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Summary

AIMS OF THE STUDY: Iron deficiency (ID) and iron deficiency anaemia (IDA) are important conditions affecting a large proportion of the general population, causing the patients physical and psychosomatic symptoms, particularly fatigue, and significantly affecting their quality of life. General practitioners (GPs) are frequently consulted with non-specific symptoms due to the ID. However, little evidence is available to guide iron treatment. The aim of the Swiss Delphi study was to generate a broad consensual Swiss expert opinion in various therapeutic areas on diagnosis and treatment of ID/IDA and their practical implications.

METHODS: Specific statements regarding clinical relevance, practical diagnostic and therapeutic approaches, and treatment were evaluated by Swiss experts in various therapeutic areas using the Delphi method. "Consensus" was defined as ≥80% agreement; the agreement of 50–79% was defined as "critical", of <50% as "disagreement".

RESULTS: Consensus was reached for most statements. In patients without systemic inflammation, the threshold of 30 µg/l provide a good accuracy for the diagnosis of ID without anaemia. Ferritin levels within the range 30–50 µg/l with TSAT <20% can indicate ID without anaemia. Iron replacement therapy is accepted for treatment, not only of IDA, but also of symptomatic ID without anaemia. GPs play a central role in diagnosis and management of ID.

CONCLUSIONS: This consensus study provides potential therapeutic strategies for management of iron deficiency and is based on opinions of a high number of contributing specialists, providing their views from a wide range of clinical perspectives.

Key words: *iron, anaemia, iron deficiency, iron replacement therapy*

Introduction

Iron deficiency (ID) and iron deficiency anaemia (IDA) are important and prevalent conditions worldwide [1, 2]. ID is the single frequent micronutrient deficiency in adults in industrialised countries with the prevalence of up to 5% [1, 3]. ID and IDA predict mortality [4] and are associated with approximately 800,000 deaths per year [5].

Women of childbearing age are particularly at risk for ID, as a result of monthly blood loss, pregnancy and delivery [6]. Moreover, many other conditions occur with ID with or without anaemia as a major co-morbidity or consequence, among them chronic heart failure [7, 8], chronic kidney disease [9], cancer [10], inflammatory bowel diseases [11, 12], and other chronic gastrointestinal and liver disorders [6, 13]. ID has been associated with fatigue and decreased functional capacity [14, 15], loss of productivity [16], impaired quality of life [8]. ID treatment leads to improvement of fatigue [14, 15], and increases in endurance and well-being [17, 18].

General practitioners (GPs) are often confronted with the broad variety of signs and symptoms of ID and/or its underlying illnesses [3], and are therefore primarily in charge of its detection and diagnosis. However, the rather nonspecific signs and symptoms of ID/IDA also occurr in other conditions, which tends to make its differential diagnosis difficult [6].

Existing guidelines on the diagnosis and treatment of ID/IDA are mainly developed for specific therapeutic areas and do not always provide practical recommendations for GPs. Furthermore, there is a paucity regarding the treatment of ID in the absence of anaemia in otherwise healthy patients.

Author contributions
The project idea was initiated and developed by the members of the Steering Committee, on which behalf LINK, an independent project executor, was involved. Vifor Pharma covered the expenses for the project. The medical department of Vifor Pharma conducted the literature search, as specified by the Steering Committee. The study protocol and the analysis plan were elaborated by LINK. The analysis was reviewed by the Steering Committee. The manuscript has been written by the first author Dr Albina Nowak, a medical doctor affiliated to the University Hospital and Psychiatry Hospital of Zurich.

Edouard Battegay and Johann Steurer were both responsible for the scientific leadership of the project, to which they contributed equally and should therefore be considered last/senior author.

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Finally, GPs tend to refer to the analysis sheets they receive from their trusted laboratory for diagnostic laboratory results, on which the serum ferritin ranges (the main diagnostic parameter for ID), which are given as reference values, are rather wide. Ferritin is a variable measurement because of its active-phase character (e.g., falsely elevated values in presence of inflammation), its value is thus sometimes difficult to interpret and may not reflect the true iron status in the body [6]. As a consequence, patients suffering from ID may be missed and left untreated or can be over-treated. Hence, indiscriminate use of iron replacement therapy and other supplements has been reported [19, 20].

Therapeutic decisions can be challenging owing to lack of or conflicting [21, 22] evidence from clinical trials.

To reduce such uncertainties and potential misuse of iron replacement therapy, consensus methods have been developed to seek the opinion of a group of experts in order to obtain an agreement on debated topics and to support the decision-making process. The Delphi study technique is such a method, which was developed to find the collective expert opinion on a question without a clear answer in an anonymous and structured manner. The Delphi study technique has been shown to be an appropriate method to elicit consensus among a large number of participating experts without the need for their face-to-face contact, to avoid bias [23–25].

In this study, we report the results of a Swiss Delphi consensus panel of experts in various therapeutic areas, organised to answer the debated questions regarding (a) the clinical relevance, (b) the practical diagnostic and therapeutic approaches, and (c) the treatment lead (if the specialist or GP should be responsible for the iron replacement).

Methods

The Swiss Delphi study on iron deficiency aimed to elaborate practical recommendations on the diagnosis and the treatment of ID and IDA. The Delphi methodology was used to elaborate consensus-based recommendations. The medical professional's views were evaluated through questions regarding ID/IDA diagnosis and management.

Selection and formulation of statements

Selection of statements

The statements were selected and formulated by the experts of the different therapeutic areas (cardiologists, nephrologists, gastroenterologists, gynaecologists, oncologists, and internists) in the first Delphi round and then discussed and, if necessary, reformulated and re-evaluated. For each therapeutic area, the choice of a particular publication as a source for a statement was based on a hierarchical approach as outlined in table 1.

Choice of sources for the statements

As the aim of the project was to elaborate a geographically based consensus, the geographical approach from a local (Swiss) to the international level was used with the assumption that local guidelines and expert opinions adapt the existing internationally recognised diagnostic and treatment modalities according to local needs and the characteristics of the local population. The top-down principle assumed that a guideline presents a higher evidence level than an expert opinion – points 1–5 in table 1. A Swiss expert opinion was assumed to be more suitable for the generation of a statement for Swiss physicians than a single Swiss clinical trial, especially if the expert opinion was based on one or more clinical trials – points 5 and 6 in table 1. Finally, a meta-analysis presents a higher level of evidence than a single clinical trial and an expert opinion, both of which is deemed to present a lower level of evidence: points 7–9 in table 1.

Literature search

The literature search was performed in March 2017. The keywords "guideline", "iron deficiency" and "anemia" were used for each therapeutic area. Additionally, specific keywords were used for the respective therapeutic area: "chronic heart failure" in cardiology; "chronic kidney disease" and "chronic renal disease" in nephrology; "inflammatory bowel disease" in gastroenterology; "gynecology", "women in childbearing age", "pregnancy" and "postpartum" in gynaecology; "cancer" and "oncology" in oncology; "geriatric" and "elderly" in internal medicine.

The selected articles had to cover the aspects of (a) clinical consequences of iron deficiency according to the goals of the current project and (b) the clinical research or expert opinions on ID published by Swiss experts in various therapeutic areas. The literature research was been performed in:

1. Journals of (in order of precedence) Swiss, European, or international societies of the respective therapeutic area;
2. Internet sites of (in order of precedence) Swiss, European, or international societies of the respective therapeutic area;
3. PubMed;
4. Internet platforms on the topic of ID supported by Swiss experts.

All publications, which resulted from the literature search, and the statements, which resulted from the selected publications, were thoroughly reviewed, discussed and approved by the members of the Steering Committee and

Table 1: Choice of sources for the statements of the Swiss Delphi study: hierarchical approach (in order of decreasing suitability).

1.	Most recent guidelines elaborated by the Swiss society of the respective therapeutic area
2.	Most recent guidelines elaborated by the European society of the respective therapeutic area
3.	Most recent guidelines elaborated by the international society of the respective therapeutic area
4.	Most recent guidelines elaborated by the (a) American or (b) other national Societies of the respective therapeutic area
5.	Expert opinion elaborated by Swiss Experts
6.	Most recent randomised controlled trial by Swiss investigators and / or with an iron preparation approved in Switzerland in the respective therapeutic area
7.	Most recent meta-analysis of randomised controlled trials in the respective therapeutic area
8.	Most recent randomised controlled in the respective therapeutic area
9.	Expert opinion elaborated by international experts in the respective therapeutic area

the Expert Board, who were responsible for ensuring the choice of the most relevant source.

Formulation of statements

The statements were formulated according to the following principles:

1. The source of the highest level (table1) was considered as basis for initial statement formulation.
2. If a guideline did not specify the diagnostic and/or therapeutic approach, but referred to a clinical trial, the diagnostic or therapeutic approach in this trial was considered as the basis for statement formulation. In this case, the study with the highest level of evidence was considered as most relevant and first-line basis for initial claim formulation.
3. If a guideline did not specify the clinical relevance of ID and/or IDA in the respective therapeutic area, the results of the most recent (in order of preference) Swiss, European, American, or other study has been considered as the most relevant and first-line basis for initial statement formulation;
4. If a guideline or an expert opinion did not specify the treatment lead (the specialty of the physician who should manage the patient), the initial statement has been formulated as a recommendation for a consultation with a specialist in the respective therapeutic area.

The sources of statements are summarised in a supplementary list of references of statements (appendix 1). The questions were formulated to match as closely as possible the respective source from literature. The formulation of the questions was furthermore thoroughly revised and adapted by experts in order to correspond to the medical language used in Switzerland. The German and French translations of the questions were tested in a specific round. Thus, a good match of the questions with the respective literature sources and also a good understanding of their sense by Swiss physicians were ensured.

Recruitment of the expert panel

Selection of panel members

To be considered an expert within the respective therapeutic area, each panellist had to fulfil the following criteria:

1. Approved by the Swiss Medical Association (FMH) as medical specialist within the respective discipline;
2. More than 40% of their working time devoted to patient care;
3. At least five years of professional experience (in the respective discipline);
4. Involved, depending on the specialist area, in the treatment of a minimum of five patients suffering from iron deficiency per year. This minimum number of five ID patients was calculated as follows:

   the estimated prevalence of ID/IDA in Switzerland (~10% of Swiss population),

   the number of Swiss residents (~8400000),

   the number of Swiss physicians (~36000) and

   the estimation that 20% of patients with ID/IDA visit a physician during 1 year.

Distributing all these patients among all existing physicians results in 4.6 patients with ID/IDA pro physician. Thus, the number of five patients seemed reasonable as a criterion determining practical experience in ID/IDA for a Swiss physician.

The potential panel members were recruited after their institution had been selected, as described below. The head physician of each institution in the respective therapeutic area or the leading private practice clinician was contacted by email or phone, informed about the study purposes and asked to participate in the study. We did so because the head physicians of the hospitals and leading private practice clinicians have years of experience and, as a result, their clinical opinions are held in high esteem and, on occasions, direct the practice of diagnosis and treatment [26]. If the physicians upon contact did not meet the recruitment criteria or were not willing to participate, they were asked to recommend an alternative physician within the same institution.

Participants were recruited over the course of 17 weeks in February to June 2017. They received written information about the project and instructions on how to fill out the questionnaire.

Selection of medical institutions

In the Swiss nationwide medical registry all medical institutions are listed by location. This registry was used to recruit physicians for each therapeutic area working in (a) public and/or university hospitals, (b) private hospitals and (c) medical (group) practices. All listed medical institutions were randomly drawn from the list. If no panellist could be recruited from an institution, another was randomly drawn from the list. The random sampling procedure for medical institutions was adopted separately for each therapeutic area.

The proposed quota sampling with the minimal proportion of physicians for each therapeutic area and the predefined sample composition delineated by the language spoken are outlined in table S1 (appendix 1).

Statement collection

The recruited panellists were invited via email to participate in an anonymous online survey. A reminder was send after 1 week if the panellist had failed to respond to the questionnaire. Participants who did not respond to the reminder were called and motivated to participate by the study group.

Each statement could be rated on a five-point Likert scale: strongly disagree (1), disagree (2), neither agree nor disagree (3), agree (4), strongly agree (5), don't know (99).

"Consensus" was defined as ≥80% agreement in the rating of the single statements by the panellists; "critical consensus" was defined as agreement of 50–79%, "disagreement" was recorded if the agreement was <50%. Agreement was if the panellists replied either "agree" or "strongly agree" and disagreement if "disagree" or "strongly disagree". The panellists also had the possibility to comment on the statements.

The Steering Committee had no contact with the panellists and filled-in questionnaire was devoid of any personal identifiers. The procedure for each panellist, displayed in

the table S1 (appendix 1), was to fill out the general part 1, the specific part on the therapeutic area of the respective panellist, and the general part 2.

Analysis

Percentages were calculated for consensus, critical consensus and disagreement for each statement. Mean ± SD was computed for the overall percentage of agreement, critical agreement and disagreement, respectively. Statistical analyses were performed using SPSS/PC (version 22.0; SPSS Inc., Chicago, IL, USA) software package.

Results

A total of 115 panellists were recruited within 99 institutions. Of the 115 panellists, 93 from 80 institutions completed the survey, which corresponds to the return rate of 81% for panellists and 81% for institutions.

Over an eight-week period, the 93 panellists, 13 of whom were cardiologists, 16 nephrologists, 14 gastroenterologists, 13 gynaecologists, 19 oncologists and 18 internists, completed the survey. Twenty surveys were completed in French, the rest in German. We performed only one consensus round because the steering committee of the study concluded that the results were already satisfactory after the first round.

Overall, there were 440 statements. Consensus has been achieved for 50% (n = 218), critical consensus for further 38% (n = 167) and disagreement for 12% (n = 54) of the statements.

The proportion of agreement, critical agreement and disagreement among the panellists of the respective therapeutic area is shown in table 2. The degree of agreement regarding each statement is summarised in table S2 in appendix 1.

Diagnosis, clinical relevance and treatment of ID/IDA

All panellists of different therapeutic areas participated in general parts 1 and 2 (table 2). Consensus was achieved on the following statements (table S2, part A).

- To diagnose ID/IDA, serum ferritin with C-reactive protein (CRP), haemoglobin, mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC) should be determined. However, ferritin can be elevated in systemic inflammatory and liver diseases, and thus is less reliable as a marker of iron stores in those conditions. Low transferrin saturation (TSAT) can be helpful indicating ID in such cases.
- The cause of ID needs to be elucidated before iron replacement therapy. The intravenous route should be preferred if oral iron is not tolerated, is inefficient (e.g., the therapeutic dose fails to produce an increase in haemoglobin of at least 1 g/l/day or of at least 20–30 g/l after 3 weeks, after exclusion of folate and vitamin B_{12} deficiency), or bears risk of complications, or if a rapid haemoglobin increase is needed, such as in the presence of very low haemoglobin values during pregnancy and postpartum or in the perioperative setting.
- To monitor treatment success, serum ferritin should be measured 8–12 weeks after iron administration.

Critical consensus was achieved on the following statements (table S2 , part A).

- ID without anaemia is clinically relevant in women of childbearing age, elderly, individuals with chronic diseases.
- ID can cause restless legs syndrome, exercise intolerance, cognitive problems, alopecia, headache, koilonychias, Plummer-Vinson syndrome, frail nails, cheilositis and atrophic glossitis. Dyspnoea at rest and even haemodynamic instability can occur in severe cases.
- In symptomatic ID patients with or without anaemia, low ferritin is sufficient to confirm iron deficiency. A serum ferritin level below 30 µg/l can be considered as a cut-off to diagnose iron deficiency without anaemia in the general population. Additionally, for ferritin levels within the range of 30–50 µg/l, a TSAT <20% can indicate ID without anaemia.
- However, TSAT can be increased by inflammation because transferrin is a negative acute-phase protein. Measurement of serum soluble transferrin receptor (sTr) concentrations and ferritin index (sTfR level / log ferritin) can be helpful in estimating the need of iron replacement therapy in unclear situations, if no disease-specific guidelines exist.
- Iron replacement therapy is indicated in symptomatic ID patients without anaemia, with the oral route as the treatment of choice. The intravenous can be used in cases of low adherence.
- In symptomatic anaemic individuals (haemoglobin <130 g/ for males and <120 g/l for females) with ID (ferritin <30 µg/l) and without chronic diseases and inflammation, oral iron is the preferred therapeutic option.
- In anaemic individuals with chronic inflammation, oral iron may not be sufficient as a therapeutic option if baseline ferritin is <100 µg/l and TSAT <20%.

Table 2: Proportion of agreement, critical agreement and disagreement among the panellists.

Therapeutic area	Number of statements	Number of panellists	Consensus n (%)	Critical consensus n (%)	Disagreement n (%)
General part 1	109	93	48 (44)	43 (39)	18 (17)
Cardiology	42	13	29 (69)	13 (31)	0 (0)
Nephrology	43	16	33 (77)	7 (16)	3 (7)
Gastroenterology	42	14	18 (43)	15 (36)	9 (21)
Gynaecology	103	13	52 (50)	42 (41.3)	9 (8.7)
Oncology	60	19	21 (35)	30 (50)	9 (15)
Geriatrics	18	18	7 (39)	7 (39)	4 (22)
General part 2	23	93	11 (48)	10 (43.3)	2 (8.7)

– In individuals with chronic disease(s), treatment of iron deficiency can be based on higher ferritin-cut-offs, according to the respective disease-specific guideline.
– Maintenance iron replacement therapy in order to avoid re-occurrence of ID and IDA is desireable.
– There is a risk of overtreatment of ID without anaemia in the Swiss healthcare system.

Diagnosis and treatment of iron deficiency in chronic heart failure

Only cardiologists participated in this section (table 2). Consensus was achieved on the following statements (table S2 , part B).

– ID and IDA are common and relevant in chronic heart failure and should be diagnosed on the basis of haemoglobin, ferritin, CRP and TSAT measurement.
– Generally, if serum ferritin is <100 µg/l, or 100–300 µg/l with concomitant TSAT <20%, ID without anaemia can be diagnosed and treated intravenously according to the treatment scheme used in the CONFIRM-HF trial [27], with a subsequent ferritin check ideally 8–12 weeks after treatment, followed by annual measurements of ferritin, TSAT and CRP.
– In compensated chronic heart failure, the responsibility for ID and IDA treatment lies with the GP; decompensated chronic heart failure the treatment responsibility is with the cardiologist.
– Iron should be administered intravenously and discontinued in the event of adverse reactions, signs of iron toxicity or iron overload.

Critical consensus was achieved on the following statements (table S2 , part B).

– IDA is associated with increased mortality.
– IDA in chronic heart failure, without further relevant comorbidities such as chronic kidney disease, is defined as haemoglobin levels <120 g/l in women and <130 g/l in men, if ferritin is <100 µg/l, or 100–300 µg/l with concomitant TSAT <20%.
– Oral iron may be ineffective in chronic heart failure. Iron supplementation should be discontinued if TSAT is >50% – a possible sign of iron overload.

Diagnosis and treatment of iron deficiency in chronic kidney disease

Only nephrologists participated in this section (table 2). Consensus was achieved on the following statements (table S2 , part C).

– Anaemia is common in chronic kidney disease and progresses with progressing renal disease.
– Anaemia causes fatigue, and cognitive and depressive disorders, and increases cardiovascular morbidity and mortality.
– IDA is the most common and reversible cause of anaemia in chronic kidney disease and is the main cause of nonresponsiveness to erythropoiesis-stimulating agents.
– Anaemia in chronic kidney disease is defined as haemoglobin <135 g/l in males and <120 g/l in females. It should be further evaluated if haemoglobin is <110 g/L in either gender.
– ID in predialysis patients should be diagnosed and treated by the GP (in coordination with a nephrologist), and in dialysis patients by the nephrologist.
– Oral iron is simple and cheap and does not require hospital visits. However, it is poorly absorbed and associated with gastrointestinal side effects. Intravenous iron is more effective in increasing haemoglobin, ferritin and TSAT; however, it can cause hypersensitivity reactions, under very rare circumstances. Thus, intravenous iron can be considered as the preferred choice for IDA in chronic kidney disease, ferritin should ideally be checked 8–12 weeks after intravenous iron administration.
– For adults with chronic kidney disease and IDA, iron replacement therapy should be started before erythropoiesis-stimulating agents if serum ferritin is <200 µg/l and/or TSAT <25%. The TSAT limit of 45% should not be exceeded.

Critical consensus has been achieved on the following statements (table S2 , part C).

– Intravenous iron requires specialist clinic services and there are theoretical concerns that individuals may be exposed to increased oxidative stress and exacerbation of infections.
– The serum ferritin limit of 500 µg/l should not be exceeded after iron replacement therapy.

Diagnosis and treatment of iron deficiency in inflammatory bowel disease

Only gastroenterologists participated in this section (table 2). Consensus was achieved on the following statements (table S2 , part D).

– Anaemia is the most common systemic complication of inflammatory bowel diseases and negatively influences various aspects of the quality of life, such as physical and emotional functioning, ability of work.
– Inflammatory bowel disease-associated anaemia can be multifactorial – a combination of blood loss, decreased iron absorption and anaemia of chronic disease.
– The current World Health Organization (WHO) definition of anaemia (haemoglobin <130 g/l in adult males and <120 g/l in non-pregnant adult females) also applies to individuals with inflammatory bowel disease.
– All individuals with inflammatory bowel disease should be assessed for the presence of anaemia.
– Diagnostic criteria for iron deficiency depend on the level of inflammation.
– In individuals without clinical, endoscopic, or biochemical evidence of inflammation, serum ferritin of <30 µg/l is an appropriate criterion for ID; with inflammation, serum ferritin <100 µg/l is appropriate.
– Iron replacement therapy can be considered when iron deficiency without anaemia is present.
– Intravenous iron should be considered the preferred treatment in clinically active inflammatory bowel disease and/or when the patient was previously intolerant to oral iron and/or with haemoglobin <100 g/l, and fer-

ritin should be checked ideally 8–12 weeks after treatment (earlier testing could lead to falsely high values).

– Cessation and re-evaluation of the therapy is required in the case of clinically relevant adverse reactions and/or signs of iron toxicity or iron overload.

Critical consensus was achieved on the following statements (table S2 , part D).

– Ferritin values of 30–50 µg/l and TSAT <20% indicate ID.
– Iron replacement therapy is required in IDA, with the goal of normalising haemoglobin and iron stores, which are best achieved by early treatment initiation.
– The estimate of iron need should be based on baseline haemoglobin and body weight. Intravenous iron should be considered as the preferred treatment in Individuals who need erythropoiesis-stimulating agents.
– Because of the frequent recurrence of IDA, individuals with inflammatory bowel disease should be monitored for recurrent ID every 3 months for at least a year after correction, and every 6–12 months thereafter.

Iron deficiency in women of childbearing age including pregnancy and postpartum

Only gynaecologists participated in this section (table 2). Consensus has been achieved on the following statements (table S2 , part E).

– ID and IDA are relevant, their treatment improves fatigue, mental quality of life and physical performance.
– Oral iron is the preferred therapy in non-pregnant women, but intravenous iron is indicated if oral iron is not tolerated, bears risk of complications (e.g. in inflammatory bowel disease), or is not efficacious, that is, fails to produce an increase of haemoglobin of at least 1 g/l/day or of at least 20–30 g/l after 3 weeks, after exclusion of folate and vitamin B_{12} deficiency.
– ID is a frequent cause of anaemia during pregnancy and can lead to an increased need for blood transfusions in the event of major bleeding. It also can lead to fatigue, reduced physical and mental performance, headache, orthostatic dizziness.
– Anaemia is defined as a haemoglobin level of <110 g/l in the first trimester, <105 g/l in the second and <110 g/l in the third; ID is defined as ferritin <30 µg/l.
– ID in pregnancy can be treated by the GP, in coordination with the gynaecologist.
– In the first trimester, ID and mild IDA haemoglobin 90–105 g/l) should be treated with 80–200 mg oral iron per day. In the second trimester, intravenous iron is indicated in mild IDA (ferritin <30 µg/l and haemoglobin 90–105 g/l) and lack of response to oral iron (haemoglobin increase less than 10 g/l within 14 days), lack of adherence, or intolerance to oral iron, as well as in advanced anaemia (haemoglobin <90 g/l). In the third trimester, intravenous iron can be considered as a means of rapid iron replenishment.
– Postpartum anaemia is defined as haemoglobin <120 g/l and is clinically relevant if haemoglobin is <100 g/l. Six weeks after delivery, ferritin can be falsely elevated. In mild postpartum anaemia (haemoglobin 95–120 g/l), 80–200 mg oral iron per day is indicated. Intravenous iron should be considered if oral iron is not tolerated or if the haemoglobin is as low as 70–95 g/l.
– The total dose of intravenous iron administered should not exceed 1000 mg (or 20 mg/kg) per week.
  – Serum ferritin should be checked, ideally 8–12 weeks after intravenous iron administration.

Critical consensus was achieved on the following statements (table S2 , part E).

– For non-pregnant women of childbearing age, ID is diagnosed if ferritin is <30 µg/l, or 30–50 µg/l with concomitant TSAT of <20%; IDA is diagnosed if ,additionally, haemoglobin is <110 g/l. If ferritin is <30 µg/l, the probability that the iron stores are empty is 90%.
– ID should be treated if symptomatic.
– Oral iron is preferred for the treatment of IDA, but intravenous iron can be considered in the event of low adherence.
– Anaemia is one of the most common problems in obstetrics, occurring in more than one third of pregnant women during the first half of pregnancy. It causes reduced lactation and bears a major risk for maternal and foetal morbidity, such as preterm delivery, intrauterine growth retardation and impaired placental development.
– In the second trimester, intravenous iron can be considered as a means of rapid replenishment, for example in patients belonging to the Jehovah's Witnesses. In the third trimester, intravenous iron therapy is indicated in mild IDA (ferritin <30 µg/l and haemoglobin 90–105 g/l) and insufficient response to oral iron (haemoglobin increase by less than 10 g/l within 14 days), in Jehovah's Witnesses and in women with increased risk for postpartum haemorrhage.
– The haemoglobin goal in pregnancy is >105 g/l. The dose of ferric carboxymaltose can be estimated as follows:
– Total dose [mg] = body weight [kg] × (target Hb – current Hb) [g/dl] × 2.4 + storage iron [mg].
– For this equation, the body weight before the beginning of pregnancy, a target haemoglobin of 150 g/l and storage iron of 500 mg for a body weight >35 kg or 15 mg/kg for a body weight <35 kg should be considered.
– Postpartum, haemoglobin should be checked, depending on blood loss, the clinical condition, the prepartum haemoglobin, the nadir of the postpartum haemoglobin 48 hours after delivery.
  – The target postpartum haemoglobin is 110 g/l.

Diagnosis and treatment of iron deficiency in cancer

Only oncologists participated in this section (table 2). Consensus was achieved on the following statements (table S2 , part F).

– In cancer patients, anaemia decreases physical fitness and quality of life.

– Ferritin may be elevated owing to malignancy, independently of the iron stores, and is therefore not a reliable marker of iron stores in cancer.
– -– Iron replacement therapy should be initiated as soon as possible in symptomatic individuals with cancer and ID.
– The therapy should be coordinated by all physicians, but particularly by the oncologist.
– Intravenous iron is indicated in symptomatic patients for a faster correction of iron deficiency.
– In individuals on erythropoiesis-stimulating agents, who have symptomatic anaemia and TSAT of <50%, intravenous iron is indicated.
– Ferric carboxymaltose allows administration of high iron doses in one infusion, enhancing individual comfort and reducing the number of visits to the clinic.
– Serum ferritin should be checked, ideally 8–12 weeks after intravenous iron administration.

Critical consensus was achieved on the following statements (table S2 , part F).

– There is a very high prevalence of functional and absolute ID and IDA in individuals with cancer.
– Anaemia can lead to poorer performance and higher mortality in cancer patients.
– Anaemia can be worsened by blunted endogenous erythropoietin production in the kidney and reduced sensitivity to erythropoietin.
– For ID diagnosis, the percentage of hypochromic red cells (%HYPO), haemoglobin content of reticulocytes (CHr), and ferritin index (sTfR/log ferritin) can be considered as helpful parameters in addition to ferritin and TSAT.
– Oral iron is a valuable option for oligo symptomatic individuals with ID and cancer in remission without systemic inflammation.
– Intravenous iron is indicated in symptomatic patients with IDA and in patients with planned surgery at risk for bleeding.
– In individuals with ferritin levels between 500 and 800 µg/l, iron replacement therapy should be based on individual decisions.
– A loading dose of 1000 mg (not exceeding 20 mg/kg) of ferric carboxymaltose will result in an adequate iron supply.
– Following iron replacement therapy, TSAT should rise more than 20–50%, ferritin by more than 100 µg/l and CHr by more than 28 pg; sTfR and sTfR/log ferritin should normalise.
– Iron replacement therapy should be discontinued if ferritin increases to >800 µg/l.

Diagnosis and treatment of iron deficiency in elderly individuals

Only geriatrists participated in this section (table 2). Consensus was achieved on the following statements (table S2 , part G).

– In the elderly population (≥65 years old), anaemia has important implications on quality of life, and ID is often multifactorial, with causes including inadequate dietary intake or absorption, occult bleeding and medication.
– Statements about diagnosis and treatment from the general part 1 also apply to elderly individuals.
– In anaemic geriatric individuals, intravenous iron replacement therapy with ferric carboxymaltose can be well tolerated.
– In elderly individuals with restless legs syndrome and ID (defined as baseline ferritin <50 µg/l or TSAT <16%), the administration of ferric carboxymaltose is associated with a significant improvement of symptoms.

Critical consensus was achieved on the following statements (table S2 , part G).

– ID is common in elderly and substantially contributes to a high prevalence of anaemia observed in the last decades of life, caused primarily by chronic inflammation and associated with mortality.
– The response to oral iron is often slow in elderly individuals.
– Iron therapy is efficacious if its therapeutic dose produces an increase of haemoglobin of at least 1 g/l/day or of at least 2–3 g/l after 3 weeks.

Discussion

The contributions of experienced clinicians, based on their daily practice, has helped overcome the lack of guidelines based on randomised interventional studies. In this context, the Delphi method represents one of the most reliable consensus methods [24]. The Delphi method has been employed in order to achieve consensus in various diseases [28–31]. So far, this is the first Delphi consensus with a joint panel of experts that addressed the unmet needs in the management of ID.

However, some study limitations merit consideration. Firstly, the Delphi consensus is not a method to introduce better evidence than that based on clinical trials; it represents a process to find a common clinical practise based on a summary of experts' opinions. Secondly, although more than one consensus round is typically applied in Delphi consensus [23], with an experts' discussion before the next round of voting process, in this study we performed only one iteration of consensus building. We did so intentionally, because a panel discussion before the next round could lead to a group dynamic putting pressure on single individuals to be compliant with the collective viewpoint. Thirdly, some therapeutic area groups of specialists were relatively small. The strength of our study is therefore that the statements remained free of bias, individual and anonymous. Furthermore, the results reported here are supported by a high number of contributing specialists, who provided information on their views from a wide range of clinical perspectives.

Diagnosis of iron deficiency is complex and has been highly debated in previous studies. Serum ferritin is a widely accepted as the most effective indicator of ID. In patients without systemic inflammation, the threshold of 30 µg/l provided the highest product of sensitivity and specificity

for the diagnosis of ID without anaemia, as shown in previous studies [6, 32] and as it is in line with the opinion of Swiss experts in this report. However, the utility of ferritin can be limited in patients with liver diseases, malignancy or acute and chronic inflammation. In those conditions, serum ferritin levels can be increased independently of the iron load [6]. Additionally, as suggested by the experts, for ferritin levels within the range of 30–50 µg/l, TSAT <20% can indicate ID without anaemia. Although, the utility of TSAT can also be limited because transferrin is a negative acute phase protein, it can be a helpful tool and is recommended in current guidelines for chronic diseases [11, 33, 34]. The combination of further laboratory parameters – CRP, MCV, MCHC and sTfR and sTfR/log – with ferritin and TSAT seem to provide the best assessment of ID [6].

Importantly, iron replacement therapy is accepted for treatment not only of IDA [35], but also of symptomatic ID without anaemia [15, 36]. As outlined above, either serum ferritin <30 µg/l or ferritin 30–50 µg/l with TSAT <20% can be used as a cut-off to initiate iron therapy. Intravenous iron replacement can be considered if oral iron is not tolerated or not efficacious. Oral iron therapy can be regarded as not efficacious if the therapeutic doses of iron fail to produce an increase of haemoglobin of at least 20–30 g/l after 3 weeks, as recommended in the respective Summary of Product Characteristics. However, the haemoglobin increase can vary between different patients. Therefore, an individual approach based on the expected Hb-increase in the particular patient may be necessary.

According to the given statements, Swiss physicians show a good adherence to a number of current EU Guidelines [11, 34, 37–43] and to local Swiss recommendations [44]. The claims in the oncology part seem to be less well accepted. One possible explanation can be the reduced utility of measuring ferritin in cancer patients: serum ferritin levels are elevated in the most cancer patients and does not reflect the iron stores [6]. A new guideline of the ESMO is available now. In contrast, the claims in the cardiology part seem to be best accepted: there was no disagreement among the cardiology panellists. One possible explanation could be that several randomised clinical trials on iron replacement therapy have been undertaken in Cardiology patients [17, 18, 45].

According to the Swiss Delphi study on iron deficiency, GPs play a central role in the diagnosis and management of ID, generally and in the particular therapeutic area. In cardiology patients, the GP is responsible for treatment of ID and IDA in compensated chronic heart failure, whereas cardiologists take responsibility in decompensated chronic heart failure. During pregnancy, the GP performs the ambulatory treatment of ID, in coordination with the gynaecologist. In patients with chronic kidney disease, the GP is responsible for the diagnosis and treatment of ID in predialysis patients and the nephrologist takes that responsibility in dialysis patients. We hope that the results summarised in this study help to support GPs in their daily practice by giving them guidance on how best to diagnose and treat patients suffering from ID.

Conclusions

This consensus study provides potential therapeutic strategies for the management of ID and the results reported here are reflective of a substantial number of respondents (physicians) covering a wide range of specialities.

Data sharing

The dataset is available from FigShare, doi:. http://dx.doi.org/10.6084/m9.figshare.6860216. 10.6084/m9.figshare.6860216 or https://figshare.com/s/645c7d90144c4de64dae.

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Potential competing interests

Albina Nowak received lecturing honoraria and research support from Sanofi Genzyme and Shire and research support from EMDO- and Hemi-foundation; Daniel Surbek received lecture honorarium and unrestricted research grant from Vifor; Pascal Juillerat has no conflict of interests to declare; Idris Guessous participated as speaker in congress sessions sponsored by Vifor, all honoraria received were directed to an independent research fund at the Geneva University Hospitals; Wolfgang Korte received lecture honorarium from Vifor; Anne Angelillo-Scherrer received lecture honorarium from Vifor; Edouard Battegay received consulting and lecturing fees as well as financial support and educational grants for meetings and symposia from Vifor; he also received consulting fee from Pierre Fabre

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Appendix 1

Supplementary tables and reference list

The appendix is available in a separate file for downloading at: https://smw.ch/en/article/doi/smw.2019.20097/