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REVIEW ARTICLE

Systematic review of guidelines for the diagnosis and treatment of iron deficiency anemia using intravenous iron across multiple indications

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ABSTRACT

Objective: To explore current recommendations for intravenous (IV) iron use in clinical guidelines for iron deficiency anemia (IDA) across different therapeutic areas and identify recommendations, if any, for the treatment of IDA.

Methods: A literature search was conducted in Medline, EMBASE, BIOSIS, Cochrane Collaboration, and on websites of relevant professional associations. Searches were limited to English publications. 1292 citations were identified, 219 papers were assessed, and 35 guidelines were identified for inclusion.

Results: The guidelines covered a variety of geographies: United States (US; $n = 10$); Europe ($n = 11$); "Rest-of-World" ($n = 9$); and "Other" organizations ($n = 5$). These covered a variety of specialties. Guidelines defined iron deficiency and IDA generally by serum ferritin and transferrin saturation levels. One-fifth of the reviewed guidelines (7 of 35) included no mention or recommendation regarding parenteral iron's utility in the management of IDA. Fifteen guidelines recommended using parenteral iron in the management of IDA. Fewer US guidelines included recommendations around IV iron than in Europe or the rest of the world. Approximately 60% of the guidelines have not been updated in $\geq$5 years and consequently do not reflect current evidence on the safety and efficacy of IV iron.

Conclusions: While national and international guidelines for management of IDA exist, many are outdated and do not reflect current evidence including, but not limited to, parenteral iron use. Urgent consideration should be given to updating and clarifying management guidelines for IDA using the latest treatment modalities and options, particularly in the US.

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Diagnosis; guidelines; iron deficiency; multiple indications; systematic review; treatment

Introduction

The World Health Organization (WHO) defines anemia as "a condition in which the number of red blood cells or the hemoglobin concentration within them is lower than normal." It is the most commonly encountered hematological abnormality and is caused by a reduction in the concentration of erythrocytes or hemoglobin (Hb) in blood.[1] The WHO estimates that over 1.6 billion people are affected by anemia globally, equating to 24.8% of the global population.[1]

The main cause of anemia is iron deficiency,[2] which is suspected as an underlying cause in 50% of all cases,[3] although anemia can be caused by other factors such as blood loss, nutritional deficiencies, hemolysis, myelosuppression, renal insufficiency, inflammation, or infection.[4,5] Iron plays an essential role in Hb formation and productive erythropoiesis.[6] If untreated, iron deficiency can lead to iron deficiency anemia (IDA). The WHO definition of iron deficiency varies according to age, sex and presence or absence of infection. In otherwise healthy individuals, serum ferritin (SFer) levels $<$15 μg/ml (or $<$12 μg/ml in pre-school children) are indicative of iron depletion, while levels below 30 μg/ml in pre-school children indicate iron depletion in the presence of infection.[7] Notably, ferritin is an acute phase reactant and can be increased in the presence of inflammatory conditions, therefore, SFer level alone may not be an ideal diagnostic parameter. Thus SFer, percent transferrin saturation (TSAT), and Hb together are generally regarded as the parameters which correlate best with iron status.[8] TSAT is calculated either as the ratio of iron to transferrin or iron to total iron-binding capacity.[9] Other measures may be used, including hypochromic red cells[10] where blood cells are pale and relatively colorless due to a disproportionate reduction of red cell Hb and reticulocyte Hb content. As reticulocytes are only 1–2 days old, the result is reflective of the iron available in the bone marrow for erythropoiesis.[11] This approach may help confirm the diagnosis of IDA since it more accurately reflects the presence of anemia than SFer alone. Many organizations and professional bodies produce their own guidelines for the definition and diagnosis of IDA, and the variability of recommendations reflects the need to carefully consider characteristics of the underlying condition and its

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effect on the parameters used to identify IDA.[12] Iron deficiency, with or without anemia, may have significant consequences in many conditions, including impact upon quality of life (QOL),[13–15] increased length of hospital stays,[16] and increased mortality[17,18] and morbidity.[19,20] In the most recent update to the Global Burden of Disease Study, IDA was ranked as the fourth highest cause of years lived with disability from a total of 328 diseases and conditions and the fifth most prevalent condition with 1.24 billion cases (95% uncertainty intervals 1.21–1.28 billion).[21]

Iron supplementation is the most commonly prescribed treatment for anemia, although other options exist, including erythropoeitic stimulating agents (ESAs) and blood transfusions.[19] Iron supplementation can be either oral or parenteral. Ever since the introduction of low-molecular-weight intravenous (IV) iron formulations, many of the adverse events traditionally associated with parenteral iron administration have declined.[22] IV iron complexes have been engineered to allow administration of high doses of iron in a relatively short time. IV iron complexes must be stable, non-reactive, and non-toxic. These features are achieved with third generation IV irons, which include ferumoxytol, iron isomaltoside and ferric carboxymaltose in which carbohydrate-stabilized polynuclear Fe (III)-oxyhydroxide/oxide nanoparticles are formulated as colloidal solutions. The third generation IV irons can be delivered in one or two doses and have higher levels of stability which contributes to an improved safety profile compared to previous parenteral formulations.[23] Accordingly, IV iron complexes are polymers, not small molecules as most pharmaceuticals, and comprise mixtures of similar but not identical macromolecules. Therefore, they belong to the class of non-biological complex drugs.[24]

Although there has been no previously published review regarding guidelines for treatment of IDA, there has been a systematic review of diagnosis and treatment of iron deficiency[12] evaluating 29 guidelines providing recommendations. Oral iron was recommended in many guidelines, but the authors found significant heterogeneity on the management (diagnosis and treatment) of iron deficiency across indications. They further noted that new options (e.g. IV iron) were emerging at that time and therefore did not feature prominently in the then-current guidelines.

The objective of this systematic review is to explore the current global and United States (US) recommendations for IV iron use in clinical guidelines for IDA across different therapeutic areas and to see what, if any, specific recommendations exist for the treatment of IDA. We also intended to evaluate differences in guideline recommendations, particularly with respect to IV iron use, between the US and rest of the world.

Methods

A literature search was conducted in Medline, EMBASE, BIOSIS and the Cochrane Collaboration. Additionally, the websites of relevant professional association including those of the WHO and the National Institute for Health and Care Excellence (NICE) were also assessed. The search string used for Medline, EMBASE and BIOSIS was "guideline* AND iron deficiency" and was limited to publications in English since 1 January 1990. The search was conducted on 24 January 2020. The Cochrane Collaborations was also searched on the same date using the term "iron AND deficiency AND guideline." Additional free text searching of the internet using the term "iron-deficiency anemia/anaemia" was conducted.

The authors screened retrieved citations and abstracts to select titles for the full-text article. All citations whose abstract or full text was not available were excluded. Reference lists of included articles were checked to find articles of interest that may not have been found in the search.

Studies were included if they included guidelines from any country, organization or consensus meeting and had a focus on the diagnosis and/or management of anemia and its use in healthy or ill patients (both adults and children). The search was limited to results in the English language and only the last update of a guideline was included. If available, information on the diagnosis and management of iron deficiency and IDA was extracted from each included article.

Results

A total of 1263 citations were identified on Medline, EMBASE and BIOSIS and an additional two in the Cochrane Collaboration. Web searches and/or checking the reference lists of those articles identified 29 additional papers (Figure 1). A total of 1,292 citations were assessed by reviewing the title and/or the abstract. A total of 220 papers were reviewed in full, and of these 35 guidelines were identified for inclusion in the systematic review.

Overview

The guidelines came from a variety of countries. There were ten from the US,[4,25–33] 6 were pan-European,[34–40] as well as five from Canada,[41–46] four from the United Kingdom (UK),[47–50] two from India,[51,52] and one each from Australia[53] and Japan.[54] There were also five "other" guidelines identified (e.g. those designed to applied anywhere in the world rather than limited to a specific geography).[1,55–59] These included one set from the WHO and two from independent expert groups (the IRON CORE study group and an International Consensus Statement on the peri-operative management of anemia and iron deficiency).[55,59] We have included the latter two studies since they offer guidance on the treatment of iron deficiency, although as they were published by independent expert groups, the guidelines may not have undergone the same development process as guidelines from national or professional bodies. Additionally we have included two papers discussing the use of Patient Blood Management (PBM) in anemia, which has been endorsed by the World Health Assembly of the WHO.[60] The guidelines covered a diverse range of indications including heart failure (HF),[25,33,35,45] pediatrics,[26,28,46] oncology,[29,30,39] chronic kidney disease (CKD),[31,37,41–43,47,50,54,58] obstetric and

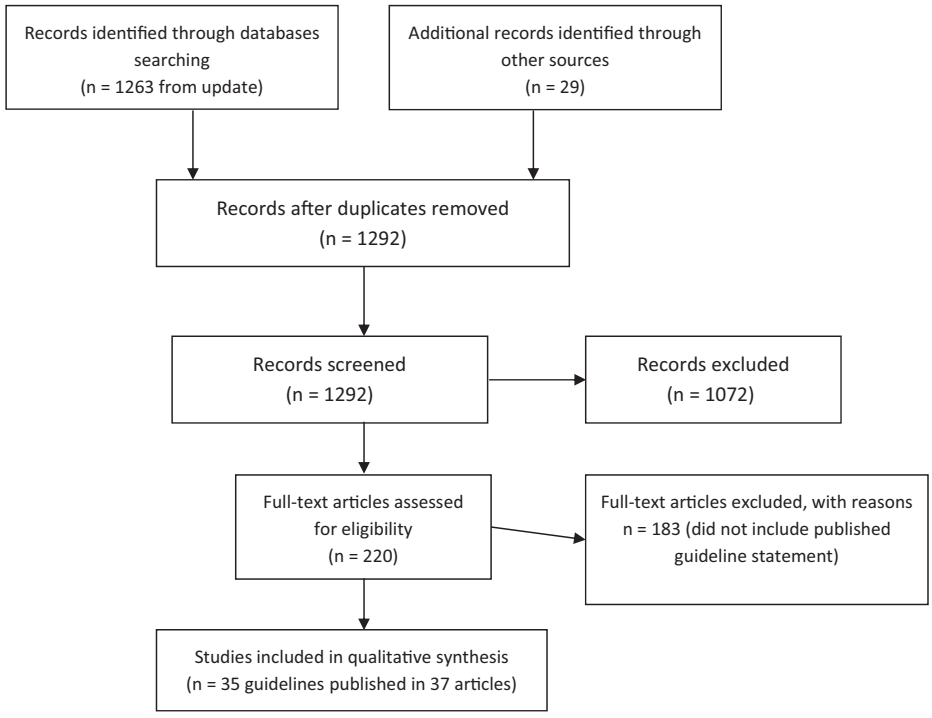

Figure 1. PRISMA 2009 flow diagram.

gynecological (OB/GYN),[4,49,52] adults,[32] gastrointestinal (including inflammatory bowel disease [IBD]),[27,38,40,48,53] general anemia,[1,44,51] surgery,[34,36,56,57,59] and inflammatory diseases (including CKD, congestive heart failure [CHF], and IBD).[55] We have categorized the guidelines by four geographical regions (US, Europe [including pan-Europe and the UK], "Rest-of-World" and "Other") and by specialty (cardiology, pediatrics, gastroenterology, oncology, OB/GYN, adults, general anemia, surgery, and one guideline which covered multiple inflammatory conditions noted above) (Figure 2).[55] While all the guidelines included in this review cover the management of the underlying conditions in the following sections we have chosen to describe guidelines as either "iron deficiency guidelines" or "IDA guidelines" based upon whether or not they defined either term.

Of the 35 guidelines identified, the single specialty with the most guidelines was nephrology with 8 (24% of all guidelines), followed by gastroenterology (6) surgery and cardiology (4 each). The US has more guidelines in the disease areas of cardiology, oncology and pediatrics than any other region, and was the only region where guidelines for adult anemia were identified. However, all but one of these guidelines (American Academy of Family Practitioners [AAFP]) referred to "iron deficiency" rather than "IDA." Nearly half of European iron deficiency guidelines covered just two specialties (gastroenterology and nephrology) and unlike the US, there were IDA guidelines in surgery but no iron deficiency guidelines in pediatric or adult patients. "Rest-of-World" guidelines, as in Europe, were most frequently in nephrology (one in IDA and one in iron deficiency), but there were no identified guidelines for either iron deficiency or IDA in surgery or oncology. "Other" IDA guidelines covered surgery and nephrology with iron deficiency guidelines in both general anemia and inflammatory conditions. Iron deficiency guidelines were developed between 2001 and 2019 and IDA guidelines between 2011 and 2018. There were 19 iron deficiency guidelines identified which also appeared in a previous published review of anemia.[12] Of these guidelines, only 8 have been updated; those from the National Comprehensive Cancer Network (NCCN),[29] the Japanese Society for Dialysis Therapy (JSDT),[54] NICE,[47] AAFP,[25] the Gastroenterological Society of Australia (GSA),[53] the British Society of Haematology (BSH),[49] the European Society of Medical Oncology (ESMO),[39] and the American Society of Clinical Oncology/American Society of Hematology (ASCO/ASH).[30] This equates to 30% of US guidelines and European guidelines updated in the last 5 years as compared to 20% of the "Rest-of-World" guidelines.

United States

US guidelines were identified from the American College of Physicians (ACP),[25] American Academy of Pediatrics (AAP),[26] the Crohn's and Colitis Foundation,[27] US Preventive Services Task Force (USPSTF),[28] NCCN,[29] ASCO/ASH,[30] the American College of Obstetricians and Gynecologists (ACOG),[4] AAFP,[32] the American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA),[33] as well as a US commentary on the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[31]

Diagnosis

Of these guidelines, 5 (AAP, Crohn's & Colitis Foundation, NCCN, ACOG, and AAFP) provided defined measurements (in terms of Hb) to assess the presence of anemia, 4 of which included definitions of iron deficiency (Crohn's & Colitis

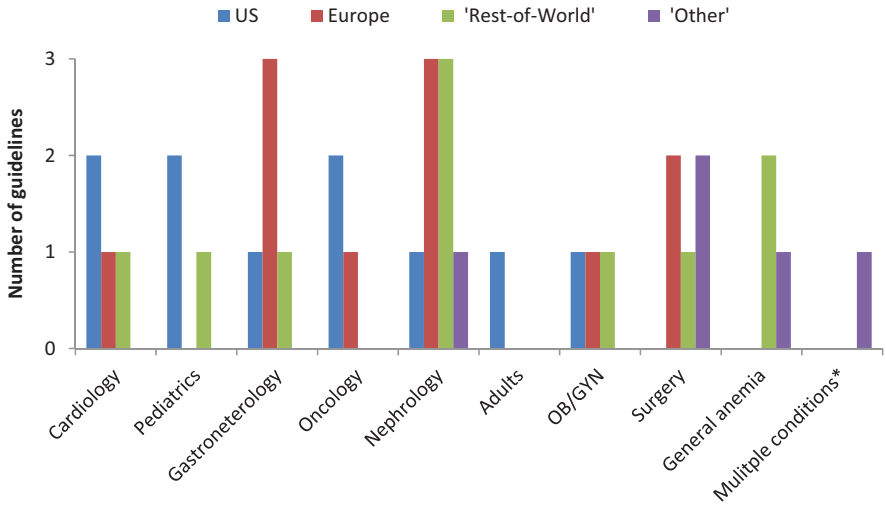

Figure 2. Guidelines for anemia, iron deficiency and/or iron deficiency anemia by therapy area and geographical region. *including CHF, CKD and IBD. Abbreviation. CHF, congestive heart failure; CKD, chronic kidney disease; IBD, inflammatory bowel disease; OB/GYN, obstetrics and gynecology; US, United States.

Foundation, NCCN, ACOG, and ACC/AHA). Only the AAFP guideline provided a clear definition of IDA.

Anemia was generally defined in reference only to measures of Hb, with exception of ACOG who also defined it in terms of hematocrit (Hct) levels. AAP defined anemia (for children aged between 12 and 25 months) as Hb level <11.0 g/dL while the Crohn's & Colitis foundation uses Hb <12 g/dL for women and <13 g/dL for men. NCCN defined it as Hb <11 g/dL or ≥2 g/dL below the individual's baseline. ACOG's definition of anemia varied by trimester from Hb <11 g/dL and Hct percentage as 33% in the first trimester to Hb <10.5 g/dL to Hct as 32% in the second, and Hb <11 g/dL and Hct percentage as 33% in the third trimester. AAFP's measures varied by age from <13 g/dL in adult males to <11 g/dL in infants.

The presence of iron deficiency was confirmed using measures of SFer and TSAT in all guidelines with the exception of ACOG who used the parameter of change in Hb level. Iron deficiency was defined by SFer <100 ng/mL or SFer >100 ng/mL with TSAT <20% by the Crohn's and Colitis Foundation, SFer 30–800 ng/mL and TSAT <20–50% by NCCN. ACOG measured increase in Hb concentration of ≥1 g/dL following iron treatment, while ACC used SFer <100 ng/mL or 100–300 ng/mL if TSAT <20%.

Only AAFP guidelines defined "IDA" (as opposed to "iron deficiency"), which was defined as mean corpuscular volume (MCV) <95 μm^3.

Management

The use of IV iron was recommended in most of the guidelines (7 of 10). The exceptions were from ACP, who felt the evidence was not yet strong enough to recommend its use but did make clear that it showed the most benefit in patients with New York Heart Association (NYHA) class III HF and low ferritin; AAP, who did not mention the use of IV iron; and USPSTF, who specifically excluded the use of IV iron as a means of iron supplementation (not unexpected, given their guidelines were to cover infants aged 6–24 months). However, none of the guidelines that included IV iron as a management option made clear whether this was to treat iron deficiency or IDA specifically, and most advised its use be restricted to those patients intolerant to oral therapy. Full details of the definitions and measurements can be found in Table 1.

Europe

We identified the following European Guidelines: Network for the Advancement of Transfusion Alternatives (NATA);[34] NICE;[47] European Society of Cardiology (ESC);[35] European Board of Anaesthesiology (EBA);[36] Anemia Working Group of European Renal Best Practice (ERBP);[37] British Society of Gastroenterology (BSG);[48] an International Working Group on Inflammatory Bowel Diseases;[38] BSH;[49,50] ESMO,[39] and the European Crohn's & Colitis Organisation (ECCO).[40]

Diagnosis

All organizations and groups provided a clear definition of anemia with the single exception of the BSH guidelines,[50] which were specific to the diagnosis of functional iron deficiency in cases of anemia of chronic diseases and CKD. Six of the guidelines (NICE, ECCO, ERBP, BSH [both guidelines] and the International Working Group on Inflammatory Bowel Diseases) all provided cut-off values to identify iron deficiency, and four provided definitions to characterize IDA (NATA, ESC, ECCO and ESMO).

In all the guidelines which defined anemia, Hb level was used. The Hb levels used were as follows: NATA, ESC, EBA and BSG (<12 g/dL for females and <13 g/dL for males); NICE (<10.5 g/dL aged under 2 otherwise <11 g/dL); ERBP (<12 g/dL for females and <13.5 g/dL for males). As in ACOG guidelines, BSH guidelines in anemia in pregnancy varied the levels used based on trimester (<11 g/dL in first and third trimesters, <10.5 g/dL in second trimester and <10 g/dL postpartum). ESMO guidelines defined anemia as Hb levels of 10–11 g/dL. ECCO used Hb according to WHO guidelines

Table 1. Definition and measurement of anemia.

Organization and guideline	Specialty	Year of guidelines	Anemia defined by	ID defined by	IDA defined by
US guidelines					
American College of Physicians (ACP)[25]	Cardiology	2013	ND	ND	ND
American Academy of Pediatrics (AAP)[26]	Pediatrics	2010	Hb <11.0 g/dL (male and female children age 12–35 months)	ND	ND
Crohn's & Colitis Foundation[27]	GI	2017	Hb <12 g/dL Women; <13 g/dL Men	Ferritin <100 ng/ml or ferritin >100 ng/ml and TSAT <20% indicate inadequate iron stores	ND
US Preventive Services Task Force Recommendation (USPSTF)[28]	Pediatrics	2015	ND	ND	ND
National Comprehensive Cancer Network (NCCN)[29]	Oncology	2019	Hb <11 g/dL or ≥2 g/dL below baseline	**Possible ID:** Ferritin >500-800 ng/mL TSAT <50% **Functional ID in patients receiving ESA:** Ferritin 30–500 ng/mL TSAT <50% **Absolute ID:** Ferritin <30 ng/mL and TSAT <20%	ND
American Society of Clinical Oncology/ American Society of Hematology (ASCO/ASH)[30]	Oncology	2019	ND	ND	ND
US Commentary on the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[31]	Nephrology	2013	ND (assumed to be as per KDIGO guidelines)	ND	ND
American College of Obstetricians and Gynecologists (ACOG)[4]	OB/GYN	2008	Hb <11 g/dL and Hct <33% (first and third trimesters); 10.5 g/dL and 32% (second trimester)	Abnormal values on biochemical test results, increases in Hb concentrations of more than 1 g/dL after iron treatment, or absent bone marrow iron stores	ND
American Academy of Family Physicians (AAFP)[32]	Adults	2013	Hb <11 g/dL (6–59 months and pregnant women), <11.5 g/dL (5–11 years); <12 g/dL (12–14 years and non-pregnant women); <13 g/dL (men)	ND	If patient has anemia and MCV <95 μm^3. SFer <30 ng/mL
American College of Cardiology/ American Heart Association/Heart Failure Society of America (ACC/ AHA/HFSA)[33]	Cardiology	2017	ND	Ferritin <100 ng/mL or 100–300 ng/mL if TSAT is <20%	ND
European guidelines					
Network for Advancement of Transfusion Alternatives (NATA)[34]	Surgery	2011	Female <12.0 g/dL, Male <13 g/dL	ND	If SFer <30 mg/L and/or TSAT <20% or SFer 30–100 mg/L and/or TSAT <20%
National Institute for Health and Care Excellence (NICE)[47]	Nephrology	2015	Hb <110 g/L or <105 g/L aged <2 years:	**Iron status:** Use percentage of hypochromic red blood cells (% HRC; more than 6%), but only if processing of blood sample is possible within 6 hours; If not, use reticulocyte Hb content (CHr; less than 29 pg) or equivalent tests	ND
European Society of Cardiology (ESC)[61]	Cardiology	2016	Hb <13.0 g/dL in men and <12.0 g/dL in women)	ND	SFer <100 µg/L, or ferritin between 100–299 µg/L and TSAT <20%)

(*continued*)

Table 1. Continued.

Organization and guideline	Specialty	Year of guidelines	Anemia defined by	ID defined by	IDA defined by
European Board of Anaesthesiology (EBA)[36]	Surgery	2013	Hb <130 g/L (men) <120 g/L (women)	ND	ND
Anaemia Working Group of European Renal Best Practice (ERBP)[37]	Nephrology	2009	Hb <12 (females) Hb <13.5 (males)	Agree with Kidney Disease Outcomes Quality Initiative (KDOQI) which defined the lower ferritin limit on the basis of CKD status (100 ng/ml in non-HD-CKD and 200 ng/mL in HD-CKD)	ND
British Society of Gastroenterology (BSG)[48]	GI	2011	Hb concentration <13 g/dL in men over 15 years of age, <12 g/dL in non-pregnant women over 15 years of age, and <11 g/dL in pregnant women	ND	ND
International Working Group on Inflammatory Bowel Diseases[38]	GI	2007	Hb <11 (6–59 months), <11.5 g/dl (5–11 years); <12 g/dl (12–14 years and non-pregnant women); <11 g/dL (pregnant women); <13 g/dL (men)	Active IBD SFer <100 μg/L and TSAT <16% Quiescent IBD SFer <30 μg/L and TSAT <16%	ND
British Society of Haematology (BSH)[49]	OB/GYN	2019	Hb <110 g/L (first trimester); <105 g/L (second/third trimesters); <100 g/L postpartum	A SFer level of <30 μg/L in pregnancy is **indicative of ID**. Levels higher than this do not rule out iron deficiency or depletion	ND
British Society of Haematology (BSH)[50]	Nephrology	2013	ND	**Classical ID** Ferritin <200 μg/L if on hemodialysis (HD); <200 μg/L (no HD) **Functional ID** Ferritin >200 μg/L (on HD); >200 μg/L but <800 μg/L (no HD)	ND
European Society for Medical Oncology (ESMO)[39]	Oncology	2018	Hb 10–11 g/dL	ND	SFer <100ng/mL and TSAT <20%
European Crohn's and Colitis Organisation (ECCO)[40]	Gastroenterology	2015	WHO definitions used which vary by age, gender and pregnancy	SFer <30 g/L (no active disease), <100 μg/L (inflammation)	With inflammation, SFer >100 μg/L and TSAT <20%. SFer level 30–100 μg/L, likely combination of true iron deficiency and ACD
'Rest-of-World' guidelines					
Japanese Society for Dialysis Therapy (JSDT)[54]	Nephrology	2015	Male: Hb <13.5 g/dL (<60 years); <12.0 g/dL (60–69 years); <11.0 g/dL >70 years Female: Hb <11.5 g/dL (<60 years); <10.5 g/dL (60–69 years); <10.5 g/dL >70 years	ND	SFer level and TSAT but no values specified
Canadian Agency for Drugs & Technology in Healthcare (CADTH)[41]	Nephrology or other types of anemia	2014	ND	ND	ND
Canadian Society of Nephrology (CSN)[42,43]	Nephrology	2008	Hb level of: <135 g/L in males ≥18 years of age, <120 g/L in females ≥18 years of age	Iron should be administered to maintain the following iron indices **ND-CKD patients (no ESA):** Hb <110 g/L: ferritin >100 ng/mL TSAT >20% **ND-CKD/PD-CKD (with ESA):** ferritin >100 ng/mL TSAT >20%	ND

(*continued*)

Table 1. Continued.

Organization and guideline	Specialty	Year of guidelines	Anemia defined by	ID defined by	IDA defined by
				HD-CKD with ESA: ferritin >200 ng/mL TSAT >20%	
Government of India (GOI)[51]	All	2013	Hb <11 (6–59 months), <11.5 g/dl (5–11 years); <12 g/dl (12–14 years and non-pregnant women); <11 g/dL (pregnant women); <13 g/dL (men)	ND	ND
Gastroenterological Society of Australia (GSA)[53]	GI	2015	ND	Low iron stores (ferritin <15 μg/L) and reduced MCV (<80 fL) but normal Hb concentration (SFer <15 μg/L; or SFer 15–20 μg/L, plus two of the following: serum iron <10 μmol/L; total iron binding capacity >68 μmol/L; serum transferrin >3.5 g/L or TSAT <15%)	While no formal definition is provided, the GSA state that IDA is characterized by low iron stores, reduced MCV and Hb concentrations
Ministry of Health, British Colombia[44]	All	2011	ND	**Adults** (μg/L) <15 diagnostic of iron deficiency 15–30 probable iron deficiency >30 iron deficiency unlikely **Children** (μg/L) <12 diagnostic of iron deficiency 12–20 possible iron deficiency	ND
Canadian Cardiovascular Society (CCS)[45]	Cardiology	2017	WHO definition is mentioned but not specifically recommended	In a practical tip, this is described as SFer <100 mg/L or SFer 100–299 mg/L and TSAT <20%	ND
Canadian Pediatric Surveillance Program (CPSP)[46]	Pediatric	2011	ND	ND	Generally characterized by a Hb level of <110 g/L, plus a measure of poor iron status
Federation of Obstetric and Gynaecological Societies of India (FOGSI)[52]	OB/GYN	2016	ND	ND	ND
'Other' guidelines					
IRON CORE[55]	Chronic Inflammatory Conditions (CHF, CKD and IBD)	2017		SFer <100μg/L or TSAT <20%	ND
World Health Organization (WHO)[1]	All	2001	Hb <11 (6–59 months), <11.5g/dL (5–11 years); <12 g/dL (12–14 years and non-pregnant women); <11 g/dL (pregnant women); <13 g/dL (men)	**Depleted iron stores** SFer <12 μg/L under 5y (<15μ g/L >5 years) **Depleted iron stores in the presence of infection**: SFer <30 μg/L	ND
Kidney Disease Improving Global Outcomes (KDIGO)[58]	Nephrology	2012	**Adults and children >15 years with CKD:** Hb concentration is <13.0 g/dL in males and <12.0 g/dL in females **Children with CKD**: Hb concentration is <11.0 g/dL in children 0.5–5 years, <11.5 g/L g/dl in children 5–12 years, and <12.0 g/dL in children 12–15 years	ND	Not defined by levels but by potential increases in Hb concentration at specified TSAT and ferritin levels.
	Surgery	2017	Hb <130g/L in both sexes	ND	**IDA:** Ferritin <30 mg/L

(*continued*)

Table 1. Continued.

Organization and guideline	Specialty	Year of guidelines	Anemia defined by	ID defined by	IDA defined by
International Consensus Statement on the peri-operative management of anemia and iron deficiency[59]					**Anemia of chronic inflammation with iron deficiency:** Ferritin 30–100 mg/L + TSAT <20% or C-reactive protein >5 mg/L **Anemia of chronic inflammation:** Ferritin >100 mg/L + TSAT <20% or C-reactive protein >5 mg/L
Patient Blood Management (PBM)[56,57]	Surgery, although potential use in other indications is noted	2019	Hb levels before elective orthopaedic surgery ; ≥12 g/dl in women; ≥13 g/dl in men.	ND	**ND**

All units of measurement appear as they are written in each guideline.
Abbreviations. CHF, congestive heart failure; CH_r, reticulate hemoglobin content; CKD, chronic kidney disease; ESAs, erythropoietic stimulating agents; GI, gastrointestinal; Hb, hemoglobin; HD-CKD, chronic kidney disease on hemodialysis; HRC, hypochromic red cells; IBD, inflammatory bowel disease; ID, iron deficiency; IDA, iron deficiency anemia; MCV, mean corpuscular volume; ND, not defined; ND-CKD, non-dialysis-dependent chronic kidney disease; OB/GYN, obstetrics and gynecology; PD-CKD, chronic kidney disease on peritoneal dialysis; SFer, serum ferritin; TSAT, transferrin saturation.

ranging from <13 g/dL in adult males to <11 g/dL in pregnant women and very young (aged 0.6–5 years) children.

Iron deficiency was defined by using both SFer and TSAT by NICE, ESMO and ERBP (<100μg/L and <20% respectively) or by SFer alone: ERBP (<100μg/L); BSH (<30 μg/L in pregnancy and <200 μg/L–<800 μg/L in CKD) and ECCO (<30 μg/L). IDA was defined in similar terms using a combination of SFer and TSAT by NATA, ESC, ECCO and ESMO (SFer <10 g/dL and TSAT <20% in most cases).

Management

Only one of the eleven guidelines (ERBP) did not mention the use of IV iron in the treatment of iron deficiency, and five of the guidelines (NICE, BSH [guidelines on anemia in pregnancy], ECCO, ESMO and the International Working Group on Inflammatory Bowel Diseases) all had specific recommendations for the use of IV iron in cases of IDA. Full details of the definitions and measurements used in European guidelines can be found in Table 1.

"Rest-of-World"

The "Rest-of-World" guidelines were produced by JSDT,[54] the Canadian Agency for Drugs and Technology in Healthcare (CADTH), the Canadian Society of Nephrology (CSN),[42,43] the Indian Ministry of Health,[51] GSA,[62] the Ministry of Health for British Colombia,[44] the Canadian Cardiovascular Society (CCS),[45] the Canadian Pediatric Surveillance Program (CPSP),[46] and the Federation of Obstetrics and Gynaecological Societies of India (FOGSI).[52]

Diagnosis

There were three guidelines (JSDT, CSN and Government of India [GOI]) which provided values to assess the presence of anemia, with four providing clear definitions as to what constitutes iron deficiency (CSN, GSA, Ministry of Health for British Colombia, and CCS). JDST defined anemia as Hb <11–13 g/dL for men and <10.5–11.5 g/dL depending upon age and gender. CSN also used Hb values (<13.5 g/dL for men and <12 g/dL for women). The GOI guidelines followed a similar age/gender pattern as JSDT with Hb values <13 g/dL for men and <11–12 g/dL for women depending upon age and pregnancy.

CSN defines iron deficiency by Hb level (<11 g/dL), SFer (>100 ng/mL), and TSAT (>20%). The GSA uses a more complex measure combining SFer and reduced MCV with ion-binding capacity and TSAT. The Ministry of Health for British Colombia used SFer (varying by age) from <12 to 15 μg/mL, while the CCS used SFer <10 g/dL of SFer 10–30 g/dL with TSAT <20%. IDA was defined by SFer and TSAT by JSDT, whereas CPSP used Hb level (<11 g/dL) in combination with another "measure of poor iron status."

Management

Two guidelines defined IDA (JSDT and CPSP) with seven mentioning the role of IV iron in cases where there is iron deficiency. CADTH discusses the specific use of IV ferumoxytol in IDA, noting that "IV ferumoxytol appears to be non-inferior to iron sucrose with regard to its efficacy in both dialysis-dependent and non-dialysis-dependent patients with or without CKD who experienced IDA. In addition, the safety profiles of ferumoxytol and iron sucrose are similar, though careful observation for potential rare and severe anaphylactic reactions has been suggested post-infusion".[41] See Table 1 for more detail.

"Other"

There were five guidelines from other independent bodies/groups: those from an expert group funded by Vifor Pharma (IRON CORE);[55] WHO;[1] KDIGO;[58] PBM[56,57]and an International Consensus Statement on the peri-operative management of anemia and iron deficiency.[59]

Diagnosis

Of the five guidelines, four defined the measurement of anemia (WHO, KDIGO, PBM and the International Consensus Statement), and two clearly outlined the parameters to indicate a diagnosis of iron deficiency (IRON CORE, WHO). Anemia, as defined by the WHO using Hb (varying by age/gender) was also used by KDIGO and the PBM guidelines, although the International Consensus Statement defined anemia as Hb <13 g/dL for both sexes (this guideline only covered peri-operative anemia). SFer was used to define iron deficiency by WHO, whereas IRON CORE and KDIGO used a combination of SFer and TSAT. The International Consensus Statement defined IDA using SFer and TSAT or C-reactive protein levels. Measures to assess IDA were clearly specified within the KDIGO guidelines and the International Consensus Statement.

Management

Four of the five guidelines recommended the use of IV iron in the treatment of iron deficiency, with only the WHO guidelines omitting any mention. Since the WHO guidelines were focused largely on prevention rather than treatment, this omission is understandable. There were specific recommendations on the use of IV in the treatment of IDA contained in the guidelines from IRON CORE, KDIGO, PBM and the International Consensus Statement. Details of the guidelines and their recommendations can be found in Table 1.

IV Iron treatment

Although IV iron is recommended in almost all the guidelines, depending upon the condition, it is often restricted in its use to those intolerant to, or non-compliant with, oral iron. This is despite evidence that oral iron-replacement therapy is often poorly tolerated or ineffective and that, based on the evidence of five studies, an Hb response <1.0 g/dL at day 14 of oral iron can be used to identify subjects with iron-deficiency anemia who should be transitioned to IV iron supplementation.[63]

Those organizations which specifically recommend the use of IV iron to treat IDA included the JSDT, IRON CORE (CHF, CKD, IBD), where IV iron is the iron deficiency/IDA treatment of choice in CHF, active/advanced IBD, and patients with CKD undergoing dialysis, and is an option (alongside oral iron) in cases of IDA in non-dialysis CKD patients; CADTH (CKD); NICE (CKD); ESC (heart failure with reduced ejection fraction); European Working Group (IBD); ECCO (IBD); KDIGO (CKD); AAFP (if intolerant to oral iron); BSH (if intolerant/non-compliant to oral iron in pregnancy or if a rapid response is needed and in CKD); the US commentary on the KDIGO guidelines (CKD); FOGSI (in people who are intolerant/non-compliant); International Consensus Statement (front-line therapy in patients who do not respond to oral iron or are not able to tolerate it, or if surgery is planned for <6 weeks after the diagnosis of peri-operative anemia); EBA (IV iron therapy should be considered particularly if rapid iron repletion is required [e.g. <2 months to none deferrable surgery]) and PBM in pre-operative surgery (with or without ESA use), although they do note it has potential in other non-surgical settings.[57]

Those who recommend IV iron in cases of iron deficiency included NATA (if intolerant to oral iron) Crohn's & Colitis Foundation (in cases where there is active IBD). CSN guidelines list IV iron as the preferred treatment option in CKD patients undergoing dialysis whilst it is an option (alongside oral iron) for the treatment of non-dialysis or peritoneal dialysis patients. Others include NCCN (in iron deficiency in cancer patients); BSG (when the patient is intolerant to oral iron); GSA (alongside dietary advice, oral iron and blood transfusion); Ministry of Health, British Colombia (cases where there is an inadequate response to oral iron, oral iron is not tolerated or there is ongoing blood loss); ESMO (functional iron deficiency or ongoing chemotherapy); ACP (NYHA class III HF and low ferritin levels); CCS (as an alternative to oral iron); ACOG (parenteral iron is used in the rare patient who cannot tolerate or will not take modest doses of oral iron. Patients with a malabsorption syndrome and severe iron deficiency anemia may benefit from parenteral therapy); AHA (NYHA class II and III HF and iron deficiency IV iron replacement might be reasonable to improve functional status and QOL). Further detail on each guideline's recommendations can be found in Table 2 and more information on IV iron use specifically is contained in Supplemental Table 1.

Those guidelines which did not contain any recommendation for the use of IV iron included AAP (pediatrics); USPSTF (where studies on IV iron use were explicitly excluded from consideration; hence, no guidance on its use was included); GOI (which included intramuscular but not IV iron); WHO (whose guidelines only cover anemia); ASCO/ASH (where the guidelines refer only to treatment using ESAs); CPSP (children); and ERBP (CKD).

This is similar to the previous review in 2015[12] where 21 of 29 guidelines recommended IV iron, although there is

Table 2. Guidelines and IV iron recommendations.

Guideline	Specialty	IV Iron management recommendations
US guidelines		
Crohn's & Colitis Foundation[27]	GI	In patients with active IBD
National Comprehensive Cancer Network (NCCN)[29]	Oncology	Can be used in patients with possible, functional and absolute ID
US Commentary on the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[31]	Nephrology	See KDIGO guidelines
American College of Obstetricians and Gynecologists (ACOG)[4]	OB/GYN	Can be used in patients intolerant to oral iron and patients with a malabsorption syndrome and severe iron deficiency anemia
American Academy of Family Physicians (AAFP)[32]	Adults	Can be used in patients who cannot tolerate or absorb oral preparations
American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA)[33]	Cardiology	IV iron replacement might be reasonable to improve functional status and QOL
Rest-of-World' guidelines		
Japanese Society for Dialysis Therapy (JSDT)[54]	Nephrology	IV iron can be administered to patients with predialysis CKD, HD-CKD and PD
Canadian Agency for Drugs & Technology CADTH[41]	Nephrology	IV ferumoxytol is non-inferior to iron sucrose in both dialysis dependent and non-dependent patients with CKD
Canadian Society of Nephrology (CSN)[42,43]	Nephrology	IV iron can be used in ND-CKD patients who either do not meet target on oral iron or are intolerant to oral iron and patients with HD-CKD or PD-CKD
Gastroenterological Society of Australia (GSA)[53]	GI	Ferrum H, FCM and Iron Sucrose are all discussed as possible treatments
Ministry of Health, British Colombia[44]	All	Oral iron replacement is almost always preferred to IV therapy
Canadian Cardiovascular Society[45]	Cardiology	IV iron therapy be considered for patients with heart failure with reduced ejection fraction and ID
Federation of Obstetric and Gynaecological Societies of India (FOGSI)[52]	OB/GYN	IV iron is recommended for patients who are intolerant to, or non-compliant with oral iron
European guidelines		
Network for Advancement of Transfusion Alternatives (NATA)[34]	Surgery	IV iron if intolerant to oral iron, gastrointestinal uptake problems or short time before surgery
National Institute for Health and Care Excellence (NICE)[47]	Nephrology	IV iron can be used for either correction or maintenance in adults or children
European Society of Cardiology (ESC)[61]	Cardiology	IV FCM should be considered in symptomatic patients
European Board of Anaesthesiology (EBA)[36]	Surgery	IV iron therapy should be considered particularly if rapid iron repletion is required or patients are unresponsive to, or intolerant of, oral iron
British Society of Gastroenterology (BSG)[48]	GI	Use of other iron compounds or formulations should be considered if patients are intolerant of oral iron
International Working Group on Inflammatory Bowel Diseases[38]	GI	The preferred route of iron supplementation in IBD is IV
British Society of Haematology (BSH)[49]	OB/GYN	IV iron should be considered from the second trimester onwards for women with confirmed IDA who are intolerant of, or do not to respond to, oral iron. It should also be considered in women who present after 34 weeks' gestation with confirmed IDA and low Hb levels.
British Society of Haematology (BSH)[50]	ACD and CKD	IV iron warranted for treatment of classic and functional ID
European Society for Medical Oncology (ESMO)[39]	Oncology	IV iron recommend in patients with IDA and solid or hematological malignancies
European Crohn's and Colitis Organisation (ECCO)[40]	GI	IV iron should be considered as first line treatment in: patients with clinically active IBD; those who are intolerant to oral iron; patients who have a low Hb level, patients who are being treated with ESAs
'Other' guidelines		
IRON CORE Study Group[55]	Chronic inflammatory conditions (CHF, CKD and IBD)	IV iron use recommended in patients with CHF or CKD who also have ID, and CKD and IBD patients who have IDA

(*continued*)

Table 2. Continued.

Guideline	Specialty	IV Iron management recommendations
Kidney Disease Improving Global Outcomes (KDIGO)[58]	Nephrology	IV iron suggested in adult CKD and pediatric HD-CKD patients with anemia not on iron or ESA therapy or patients on ESA therapy who are not currently receiving iron. It can also be used on ND-CKD patients
International Consensus Statement on the peri-operative management of anemia and iron deficiency[59]	Surgery	IV iron can be used if patients are intolerant to oral iron, or where oral iron is contraindicated or a short time to surgery. It should also be used where there is iron deficiency which is either functional or related to anemia of chronic inflammation
Patient Blood Management (PBM)[56,57]	Surgery	IV iron recommended in cases of IDA in orthopedic surgery. Has potential to be used in other non-surgical settings including CHF, obstetrics and liver disease.

Abbreviations. ACD, anemia of chronic disease; CHF, congestive heart failure; CKD, chronic kidney disease; ESAs, erythropoietin-stimulating agents; FCM, ferric carboxymaltose; GI, gastrointestinal; Hb, hemoglobin; HD-CKD, hemodialysis-dependent chronic kidney disease; IBD, inflammatory bowel disease; ID, iron deficiency; IDA, iron deficient anemia; IV, intravenous; ND-CKD, non-dialysis dependent chronic kidney disease; OB/GYN, obstetrics and gynecology; PD-CKD, peritoneal dialysis-dependent chronic kidney disease; QOL, quality of life; TSAT, transferrin saturation.

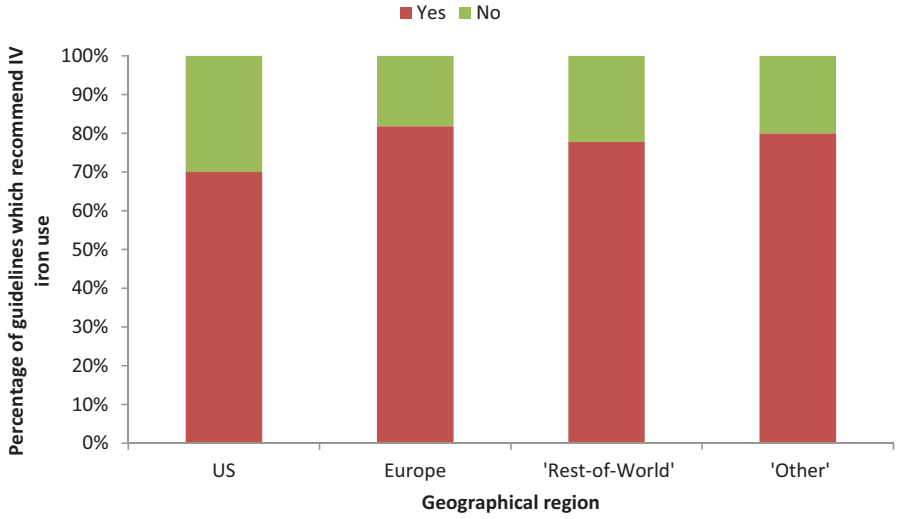

Figure 3. Percentage of guidelines for anemia, iron deficiency and/or iron deficiency anemia which include any recommendations for the use of IV iron. Abbreviation. IV, intravenous; US, United States.

considerable variation by geography: 30% of US guidelines compared to 10% of European, 22% of "Rest-of-World," and 20% of "Other" guidelines had no recommendation for IV iron use (Figure 3). It is also notable that only one US guideline (US Commentary on the KDIGO guidelines) had IV iron as first-line treatment.

Relatively few guidelines discuss specific IV iron formulations, and where they do, they do not recommend one over another. The ESC guidelines are an exception to this and recommend the use of IV ferric carboxymaltose (FCM).[35]

Discussion

Iron deficiency has been identified as the leading cause of anemia, a condition which causes death and morbidity for large numbers of people worldwide, as noted in the introduction the latest version of the Global Burden of Disease Study has IDA as one of the leading causes of disability worldwide. The objective of our review was to explore the current recommendations for IV iron use in clinical guidelines for iron deficiency across different therapeutic areas and evaluate the absence or presence of specific recommendations for the treatment of IDA. We also intended to see if there were differences in guideline recommendations, particularly with respect to IV iron use, between the US and other regions.

Our results have shown that whilst anemia itself is well-defined, generally agreeing in many cases with the Hb values recommended by the WHO (although it should be noted that recently there has been increasing discussion about the appropriateness of the gender distinctions in the WHO values[64]) the concepts of iron deficiency and IDA are generally much vaguer, with many of the guidelines using the terms almost interchangeably. This is reflected in the fact that many guidelines fail to give clear recommendations for treatment, particularly with regards to the use of parenteral iron in management in cases of IDA. This is largely consistent with the results of the previous systematic review by Peyrin-Boulet et al.,[12] however, where they seemed optimistic that the then emerging IV iron treatments would be included in future iterations of the guidelines, we have found relatively

little evidence that this has happened. Of the 19 guidelines which were reviewed in both studies, only eight had been updated within the last five years, meaning that many guidelines were still over a decade old and may no longer reflect the best available practice in their specialty area. It is interesting to note that many of the guidelines which consider the use of IV iron come from inflammatory conditions such as CHF and nephrology where the absorption of oral iron might be problematic. On the other hand, there is a noticeable lack of identified guidelines in the area of pediatric care, despite much recent research pointing to the potential role of IV iron in children.[65–67] There was also considerable variation by geography, with US guidelines on the whole having fewer that included recommendations around IV iron. The issue of the lack of updating of guidelines means that many of the guidelines are not reflecting the current evidence on the efficacy and safety of IV iron. See Auerbach and DeLoughery[68] which reported that "although oral iron is often viewed as front-line therapy, extensive published evidence has accumulated that IV iron is superior, in both efficacy and safety, to oral iron in many clinical situations and should be introduced much sooner in the treatment paradigm of iron-deficient patients." Furthermore, the recent review by DeLoughery[69] notes that "physicians'" treatment practices may be based on old and out-of-date understanding and information, especially with regard to the safety of oral and IV iron therapy and that "the preponderance of the data reinforces the safety and low reaction rates of IV iron." This is also supported by other recent studies, including an e-Delphi survey for IDA in gastrointestinal bleeding concluded "that current use of iron therapy by experts in the field is driven by clinical and cost-orientated considerations, rather than by clinical assessment and therapeutic targets or treatment thresholds".[70] A recent meta-analysis of the safety of IV iron compounds in IBD treatments found that FCM was associated with fewer adverse events, although, its statistical significance remains unproven due to the lack of data from randomized controlled trials.[71] A cost-effectiveness study in the Nordic countries suggested that implementing the ESC guidelines for the treatment of iron deficiency in heart failure using FCM would improve both health-related QOL and reduce healthcare costs.[72] In addition to a lack of consideration of the cost-effectiveness of different treatment options, many of the guidelines fail to clarify the clinical criteria that indicate oral vs IV iron replacement beyond cases where patients might be intolerant to oral iron, and almost none recommended preparations of iron which should be used, given the differences in their efficacy/safety profiles. There was also a lack of consideration about the trigger and target iron and Hb levels, and about the timing allowed to obtain such target values based on a patient's status and hemodynamic conditions.

The principle strength of our study is that it uses a well-defined and accepted methodology (i.e. that of a systematic review) to identify suitable studies for inclusion. It has also built upon a previous systematic review by Peryin-Biroulet et al.[12] to identify both a larger number of guidelines and to ensure that the latest available guidelines are now assessed, since the previous review was published in 2015. This study is subject to several limitations. First, as the literature review has shown many guidelines are either not published in peer-reviewed journals, or, since IDA is not the main focus of many of the guidelines (it is a consequence of other conditions and so is treated as a sub-section of most guidelines), it is not mentioned in the title/abstract of a paper. They are consequently difficult to identify. Therefore, some relevant guidelines may have been omitted for these reasons. Second, we have restricted our search to guidelines published in English, which may have excluded some guidelines (although this is likely to disproportionately affect guidelines from non-US countries/regions).

This review has shown that diagnosis and treatment of iron deficiency/IDA is still subject to heterogeneity and that many of the guidelines urgently need to be updated to reflect growing evidence for the benefits of IV iron, which would encourage changes in clinical practice to ensure the optimal management of patients with IDA.

Conclusions

While many national and international guidelines exist regarding anemia, there remains a lack of clarity on the diagnosis of iron deficiency and around the management modality of IDA, despite the recognition of the worldwide burden that this condition imposes. Many of the guidelines are outdated and do not reflect the current evidence available for the use of IV iron. Urgent consideration should be given to updating and clarifying guidelines around IDA. This is particularly true for the US (the region with the highest percentage of guidelines making no recommendations on IV use) where the only professional organization to endorse the use of IV iron in IDA currently is the AAFP.

Transparency

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Declaration of financial/other relationships

SN and KK are both employees of American Regent. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

SN and KK were involved in the conception, design, analysis and interpretation of the data; revised it critically for intellectual content; and have given final approval of the version to be published. Both authors agree to be accountable for all aspects of the work.

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Data availability statement

There is no data set for this review. All guidelines are available online.

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