AJCN. First published ahead of print November 11, 2015 as doi: 10.3945/ajcn.114.103366.

Guidelines on the diagnosis and treatment of iron deficiency across indications: a systematic review[1]

Laurent Peyrin-Biroulet,[2,7] Nicolas Williet,[2,7] and Patrice Cacoub[3–6]*

[2]National Institute of Health and Medical Research, U954, and Hepato-Gastroenterology Department of Lorraine University, Vandoeuvre-les-Nancy, France; [3]Sorbonne University and Inflammation-Immunopathology-Biotherapy Department, Paris, France; [4]National Institute of Health and Medical Research, UMR_S 959, Paris, France; [5]National Scientific Research Center, FRE3632, Paris, France; and [6]Department of Internal Medicine and Clinical Immunology, Salpetriere Hospital, Paris, France

ABSTRACT

Background: Guidelines on the diagnosis and treatment of iron deficiency (ID) vary widely across indications.

Objective: We reviewed all available guidelines on the management of ID worldwide.

Design: A literature search was conducted in PubMed, Cochrane, and EMBASE and in main professional association websites, limited to documents published between 1 January 2004 and 30 June 2014.

Results: Of 127 guidelines identified, 29 were selected, involving 29 professional associations and issued from the United States (n = 8), Europe (n = 6), Britain (n = 4), Canada (n = 3), international organizations (n = 2), France (n = 2), Poland (n = 1), Australia (n = 1), Mexico (n = 1), and Japan (n = 1). A total of 22 and 27 guidelines provided recommendations on diagnosis and treatment of ID, respectively. To define ID, all guidelines recommended a concentration for serum ferritin. One-half of them (10 of 22) proposed transferrin saturation (TSAT) as an alternative or complementary diagnostic test. To treat ID, most of the guidelines (18 of 27) recommended preferentially the oral route if possible, particularly in children and in women in the pre- or postpregnancy period. Iron supplementation should be administered intravenously according to 13 of 27 guidelines, particularly in patients with chronic kidney disease (CKD) (n = 7) and chemotherapy-induced anemia (n = 5). Treatment targets for ID included an increase in hemoglobin concentrations to 10–12 g/dL or normalization (n = 8) and serum ferritin >100 μg/L (n = 7) or 200 μg/L (n = 4). For the latter, in some situations, such as CKD, ferritin concentrations should not exceed 500 μg/L (n = 5) or 800 μg/L (n = 5). Only 9 guidelines recommended TSAT as a target, proposing various thresholds ranging from 20% to 50%.

Conclusions: It appears that for the diagnosis of ID, a cutoff of 100 μg/L for serum ferritin concentration should be considered in most conditions and 20% for TSAT, except in particular situations, including young healthy women with heavy menstrual flow. New indications of intravenous iron supplementation are emerging.

Am J Clin Nutr doi: 10.3945/ajcn.114.103366.

Keywords: iron deficiency, diagnosis, management systematic review, guidelines, ferritin, TSAT

INTRODUCTION

Iron deficiency (ID)[8] is the most common and widespread nutritional disorder in the world; 2 billion people—>30% of the world's population—are anemic, many because of ID (1, 2). ID is the only nutrient deficiency that is also prevalent in industrialized countries (1), particularly in women of childbearing age with heavy menstrual flow and miscarriages. In clinical practice, several chronic conditions are also associated with ID.

ID, with or without anemia, is a common complication of cancers (42.6% across different tumors) (3). ID is also frequent in inflammatory bowel disease (IBD) (45%) (4), chronic kidney disease (CKD) (24–85%) (5), chronic heart failure (CHF) (43–100%) (6, 7) and other chronic inflammatory diseases. ID may be absolute when the total body iron stock is low (i.e., after hemorrhages). Functional ID occurs when the iron is not able to go out of the macrophages trapped in macrophages, in the reticuloendothelial system (RES), with as consequence a kinetic imbalance between the increased iron demand of the stimulated erythroid marrow and iron supply. In functional ID, iron is therefore sequestered in the reticuloendothelial system (among which are the Kupffer cells). The hepatocytes comprise relatively low iron concentrations in this condition (i.e., IBD, CKD, and many other inflammatory situations).

ID is associated with impaired quality of life (8), work productivity (9), and fatigue (10). There is also a strong relation between iron status and depression and cognitive functioning (11). Furthermore, ID is a strong predictor of mortality in CHF (7) and CKD (12, 13). Hence, diagnosing and treating ID with or without anemia is a major issue in clinical practice.

Several diagnostic tests and definitions of ID have been proposed so far. In 2001, the WHO defined ID with thresholds of serum ferritin concentrations varying according to sex, age, and the infectious context (14). However, this definition is inadequate in many clinical situations, including inflammation and CKD, in

[1] The authors reported no funding received for this study.

[7] These authors contributed equally to this work.

*To whom correspondence should be addressed. E-mail: peyrinbiroulet@gmail.com.

[8] Abbreviations used: CHF, chronic heart failure; CKD, chronic kidney disease; HFE, High Iron Fe; IBD, inflammatory bowel disease; ID, iron deficiency; NICE, National Institute for Health and Care Excellence; sTfR, soluble transferrin receptor; TSAT, transferrin saturation.

Received November 15, 2014. Accepted for publication October 7, 2015.
doi: 10.3945/ajcn.114.103366.

which ferritin concentrations tend to increase, and thus are falsely normal when associated with ID (12, 15). Moreover, definitions and recommendations proposed by the WHO were focused on ID in children and women during the perigestational period, a major public health problem throughout the world. Treating ID leads to better outcomes, including scores of self-reported Patient Global Assessment and those of the New York Heart Association, and quality of life in patients with New York Heart Association functional class II or III CHF (16).

Over the past decade, professional associations for each specialty have developed their own guidelines. Accordingly, recommendations for treating ID vary across indications. Herein, we review available definitions of ID across indications and current recommendations on the diagnosis and management of ID in human diseases before giving some recommendations for clinical practice based on the available evidence.

METHODS

Literature search strategy

A literature search was conducted in PubMed, EMBASE, Cochrane, and main professional association websites, including those of the WHO and the National Institute for Health and Care Excellence (NICE) and those of each concerned medical specialty, such as cardiology, nephrology, oncology-hematology, orthopedics, anesthesiology, and obstetrics-gynecology, issued from any country worldwide. We used the following search terms: "Anemia" (MeSH) or "Anemia, iron deficiency" (MAJR), and "iron" and ["deficiency" or "ferritin" or "definition", "diagnosis", "supplementation" or "treatment" or "transferrin saturation" (TSAT) or "TSAT" or "soluble transferrin receptor" (sTfR) or "sTfR"].

Selection criteria

Only guidelines focusing on diagnosis and/or management of ID in healthy or ill patients (both adults and children) were selected. The search was limited to English- and French-language documents published between 1 January 2004 and 30 June 2014. Only the last update of guidelines was included in this article. Three independent researchers (LP-B, NW, and PC) 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.

Data collection

Information on thresholds of ferritin and/or transferrin saturation for the diagnosis of ID was extracted from each included article. If available, the preferential route of iron supplementation, objectives of treatment, and/or target values of ferritin, TSAT, and/or hemoglobin were also collected. We also identified new biomarkers of iron status, such as sTfR.

RESULTS

Literature search results

A total of 107 guidelines from the past decade were identified in PubMed, EMBASE, and Cochrane with the use of the search keywords listed above (**Figure 1**). After reviewing the title and/or the abstract of the 107 guidelines that were identified with the predefined search terms, a total of 26 guidelines were included in the systematic review. By searching on the websites from the professional associations of each specialty, 20 additional guidelines were selected, including a 2014 update of the National Comprehensive Cancer Network focused on the management of chemotherapy-induced anemia and 2 referral guidelines issued from general medical websites such as those of the NICE and the American Academy of Family Physicians. Of these 46 guidelines selected, 10 duplicates were excluded (because only the last update was included in the systematic review) and 7 articles were excluded because the full text was not available. Thus, a total of 29 guidelines were included in this systematic review: British (n = 5) (17–21), American (n = 7) (22–28), European (n = 9, including 2 French, 1 Polish, and 6 European societies) (4, 29–36), Canadian (n = 3) (37–39), Australian (n = 1) (40), Mexican (n = 1) (41), and Japanese (n = 1) (42) recommendations. Some professional associations and experts worked together to provide international recommendations (n = 2) (43, 44) through an article focused on the treatment of ID in IBD (n = 1) (43) or CKD (45). Overall, 29 professional associations provided recommendations on the diagnosis and treatment of ID, whether in the general population (n = 4) (17, 18, 27, 40) or in 9 specific conditions (n = 54), including CKD (n = 8) (18, 19, 26, 32, 38, 39, 42, 45), chemotherapy-induced anemia (n = 5) (24, 25, 30, 31, 34), the perigestational period (n = 4) (21, 35, 36, 41), children (n = 3) (17, 23, 37), digestive diseases (n = 3) (4, 43, 46), IBD (n = 2) (4, 43), heart diseases (n = 2) (28, 33), severe perioperative bleeding (n = 1) (29), and preoperative anemia in elective orthopedic surgery patients (n = 1) (22).

Nine different specialties (anesthesia, cardiology, gastroenterology, obstetrics and gynecology, hematology, nephrology, oncology, orthopedics, and pediatrics) have developed guidelines on the diagnosis and treatment of ID. For each specialty, we identified the following organizations and documents:

- the European Best Practice Guidelines, the European Renal Best Practice, the Japanese Society for Dialysis Therapy, the Kidney Disease: Improving Global Outcomes organization, the Kidney Disease Outcomes Quality Initiative, the International Society of Nephrology, and the NICE for nephrology;
- the American Society of Clinical Oncology, the American Society of Hematology, the European Society for Medical Oncology, the European Organisation for Research and Treatment of Cancer, the National Foundation of Centers for the Fight against Cancer, the National Foundation of the University Regional Institute for Oncology, the National Unit of Clinics for Oncology, and the National Comprehensive Cancer Network for Oncology;
- the American College of Obstetricians and Gynecologists, the French National College of Gynecologists and Obstetricians, the Polish Gynecological Society Expert Group, and the Federation of Mexican Colleges of Obstetrics and Gynecology;
- the American Academy of Pediatrics and the Canadian Pediatric Surveillance Program;
- experts groups from international, European (European Crohn's and Colitis Organisation), British (British Society of Gastroenterology), or Australian (Gastroenterological Society of Australia) societies for gastroenterology;

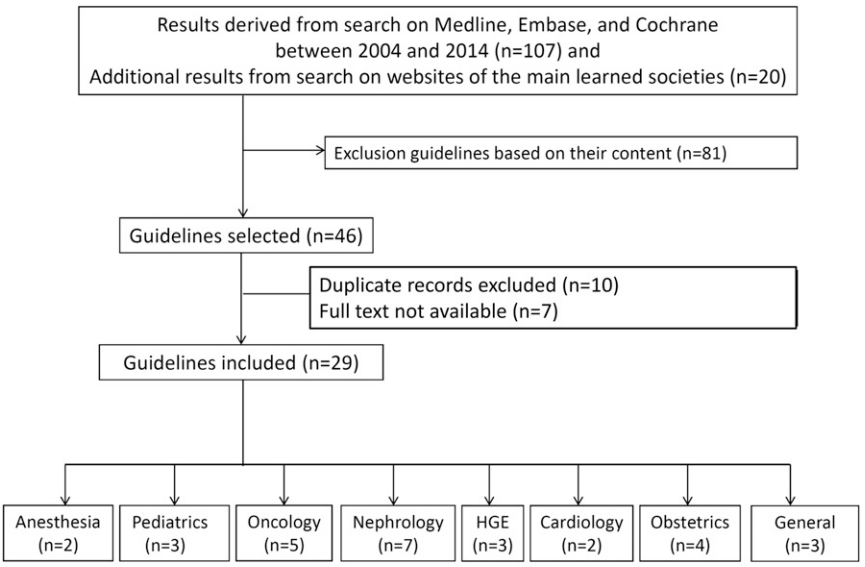

FIGURE 1 Flowchart of the study selection process for the systematic review. HGE, hepatogastroenterology.

- the American College of Physicians and the European Society of Cardiology for cardiology;
- the European Society of Anaesthesiology and the Network for Advancement of Transfusion Alternatives for anesthesia; and
- the American Academy of Family Physicians, British Columbia Guidance, and the British Committee for Standards in Haematology.

Twenty-two guidelines provided recommendations on ID diagnosis (**Table 1**), whereas 27 were on the modalities of treatment of ID (**Table 2**). It is noteworthy that 18 guidelines reported the level of evidence, including guidelines on anesthesia (n = 1) (29), heart diseases (n = 2) (28, 33), digestive diseases (n = 3) (4, 43, 46), CKD (n = 6) (18, 21, 39, 42, 44, 45), and chemotherapy-induced anemia (n = 2) (3, 34).

Diagnosis of ID

To define ID (Table 1), all guidelines recommended the measurement of serum ferritin concentrations. One-half of them (10 of 22) proposed TSAT as an alternative or complementary diagnostic test (4, 18, 19, 22, 25, 32, 42, 43, 45, 47). Four guidelines (18, 20, 23, 35) mentioned the potential diagnostic role of sTfR, especially in children <3 y of age (23, 35) and women in the perigestational period (23, 35). Only 1 of these 4 guidelines specified a threshold in pregnant women (18) for sTfR, and one other did not recommend its routine use because of lack of supportive evidence (18). A decrease in mean corpuscular volume (<80 fL), an increase in total iron-binding capacity (>68 μmol/L) or hypochromic red cells (+6%), and a low reticulocyte hemoglobin content (<29 pg) may also support diagnosis of ID, as mentioned in some guidelines (18, 19, 40). The clinical utility of plasma erythropoietin and/or hepcidin has yet to be determined (18).

Eight guidelines took into account the presence of an inflammatory syndrome when interpreting ferritin concentration, which may be falsely normal despite a low iron store (4, 14, 19–23, 43). Indeed it is well known that this clinical situation defines functional ID, as opposed to absolute ID. Functional ID is mainly observed during infection, active inflammatory disorders such as IBD, and chemotherapy-induced anemia. Two guidelines defined the anemia of chronic disease, including IBD, and proposed thresholds for ferritin and TSAT to distinguish functional ID from absolute ID (4, 43).

Ferritin concentration to define ID

According the NHANES, ferritin references range from 30 to 400 μg/L for men and from 13 to 150 μg/L for women. Several thresholds were proposed for the diagnosis of ID with the use of ferritin concentrations across specialties and indications.

The 12–15-μg/L threshold for ferritin was proposed in 10 guidelines, including those in the general population (n = 4) (17, 18, 40, 46), women (n = 3) (21, 35, 38), children (n = 3) (17, 23, 37), and patients with CKD (n = 2) (18, 38) or digestive diseases (n = 1) (46).

The 25–30-μg/L threshold for ferritin was proposed in 9 guidelines for the general population (n = 3) (22, 29, 43), IBD (n = 2) (4, 43), CKD (n = 3) (38, 45, 47), chemotherapy-induced anemia (n = 1) (25), and the perigestational period (n = 1) (21). Of note, when referring to the general population (22, 29, 43), all patients either had a chronic disease such as inactive IBD or were in the particular situation of perioperative bleeding.

The 45–50-μg/L threshold for ferritin was proposed in 3 guidelines, and involved the general population (n = 2) (17, 27) with a diagnosis of ID that was estimated as "probable," as well as digestive diseases (n = 1) (46).

The 100-μg/L threshold for ferritin was proposed in 12 guidelines, mainly in the context of CKD (n = 5) (18, 19, 32, 42, 45), in the general population (n = 2) (17, 18), for which the diagnosis of ID is estimated as "possible" with the use of this cutoff, in patients with heart disease (n = 2) (28, 33), in active IBD (n = 2) (4, 43), and for anesthesia (n = 2) (22, 29).

The 200-μg/L threshold for ferritin was proposed in 2 guidelines, exclusively for patients with hemodialysis CKD who are receiving hemodialysis (18, 32).

TABLE 1
Definition of ID across indications[1]

Professional association (reference)	Origin	Year	Context	Ferritin, μg/L	TSAT, %	Other biomarkers
Anesthesia (n = 2)						
NATA (22)	American	2011	Preoperative anemia in the elective orthopedic surgical patient			
			ID	<30	<20	—
			FID or CKD	30–100	<20	—
ESA (34)	European	2013	Severe perioperative bleeding			
			Healthy adults	<30	—	—
			Chronic disease, inflammation	30–100		
Children (n = 3)			0–3 y old			
BCG* (17)	British	2010		<12	—	
AAP (23)	American	2010		<10	N/A	sTfR assay is promising
CPSP (37)	Canadian	2011		<10	—	—
Chemotherapy induced-anemia (n = 1)						
NCCN (25)	American	2014	Absolute ID	<30	<20	
			FID	30–800	20–50	
CKD (n = 7)						
KDOQI (26)	American	2006	ND-CKD			
			In male subjects	<25	<16	
			In female subjects	<11	<16	
JSDT (42)	Japanese	2008	ID in HD-CKD	≤100	≤20	
ISN (38)	Canadian	2008	ND-CKD not exposed to erythropoiesis-stimulating agent			
			In male subjects	25	—	—
			In female subjects	11	—	—
ERBP (44)	European	2009	ND-CKD	<100	<20	—
			HD-CKD	<200	<20	—
NICE (19)	British	2011	ND-CKD	<100		
			HD-CKD	<100		
			FID	>100	<20	or HRC >6%
KDIGO (45)	International	2012	Severe ID	<30	—	—
			ND-CKD	<500	<30	—
			HD-CKD	<500	<30	—
			Children with CKD	<100	<20	—
BCSH** (18)	British	2013	Severe ID	<12	—	
			ND-CKD			
			ID	<100	<25	
			FID	100–800	<25	HRC >6% + CHr <29 pg may be useful. The utility of erythropoiesis-stimulating agent and hepcidin measurement is uncertain
			HD-CKD			
			ID	<200	<25	
			FID	200–800	<25	
Digestive diseases (n = 3)						
N/A (43)	International	2007	IBD			
			Quiescent disease	<30 (or)	<16	
			Active disease	30–100 (and/or)	<16	
			ACD without ID	>100 (and)	<16	
BSGE (46)	British	2011	Digestive diseases			
			Healthy patients	12–15	—	sTfR
			Chronic disease	<50		
ECCO (4)	European	2012	IBD			
			Quiescent disease	<30 (or)	<16	
			Active disease	30–100 (and/or)	<16	
			ACD without ID	>100 (and)	<16	
Healthy adults (n = 4)						

(Continued)

TABLE 1 (*Continued*)

Professional association (reference)	Origin	Year	Context	Ferritin, μg/L	TSAT, %	Other biomarkers
AAFP (27)	American	2007		≤45	—	
BCG* (17)	British	2010	ID	<15	—	
			Probable ID	15–50	—	
			Possible ID	50–100	—	
			Unlikely ID	>100	—	
GESA (40)	Australian	2011		<15	—	and MCV <80 fL
BCSH** (18)	British	2013		<12	<20	sTfR test is not recommended routinely
Heart disease (n = 2)						
ESC (33)	European	2012	Acute and chronic heart failure	<100	—	
ACP (28)	American	2013	Heart disease	<100	—	
Pregnancy (n = 2)						
BCSH (48)	British	2012	Pregnancy			
			ID	<15		
			Probable ID (hemodilution)	<30		
CNGOF (35)	French	2014		<12	—	sTfR +8.5 mg/L

[1]Guidelines for * and ** are reported in 2 distinct indications in this table. AAFP, American Academy of Family Physicians; AAP, American Academy of Pediatrics; ACD, anemia due to chronic disease; ACP, American College of Physicians; BCG, British Columbia Guidance; BCSH, British Committee for Standards in Haematology; BSGE, British Society of Gastroenterology; CHr, content of reticulocyte hemoglobin; CKD, chronic kidney disease; CNGOF, National College of French Gynecologists and Obstetricians; CPSP, Canadian Paediatric Surveillance Program; ECCO, European Crohn's and Colitis Organisation; ERBP, European Renal Best Practice; ESA, European Society of Anaesthesiology; ESC, European Society of Cardiology; FID, functional iron defficiency; GESA, Gastroenterological Society of Australia; HD, hemodialysis; HRC, hypochromic red cell; IBD, inflammatory bowel disease; ID, iron deficiency; ISN, International Society of Nephrology; JSDT, Japanese Society for Dialysis Therapy; KDIGO, Kidney Disease, Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; MCV, mean corpuscular volume; NATA, Network for Advancement of Transfusion Alternatives; NCCN, National Comprehensive Cancer Network; ND, nonhemodialysis; NICE, National Institute for Health and Care Excellence; N/A, not available; sTfR, soluble transferrin receptor; TSAT, transferrin saturation.

The 500-μg/L threshold for ferritin was proposed in 1 guideline focusing on patients with CKD (45).

The 800-μg/L threshold for ferritin, which defines functional ID, was proposed in 2 guidelines for chemotherapy-induced anemia (n = 1) (25) and CKD, whether hemodialyzed or not (n = 1) (18). For functional ID, ferritin concentration is usually between 100 and 800 μg/L and TSAT is between 30% and 50% (25).

TSAT to define ID

With respect to TSAT, about one-half of selected guidelines (10 of 22) proposed various thresholds.

Three guidelines proposed the 15–16% threshold for TSAT; indications included IBD (n = 2) (4, 43), CKD (n = 1) (26), and the general population (n = 1) (43).

Seven guidelines proposed the 20% threshold for TSAT in CKD (n = 5) (19, 22, 32, 42, 45), the general population (n = 2) (18, 22), children (n = 1) (45), and IBD (n = 1) (4).

Other guidelines proposed higher thresholds for TSAT, such as 25% (n = 1) (18) and 30% (n = 1) (45) in patients with CKD, whether undergoing hemodialysis or not. The highest threshold was reported in the situation of functional ID in chemotherapy-induced anemia, because TSAT may rise to 50% (ferritin between 30 and 800 μg/L) in these patients (n = 1) (25).

Treatment of ID

Oral compared with intravenous route of administration

Of the 27 guidelines focusing on the treatment of ID (Table 2), all indicated the preferential route for iron supplementation (oral or intravenous). Most of these guidelines (18 of 27) (4, 17, 19, 21–23, 26, 27, 29, 32, 36, 37, 39–41, 43, 45, 46) recommended the oral route as a first-line treatment for ID. The intravenous route was proposed as an alternative in case of inefficiency, intolerance, or malabsorption of iron salts. This is particularly true in CKD (n = 5) (19, 26, 32, 39, 45), in the general population (n = 4) (17, 22, 27, 40), in women in the perigestational period (n = 3) (21, 36, 41), and in IBD (n = 2) (4, 43).

Intravenous iron supplementation only was recommended in 13 guidelines (18, 19, 24, 25, 28, 30, 31, 33, 34, 39, 42, 45, 47), particularly in chemotherapy-induced anemia (n = 5) (24, 25, 30, 31, 34) in the case of either absolute or functional ID. Indeed, in this indication, the oral route of iron supplementation is no more effective than placebo. The context of heart disease requires a quick correction of anemia without exposing patients to the risk of transfusion associated circulatory overload. Also, the intravenous route (n = 2) (28, 33), appears the preferential route in this context and in patients with CKD, according to Japanese CKD guidelines (n = 1) (42), particularly in patients with hemodialysis.

The oral route was recommended in 7 guidelines for the treatment of ID in children (n = 2) (23, 37), the pre- or post-pregnancy situation (n = 3) (21, 36, 41), CKD (n = 1) (45), and the general population (n = 1) (27).

Treatment targets of ID: hemoglobin, ferritin, and/or TSAT

Of the 13 guidelines reporting the target value of hemoglobin (Table 2) (4, 19, 23–25, 28–32, 34, 41, 43), 8 recommended a value of 10–12 g/dL in chemotherapy-induced anemia (n = 5)

TABLE 2
Iron supplementation: guidelines for clinical practice across indications[1]

Professional association (reference)	Origin	Year	Context	Preferential route of supplementation	Target hemoglobin, g/dL	Target ferritin, μg/L	Target TSAT, %	Others
Anesthesia (n = 2)								
NATA (22)	American	2011	Preoperative anemia in the elective orthopedic surgery patient	Oral or i.v.	—	—	—	—
ESA (34)	European	2013	Severe perioperative bleeding	Oral or i.v.	7–9 g/dL during bleeding			
Children (n = 2)			0–3 y old					
AAP (23)	American	2010		Oral	+1 g/dL after 1 mo	—	—	—
CPSP (37)	Canadian	2011		Oral				
Chemotherapy induced-anemia (n = 5)								
FNCLCC/FNCHRU/UNHPC (34)	French	2008		i.v.	12	100–500	>20	
EORTC (31)	European	2008		i.v.	12	—	—	
ESMO (30)	European	2010		i.v.	12	—	—	—
ASCO/ASH (24)	American	2010		i.v.	12	—	—	—
NCCN (25)	American	2014	Absolute ID	Oral or i.v.	>12 (<13)	—	—	Ht normal
			FID	i.v.	10–12 g/dL (CKD)	—	—	—
CKD (n = 7)								
KDOQI (26)	American	2006	ND-CKD	Oral or i.v.		>100	>20	
			HD-CKD	i.v.		200–500	>20	RHC >29
			Children	Oral (ND) i.v. (HD)		>100	>20	
JSDT (42)	Japanese	2008	HD-CKD	i.v.		100–800	20–50	
ISN (39)	Canadian	2008	ND-CKD or PD-CKD	Oral or i.v.		>100	>20	—
			HD-CKD	i.v.		>200	>20	
ERBP (44)	European	2009	ND-CKD	Oral or i.v.	11–12 (<13)	200–500	30–50	
			HD-CKD	i.v.	11–12 (<13)	200–500	30–50	
NICE (19)	British	2011	ND-CKD	Oral or i.v.	+1–2 g/mo 10–12 g/dL	200–500	>20 (unless ferritin is >800 μg/L)	HRBC <6% (unless ferritin is >800 μg/L)
			HD-CKD	Oral or i.v.	Idem	Idem		
			FID	i.v.		<800		
KDIGO (45)	International	2012	FID	i.v.	N/A	N/A	N/A	N/A
			ND-CKD	Oral or i.v.	N/A	<500	<30	N/A
			HD-CKD	i.v.		<500	<30	
			Children	Oral		>100	>20	
BCSH (18)	British	2013	ND-CKD	i.v.	—	—	—	—
			HD-CKD	i.v. (option if ferritin <800 μg/L)	—	—	—	—
Digestive diseases (n = 3)								
N/A (43)	International	2007	IBD	Oral or i.v.	Normalization or improvement of QoL	100–800	16–50	
BSGE (46)	British	2011		Oral or i.v.				
ECCO (4)	European	2012	IBD	Oral or i.v.	Normalization or improvement of QoL			
Healthy adults (n = 3)								
AAFP (27)	American	2007		Oral	—	—	—	—
BCG (17)	British	2010		Oral or i.v.	—	—	—	—
GESA (40)	Australian	2011		Oral or i.v.	—	—	—	—

(Continued)

TABLE 2 (*Continued*)

Professional association (reference)	Origin	Year	Context	Preferential route of supplementation	Target hemoglobin, g/dL	Target ferritin, μg/L	Target TSAT, %	Others
Heart disease (n = 2)								
ESC (33)	European	2012	Acute and chronic heart failure	i.v.				
ACP (28)	American	2013	Heart disease	i.v.	>7	>100		
Pregnancy (n = 3)								
BCSH (48)	British	2012	ID	Oral				
			probable ID (hemodilution)	Oral				
FMCOG (41)	Mexican	2012	pregnancy	Oral	>10.5	300–360	—	—
PGSEG (36)	Polish	2013	pregnancy	Oral	N/A	N/A	N/A	N/A

[1]AAFP, American Academy of Family Physicians; AAP, American Academy of Pediatrics; ACP, American College of Physicians; ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; BCG, British Columbia Guidance; BCSH, British Committee for Standards in Haematology; BSGE, British Society of Gastroenterology; CKD, chronic kidney disease; CPSP, Canadian Paediatric Surveillance Program; ECCO, European Crohn's and Colitis Organisation; EORTC, European Organisation for Research and Treatment of Cancer; ERBP, European Renal Best Practice; ESA, European Society of Anaesthesiology; ESC, European Society of Cardiology; ESMO, European Society for Medical Oncology; FID, functional iron defficiency; FMCOG, Mexican College of Gynecologists and Obstetricians; FNCHRU, National Foundation of Regional University Hospitals for Oncology; FNCLCC, National Foundation of Centers for the Fight against Cancer; GESA, Gastroenterological Society of Australia; HD, hemodialysis; HRBC, hypochromic binding red cell; Ht, hematocrit; IBD, inflammatory bowel disease; ID, iron deficiency; ISN, International Society of Nephrology; i.v., intravenous; JSDT, Japanese Society for Dialysis Therapy; KDIGO, Kidney Disease, Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; NATA, Network for Advancement of Transfusion Alternatives; NCCN, National Comprehensive Cancer Network; ND, nonhemodialysis; NICE, National Institute for Health and Care Excellence; N/A, not available; PD, peritoneal dialysis; PGSEG, Polish Gynecological Society Expert Group; QoL, quality of life; RHC, reticulocyte hemoglobin content; TSAT, transferrin saturation; UNHPC, National Unit of Oncology Clinics.

(24, 25, 30, 31, 34), nephrology (n = 2) (19, 32), and pregnancy (n = 1) (41). Other guidelines, mainly for nephrology and pediatrics, recommended an increase in hemoglobin concentrations of +1–2 g/dL monthly as a therapeutic target (n = 2) (19, 23). Some restrictive strategies recommend a hemoglobin concentration >7 g/dL in the particular situation of severe perioperative bleeding and in case of heart failure because of the risk of volumetric overload related to intravenous iron supplementation (28, 29).

Regarding ferritin, 6 of 11 guidelines focused on patients with CKD (19, 26, 32, 39, 45, 47), 1 focused on patients with heart disease (28), 1 focused on IBD (43), 2 focused on chemotherapy-induced anemia (25, 34), and 1 focused on pregnancy (36). All of the 11 guidelines recommended exceeding the 100 μg/dL threshold for ferritin after iron supplementation. Five of the 11 guidelines (19, 26, 32, 39, 41) recommended a cutoff value of ferritin >200 μg/L, particularly in nephrology. Ferritin concentrations should not exceed 500 μg/L (19, 32, 34, 44, 45) or 800 μg/L (19, 25, 26, 42, 43) because of the risk of exposing patients to iatrogenic complications, including infections. Thus, it is advisable to stop intravenous supplementation if serum ferritin concentrations are >500 μg/L (26, 32, 42). In this situation, oral iron supplementation remains an option if the dose is adapted (26, 32).

Of the 9 guidelines recommending TSAT as a target (19, 26, 32, 34, 39, 42, 43, 45, 48), 6 proposed exceeding the TSAT threshold by 20% (19, 26, 34, 39, 42, 45), and 1 proposed exceeding it by 30% (32). Only 3 guidelines defined a maximum threshold of 50% (25, 42, 43), particularly in patients with CKD (n = 1) (42), IBD (n = 1) (43), or chemotherapy-induced anemia (n = 1) (25). Only one guideline focused on the general population and did not recommend a TSAT rate for assessing therapy response, but only ferritin concentration (18).

DISCUSSION

ID is one of the leading risk factors for disability and death worldwide, affecting an estimated 2 billion people (48).

All guidelines recommend measuring ferritin concentrations for the diagnosis of ID. The main advantages of this test are its accessibility, its cost, and especially its sensitivity to variations of the iron store in case of ID, iron overload, or during normalization (on iron supplementation). However, it is well established that serum ferritin concentrations may increase in the event of inflammation, liver or muscular cytolysis, decompensated diabetes, chronic alcoholism, hyperthyroidism, macrophage activation syndrome, and certain metabolic syndromes (49). Of note, the only cause of low ferritin serum concentration is ID. Reference values for serum ferritin also vary depending on age and sex, especially in children and pregnant women. Over the various medical situations, the definition of ID and its range of approaches appears unclear because studies were performed in different laboratories and at different times in previous decades, and there has been variation and evolution in assay techniques and platforms (50). Only one review, including studies published before 1988, recommended cutoffs that were proposed by the second and third WHO International Standards: ferritin can effectively rule out ID anemia in patients with or without inflammatory disease at cutoffs of 70 and 40 μg/L, respectively (51). Accordingly, in our systematic review, ranges of ferritin defining ID varied across studies from 12 to 200 μg/L for absolute ID and from 100 to 800 μg/L for functional ID. Overall,

a serum ferritin concentration cutoff of 100 μg/L should be considered in current practices and further clinical trials to define an ID in most conditions. Indeed, at a cellular level, the cell cannot make ferritin unless cellular iron is present, which is why a cutoff of 100 is effective.

TSAT was proposed as an alternative or complementary diagnostic test for ID by 45.5% (10 of 22) of guidelines. TSAT reflects iron availability for erythropoiesis (18). TSAT decrease is one of the earliest biomarkers of ID, whether absolute or functional. Its main advantage is a normal range that is narrower (between 20% and 40% in adults) than that of ferritin, which is attributable to lower physiologic variation (18). In our systematic review, the TSAT threshold for the diagnosis of ID ranged from 15% to 25%. This threshold was broadly similar for absolute and functional ID. Seven of 10 guidelines recommending TSAT for ID diagnosis proposed 20% as a threshold for TSAT in CKD (n = 5), the general population (n = 2), children (n = 1), and IBD (n = 1). TSAT alone cannot differentiate absolute ID from functional ID. Functional ID is defined by serum ferritin concentrations $>$100 μg/L and TSAT $<$20%, whereas absolute ID is defined by serum ferritin concentrations $<$100 μg/L and TSAT $<$20%.

Other diagnostic tests have been proposed for ID diagnosis. Hepcidin, a small peptide produced by the liver, has hyposideremic properties by blocking ferroportin transporter activity. Its activity in normal individuals is increased in the setting of inflammation/infection, which also limits its utility (52, 53). In contrast, sTfR, a fragment of the membrane receptor, varies independently of inflammation and has been described as a useful marker in patients with absolute ID (increased sTfR concentration) or functional ID (normal sTfR). The sTfR concentration correlates with the expression of the transferrin receptor on the erythroblast membrane. sTfR tends to be elevated in patients treated with an erythropoiesis-stimulating agent by increasing the total erythroblast mass (54), which limits its use in patients with CKD and those treated for chemotherapy-related anemia. Its concentration is less accurate than ferritin concentrations (55) because of variable sensitivity and a specificity of 70–81% or 59–71% based on a cutoff of 1.5 mg/L or 2.6 mg/L, respectively, in patients with CKD (55, 56). Furthermore, sTfR testing is not widely available and is not reimbursed in France. One of the problems of sTfR and hepcidin might also be their lack of standardization, which precludes the assessment of uniform clinical decision limits. Only 7 guidelines mentioned hepcidin and sTfR tests (18, 19, 23, 35, 40, 46).

Regarding treatment of ID, oral supplementation remains the first-line treatment, according to most of the guidelines (18 of 27) because of safety concerns with intravenous supplementation (57). Two main drugs are commonly used for oral iron supplementation, i.e., ferrous sulfate and ferrous fumarate. The advantages of these drugs are their availability, low cost, and safety. Surprisingly, the oral route is also recommended in patients with functional ID, i.e., CKD (19, 26, 32, 39, 45), and IBD (4, 43). However, in such conditions, as well as in many other conditions where chronic inflammation is present, negative hepcidin feedback on the ferroportin transporter blocks the absorption of iron by the digestive tract (53) and the release of iron from macrophages. Hepcidin has been described as a useful marker to predict the efficacy and safety of oral iron supplementation (58). Moreover, the oral route is often poorly tolerated, with an oral iron malabsorption reported in more than 90% of cases. Thus, adherence to oral iron treatment is poor. The possibility that intestinal inflammation will worsen with oral iron is also debated (59). Oral heme iron polypeptide is a newer form that has been reported to have higher bioavailability and fewer side effects than nonheme iron in healthy subjects, but data in patients with chronic conditions such as CKD are limited (60).

Several intravenous preparations are available, such as iron isomaltoside, ferric carboxymaltose, ferric gluconate, ferric sucrose, ferumoxytol, and low-molecular-weight iron dextran. In chemotherapy-induced anemia, several clinical trials demonstrated the superiority of the intravenous route over the oral route (61, 62). Of note, the latter proved to be as effective as a placebo in these patients (63). The other advantages of the intravenous route compared with the oral route are its good tolerability in terms of gastrointestinal symptoms (61, 62), good adherence, and its rapid contribution of a large amount of iron. The main limit of the intravenous route is the risk of anaphylactic reactions whose gravity may be variable. There is a plethora of laboratory and animal data to suggest that intravenous iron can exacerbate oxidative stress and potentiate infections. There are also observational studies that suggest an increased HR for all-cause, cardiovascular, and infection-related mortality, although there are other observational studies that do not show any increased risk. Data from randomized controlled trials are very sparse, particularly with regard to hard clinical endpoints. The amount of intravenous iron that can be safely administered is also not clear, and the traditional biomarkers of iron status, such as serum ferritin and transferrin saturation, are not particularly helpful in this regard. Manifestations of organ dysfunction as seen in High Iron Fe (HFE)-hereditary hemochromatosis, a genetic condition of iron overload, is believed to be rare, but it is possible that patients receiving HD do not live long enough to develop this. Hypersensitivity reactions may occur with all intravenous iron preparations, but are extremely rare now that the high-molecular-weight iron dextran compound is no longer available. Randomized controlled trials are urgently required to address the shortfall in the evidence base. One such trial, Proactive IV irOn therapy for HaemodiALysis patients (64), is already well under way. The study is recruiting 2080 patients receiving maintenance hemodialysis across $>$50 sites in the United Kingdom who are being randomly assigned to a high-dose or a low-dose intravenous iron regimen with a planned follow-up of between 2 and 4 y. Hard clinical endpoints such as death, myocardial infarction, stroke, heart failure, and infections will be assessed.

In the meantime, nephrologists would do well to recognize both the benefits and the limitations of intravenous iron therapy pending further robust scientific data. The cost-benefit ratio of these drugs is an issue that should be analyzed.

The application of recommendations is not simple in daily clinical practice. For example, although intravenous iron supplementation is recommended in IBD patients in most guidelines, current German practice still relies on oral therapy, even in patients with severe anemia (65). Targets for concentrations of hemoglobin, ferritin, and TSAT after iron supplementation have not been specified in most guidelines. When a target for hemoglobin concentrations is proposed, it could appear surprisingly low—i.e., hemoglobin $>$7 g/dL (28) or $>$10 g/dL (41). Only 2 clinical situations are relatively well defined by the guidelines, i.e., chemotherapy-induced anemia and CKD. In all other clinical situations for which no target concentration is specified in

guidelines, it seems logical to maintain iron supplementation until a return to reference values for ferritin and TSAT. In obese patients and during bariatric surgery, except for the recommendations of the Spain Anemia Working Group (66), there have been no guidelines issued from any international professional association. Also, mechanisms of ID in these patients are complex and not fully understood (67). Pending an international consensus, some tools have been specifically developed for the management of ID, such as the website iron.therapy.org, which is reporting expert opinions sponsored by Vifor Pharma and could be helpful in clinical practice to guide decision making. To better define the optimal cutoff for diagnosis of ID and the need to treat these patients, it is important to consider the impact of ID on disease and patient-related outcomes. In this regard, intervention studies should be conducted in other conditions. Also, large prospective cohort studies should be initiated to investigate the correlation between different cutoffs for ferritin concentration and TSAT and disease course (e.g., hospitalizations, morbidity, health-related quality of life, and mortality, among others) in patients with ID.

In conclusion, diagnosing and treating ID is a challenge in clinical practice. Over the past decade, 29 guidelines were published by professional associations worldwide. By reviewing all these guidelines, we found significant heterogeneity on the management (diagnosis and treatment) of ID across indications. Some tools have been specifically developed for the management of ID, such as the website iron.therapy.org, and could be helpful in clinical practice to guide decision making.

The authors' responsibilities were as follows—LP-B: designed the research and had primary responsibility for the final content; LP-B and NW: conducted the literature search and wrote the manuscript; PC: provided a critical review of the manuscript; and all authors: analyzed the data and read and approved the final manuscript. LP-B and PC received consulting and lecture fees from Vifor, and LP-B received consulting fees from Pharmacosmos. NW reported no conflict of interest related to the study.

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