guidance.[55]

Research gaps and needs

Standardising diagnostic criteria

Research is needed to better inform and standardise diagnostic cutoff values for iron deficiency across various populations and settings. Different thresholds are used across various populations, many of which are based on low-quality data.

Research on disparities in care and access

The strength of our recommendations were often affected or influenced by higher costs, variable insurance coverage, less availability of intravenous iron, and the necessity for intravenous iron administration to be in a health-care setting. Studies should focus on how socioeconomic, geographic, racial or ethnic, and systemic factors influence access to care and treatment outcomes, aiming to develop strategies that bridge gaps and promote equity in health care.

Iron deficiency in pregnancy

Further studies are required to explore the benefits and harms of screening for and treatment of non-anaemic iron deficiency on maternal, fetal, neonatal, and childhood outcomes.

Patient-centred treatment approaches

Research should address the effectiveness of treatments for iron deficiency with a specific focus on clinical outcomes, quality of life, cost-effectiveness, and patient preferences.

Evaluation of iron repletion strategies

A rigorous investigation is needed to compare different iron supplementation strategies, including differences in formulations, route of administration, dosing, and monitoring.

Targeted research in specific populations

Research focused on specific patient groups (eg, individuals with cancer, inflammatory bowel disease, post-bariatric surgery, or heavy menstrual bleeding) will help direct appropriate interventions and improve outcomes.

Long-term follow-up studies

Investigation of the long-term outcomes of iron deficiency is necessary to understand the sustained effects and potential late consequences and inform patient decision making.

Conclusion

This framework provides a structured approach to the treatment and management of iron deficiency, combining evidence-based recommendations with expert consensus to guide clinical decision making. This approach to treatment is illustrated in the figure, highlighting key decision points and best practices tailored to individual patient needs. By addressing gaps in care and standardising management strategies, this guidance is aimed to improve clinical outcomes and enhance patient quality of life, and identify priorities for future research and development.

Contributors

AEB, JOL, AMT, II, and JJS contributed to conceptualisation, methodology, data curation, analysis, supervision, validation, visualisation, writing of the original manuscript draft, and manuscript review and editing. MOA, JSA, MA, BTSB, MJB, TGD, JD, LVD, GWD, PAF, JAF, MKG, KMH, CIH, AKL, KLM, RTM, EN, SRO, JMP, KCP, TR, DCR, EJR, KSR, HA-S, MS, MGT, ACW, and MPZ contributed to manuscript review and editing. All authors reviewed and approved the final version.

Declaration of interests

LVD reports speaking engagements and advisory board participation with Pharmacosmos and Daiichi Sankyo. AKL discloses receipt of honoraria for advisory boards and speaking engagements from Pharmacosmos, some of which were not directly related to the topic of the current guidelines. MPZ discloses receipt of honoraria for advisory boards and speaking engagements from the American Society of Hematology, McMaster University (ON, Canada), Pfizer, Transfusion Transmitted Injury Surveillance System, and Queen's University (ON, Canada), some of which were not directly related to the topic of the current guidelines. MGT reports direct payments, including honoraria and research funding, from Pharmacosmos. AEB, MKG, and HA-S report that their institutions received research funding from Pharmacosmos. HA-S reports consultancy fees and grants from several Agios, Amgen, Novartis, Pharmacosmos, Sobi, and Vaderis. All other authors declare no competing interests.

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