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Treatment of iron deficiency anemia: practical considerations

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Abstract

Iron deficiency anemia is a common problem world-wide, and doctors from all specialties need to be competent in its treatment. While most patients respond well to oral iron preparations, a substantial minority have side effects which make them adhere poorly to their treatment. For oral iron-intolerant patients, those responding poorly despite good adherence, and those with severe and/or symptomatic anemia, intravenous iron is an excellent alternative. It is, however, more expensive and carries a very small but potentially life-threatening risk of severe infusion-related hypersensitivity reactions. After outlining the main features of iron metabolism, in this review we compare the indications for therapy with oral and intravenous iron, and then focus on how to maximize the efficacy and safety of the two different routes.

Key words: oral iron, intravenous iron, anemia, iron deficiency, hypersensitivity reactions

Introduction

Anemia is common in all populations worldwide and is frequently due to iron deficiency. In developed countries, the prevalence of iron deficiency anemia (IDA) is 2-5% in adult men and post-menopausal women and about 10% in women of child-bearing age; it is much more common in hospitalized patients [1, 2, 3].

Iron deficiency occurs when iron losses exceed its intestinal absorption. This happens in patients with decreased iron intake, malabsorption of iron, increased demand for iron or through ongoing iron loss. In the Western world, while IDA is often multifactorial, menstruation is the commonest single cause. Reduced dietary intake of iron (vegetarians and the elderly being particularly at risk), bleeding from the gastrointestinal tract (for example due to neoplasia or use of aspirin or non-steroidal anti-inflammatory drugs), malabsorption (particularly in coeliac disease), pregnancy and blood donation are other frequent causes [3, 4].

IDA is associated with worsened quality of life, impaired physical and cognitive performance [2, 5], and in hospitalized patients, longer length of hospital stay and poorer clinical outcomes [1, 6]. It also increases the likelihood of patients receiving blood transfusions with their attendant risks [1]. Effective treatment of patients with IDA is therefore extremely worthwhile.

The aims of this article, which is directed primarily at generalists, are to outline the relevant features of iron metabolism, to summarize the indications for treatment of IDA and to compare the advantages and disadvantages of treatment with oral and intravenous iron. We shall then focus particularly on practical aspects of treatment with iron. Topics which we

shall not cover include investigation of the cause of IDA (for guidance see reference [3]) and use of blood transfusion. We shall also omit mention of therapy with erythropoietin, as this is a specialist treatment restricted primarily to patients with chronic kidney disease or having cancer chemotherapy.

Iron Metabolism

As a background to our focus on management of IDA, we provide below a brief overview of iron metabolism (for a comprehensive recent review, see reference [7]).

Iron absorption and turnover

The human body contains 30-40mg/kg body weight of iron. It is mostly contained in haemoglobin (Hb), ferritin and other heme and non-heme proteins. Iron is an essential element, being a constituent of a range of enzymes involved in redox reactions and oxygen delivery. Red blood cells have the highest demand for iron of all cells.

A normal Western diet provides 10-15mg of iron daily, of which only about 10% is absorbed (1-2mg each day). Iron absorption occurs only in the duodenum and jejunum. Most iron ingested in food is in the ferric form (Fe^{3+}) and requires reduction to the ferrous form (Fe^{2+}) for absorption across the mucosal barrier. Factors influencing iron uptake in the gut include: the form of iron and its redox state within food, the pH of the intestinal lumen, the presence or absence of chelating agents in food (e.g. phytate or oxalate) and the expression levels of several iron transporters in enterocytes.

Within enterocytes, iron is either stored as ferritin or is actively exported as ferrous iron by the transporter protein ferroportin, into the plasma. The ferrous iron is then oxidized back to ferric iron which can bind to the circulating carrier protein, transferrin.

As the amount of iron absorbed is not sufficient to cover the requirements of erythropoiesis, iron is recycled. Heme complexes are degraded in the liver and spleen by cells of the monocyte-macrophage system. These reticulo-endothelial cells and hepatocytes store the iron released from heme complexes as ferritin and release it into the plasma, again through ferroportin, when serum iron levels drop [8].

Role of hepcidin

There is no excretion method for iron and therefore iron homeostasis is regulated by its absorption into and release from the macrophage and hepatocyte iron stores. Hepcidin is a peptide hormone synthesized in hepatocytes (for recent review, see reference [8]). It regulates plasma iron concentrations by binding with ferroportin and causing degradation of the ligand-receptor complex. By causing loss of ferroportin from cell membranes, high levels of hepcidin reduce both iron absorption from the gut and also its release from macrophages and hepatocytes into plasma.

Serum hepcidin levels increase in response to increased plasma iron levels and prevent iron overload. This regulation is important because, as in hemochromatosis, excessive tissue iron can cause widespread organ damage, probably as a result of generation of free radicals. Hepcidin is also an acute phase reactant and its production is increased in inflammatory disease, infection and cancer by interleukin-6 and other cytokines. Affected patients typically show the blood indices of the anemia of chronic disease (see Table 1 below). Conversely, in

conditions such as iron deficiency, hemorrhage, hemolysis and treatment with erythropoietin, a decrease in hepcidin levels occurs, so that maximal iron is made available for erythropoiesis [8].

Definition of Iron Deficiency Anemia

The World Health Organisation (WHO) defines anemia as a hemoglobin concentration below 13g/dl in adult men and below 12g/dl in non-pregnant adult women (see Table 2) [2].

Before considering giving oral or intravenous iron to patients with anemia, it is essential, in order to avoid the risk of iron overload, to confirm that they are indeed iron deficient, and do not have the anemia of chronic disease (Table 1). Classically, patients with IDA have low serum iron, ferritin and transferrin saturation, with high serum transferrin and total iron-binding capacity. In many instances, however, the anemia is of mixed type and a clear distinction between the two is difficult to make.

Management of iron deficiency anemia

An early step in the management of IDA, which can of course be undertaken at the same time as treatment of the anemia itself, is to find and treat the underlying cause. That process is beyond the scope of this review (see instead reference [3]).

Iron therapy is used to replenish iron stores and restore hemoglobin concentrations to normal, thereby preventing and treating symptoms arising from IDA [3,5]**.** Potential benefits of iron replacement include improved quality of life, physical performance, thermoregulation, cognitive function and immune function [5,10,11]. Restless leg syndrome may also respond to iron replenishment [10,12].

In practice, the commonest indications for therapy are anemia (Hb < 12g/dl (non-pregnant women), Hb < 13g/dl (men)) and iron deficiency without anemia, the latter especially if the primary cause is on-going (eg chronic blood loss, pregnancy or in patients with concurrent diseases such as chronic renal failure, inflammatory bowel disease or cancer requiring chemotherapy) [5].

Oral or intravenous iron?

When deciding on the most appropriate therapy for patients with IDA there are several factors to take into account.

Availability, patient adherence to treatment

Oral iron salts are the most readily available way of replacing iron. Taken once or twice a day in tablet form, they are the first line treatment for most indications [4,13]. Intravenous iron, in contrast, needs to be administered by trained staff in a centre where resuscitation facilities are immediately available due to the risk of severe hypersensitivity reactions (see below) [14,15]**.** High molecular weight dextran parenteral iron preparations are no longer available, and there is also only a very limited place now for intramuscular iron because of its potential side effects (brown staining of subcutaneous tissues, local pain, sterile abscess, atrophy and fibrosis) and because of the ready availability of iv iron. Non-adherence to treatment with oral iron is common, particularly in patients with iron intolerance (see below) but this is not a problem with iv iron.

Efficacy

Both routes of administration are adept at raising iron stores and hemoglobin concentrations. The initial rise in hemoglobin tends to be faster with iv iron, but at about 6 weeks the rise is

similar to that seen with oral therapy [16,17,18]. Accordingly, in patients with severe iron deficiency anemia or in those who are symptomatic from their anemia, the iv route may be preferred. Intravenous iron may also be preferable in patients with malabsorption syndromes and in those with chronic inflammatory diseases such as inflammatory bowel disease. In such cases a raised serum hepcidin may, as suggested above, inhibit absorption of oral iron [5,9].

Although there is not yet a routinely available assay for hepcidin, it is possible from what is known about its actions (see above) that in the future, a pre-treatment hepcidin measurement could be used to predict response to iron therapy and/or the optimum route of iron administration. The oral route might be most effective when pre-treatment hepcidin levels are low, and the intravenous route more effective when they are raised.

Side effects

Gastro-intestinal symptoms, which occur in up to 30% of people taking oral iron, include nausea, flatulence, abdominal pain, constipation and diarrhoea. The clinical impression that these side-effects are dose-related has not been confirmed in a recent meta-analysis [19]. Dark coloured stools simply reflect the presence of unabsorbed iron and are of no clinical significance.

The side effects of iv iron are diverse and occur acutely during or shortly after infusions (see below, Fig 1). The risks of severe reactions are now much lower than they were when the now obsolete high molecular weight dextran preparations were used, but it has been suggested that fatal hypersensitivity reactions still occur during infusions in about 1 in every 5 million doses of iv iron [20,21].

Iron overload is a rare but potentially serious side-effect in patients mistakenly given long courses of iron by either route when they are not actually iron deficient. Theoretical but unsubstantiated further risks of oral iron include free radical-induced gastrointestinal inflammation, changes in gut microbiota and even neoplasia [22,23,24,25]. Conversely, after iv iron they include endothelial damage and enhanced atherosclerosis mediated by intravascular oxidant stress [26], and a predisposition to infection resulting from iron-mediated cellular immune dysfunction and stimulation of bacterial growth [25,27].

Cost

The cost of oral iron salts varies between preparations but is very low (about 15-45 euros per 3 month course depending on dose and formulation prescribed). In contrast, the prescribing costs of iv iron preparations, depending on how much elemental iron is needed to replace iron stores, range from about 120-500 euros. The costs of iron infusions must also take into account those of its administration by trained nursing staff in a medically supervised environment.

Treatment of IDA with oral iron: practical guidance.

Oral iron replacement therapy with gradual replenishment of iron stores and restoration of hemoglobin is the preferred first line treatment for most patients with IDA [4,13] (Fig 2).

Dosage

The dose of oral iron for IDA should be 30-80mg elemental iron daily, given for 3-6 months, and for longer if the cause of iron deficiency is on-going. Depending on the cause of the IDA, hemoglobin concentration should rise by 0.5-1g/dl (5-10 g/litre) per week [4].

Administration of oral iron

Oral ferrous salts are the treatment of choice as ferric salts are less well absorbed. Selection of preparation is often decided by cost. Although iron preparations are best absorbed when the patient has not eaten, they can be taken after food to reduce gastro-intestinal side-effects.

There is little evidence to support the recommendation that patients should take vitamin C or orange juice to improve iron absorption though the advice is still given [2,3]. It is also advised that, before taking iron tablets, patients avoid eating food high in phytates, phosphates or tannates (eg cereals, beans) each of which can reduce the absorption of iron [2,7]. Proton pump inhibitors should also be avoided if possible, as they reduce production of gastric acid which normally helps promote iron absorption by converting the ferric to the ferrous salt.

Management of side-effects

The gastro-intestinal side effects described above should be taken seriously as even mild symptoms may reduce adherence to oral iron supplementation. There is limited evidence to suggest that switching to an alternative oral product can reduce side effects [28]. Despite the lack of supportive meta-analytic data [19], a dose reduction is sometimes effective and, because of the saturability of intestinal iron absorption, can be equally efficacious in replenishing iron stores [29,30,31].

Modified-release preparations of iron are licensed for once-daily dosage, but have no proven therapeutic advantage over conventional formulations. Contrary to some reports [28], meta-analysis suggests that they are no better tolerated than standard formulations [19]. Furthermore, it may be advisable to avoid slow-release preparations in patients with Crohn's disease because of a risk that they impact upstream of small bowel strictures [32].

Several new formulations of oral iron are the focus of clinical trials and show promise in relation to efficacy and tolerability [33,34] but they are not yet routinely available.

Monitoring of response

The response to oral iron should be assessed by measurement of serum hemoglobin concentration, ferritin and/or transferrin saturation after 6-12 weeks (Fig 2). In patients in whom these indices fail to respond adequately, the physician should check on adherence to the medication and consider a switch to iv iron.

Treatment of IDA with intravenous iron: practical guidance.

Indications

It follows from what has been discussed above that iv is preferable to oral iron in the following situations:

- When oral iron is not tolerated or is ineffective in raising or in maintaining hemoglobin concentration
- When hemoglobin is <10g/dl (depends on clinical setting)
- When anemia is symptomatic
- In chronic inflammatory disease, chronic renal failure, chemotherapy-induced anemia, malabsorption and intestinal failure
- To avoid non-urgent blood transfusions

Selection and dosing of iv iron

The formulations of iv iron now available in Europe are sodium ferric gluconate (Ferrlecit), iron sucrose (Venofer), iron (III)-hydroxide dextran complex (Cosmofer), ferric

carboxymaltose (Ferinject) and iron (III) isomaltoside 1000 (Monofer). The European Medicines Agency (EMA) has recently reported that they were unable to differentiate between these products in relation to the risk of severe hypersensitivity reactions [14]. The choice of product therefore depends on factors such as cost, convenience to the patient and the indication for the treatment [35]. The dosing regimen used (e.g. dose of iron, duration of infusion, single dose or multiple infusions) varies with each preparation, and *must* be applied in strict accordance with the Summary of Product Characteristics (SmPC) of each individual product. In many centres, ferric carboxymaltose (Ferinject) and iron isomaltoside 1000 (Monofer) have become widely used as first-line infusions, as they offer the option of rapid infusion of a high dose of iron (eg up to 1000 mg in 15 minutes for a man weighing >50kg).

The total dose of iron needed to be given to replete a patient's iron stores is based on the patient's Hb and body weight and can be calculated using either the Ganzoni formula **[36]** or a Simplified Method [37].

The Ganzoni formula calculates the total iron deficit requiring intravenous replacement as: Body weight [kg] x (Target Hb – Actual Hb) [g/l] x 0.24 + iron stores [mg], where the iron stores for a patient >35kg are assumed to be 500mg. In contrast, the Simplified Method, derived initially from a trial using ferric carboxymaltose in patients with inflammatory bowel disease [37] allows calculation of the dose of iron needed from the patient's hemoglobin concentration and weight (Table 3).

The response to iv iron should be determined by monitoring the serum hemoglobin concentration, transferrin saturation and/or ferritin levels at about 6 weeks after infusion (Fig 2). Oral iron is not required after iv iron if the total iron deficit has been corrected.

Side-effects and terminology

As indicated above, acute side-effects during iron infusions are rare but can be life-threatening. Current nomenclature relating to adverse reactions to iv drugs in general is confusing and inconsistent. As elsewhere [15], we find it simplest to refer to all acute reactions to iv iron as hypersensitivity reactions (HSRs), sub-dividing them into mild, moderate or severe/life-threatening, depending on their clinical presentation (Fig 1). As suggested by the World Allergy Organisation [38], we reserve the term "anaphylaxis" for severe HSRs, irrespective of pathogenesis, and avoid the ill-defined term "anaphylactoid". This approach is rational insofar as there is little or no evidence that acute reactions to iv iron are IgE-mediated. Indeed, their commonest mechanism is probably complement activation-related pseudo-allergy (CARPA) evoked by infusion of nanoparticles [39,40].

Reducing risks of side-effects

As already mentioned, in 2013 the EMA published a report of their 2-year investigation of the adverse drug reactions to all iv iron drugs available in Europe [14]. Their main conclusions are outlined below, and should be applied in all settings where iron infusions are given.

- All iv iron preparations carry a small risk of reactions which can be life-threatening
- The benefits of iv iron outweigh the risks when oral iron is inappropriate
- iv iron should be given only where trained staff and resuscitation available
- A test dose is not needed (as it can give false reassurance about the safety of the subsequent infusion)
- Patients should be monitored during and for > 30 minutes after the infusion
- All iv iron is contraindicated in patients with known serious HSR to any iv iron product
- iv iron should never be given in the first trimester of pregnancy

- Special care should be taken if giving iv iron to patients with known allergies (including drug allergies) or severe atopy

In practice, minimising the risk of HSRs in patients to be given iv iron involves five main considerations:

- Patients at particularly high risk of HSRs should be identified. These include those who have had a previous reaction to iv iron, who are given iv infusion too fast, or who have a history of other drug or other allergies. There is an increased risk also in patients with severe asthma or eczema, systemic mastocytosis, severe respiratory or cardiac disease and in the elderly. Treatment with beta-blockers or angiotensin converting enzyme (ACE) inhibitors can worsen HSRs if they occur, and, as pointed out by the EMA (see above), iv iron is strictly contra-indicated in early pregnancy because of the potential for acute adverse effects on the foetus.
- Iron infusions should be given only in appropriately staffed sites equipped with resuscitation facilities. If iv iron is to be given outside hospital, there should be arrangements in place for immediate treat-and-transfer to an intensive care facility in the event of a severe reaction. EMA states that iv iron should not be given in patients' homes [14].
- If not given by a doctor, iv iron should be administered by nursing staff with immediate access to on-site medical help in the event of an adverse reaction. All staff should have regular training in management of iv infusions and HSRs. The nurse administering the iron infusion should be in the infusion area and easily accessible by the patient throughout its course, as HSRs can develop rapidly.

- The patient should be provided with information about the risk of an HSR before the iron infusion; the relevant symptoms should be described, with advice that the patient tells the nurse administering the infusion immediately if any occur.
- The final steps involved in reducing the risks of HSRs to iv iron relate to the infusion itself.
    - If the patient has previously had a severe HSR to any iv iron preparation, he/she should *never* again be given iv iron. In the event of a previously mild HSR to iv iron, a different iv iron product should be given very cautiously.
    - Before starting any infusion, base-line clinical observations should be undertaken, including pulse, blood pressure, respiratory rate and oxygen saturation.
    - No test dose is necessary.
    - The infusion should be started at 50% of the recommended infusion rate (10% if the patient has been identified as being at high risk - see above), accelerating after 15 minutes to the recommended rate if the infusion is well tolerated.
    - Observations should be continued every 15 minutes until at least 30 minutes after the infusion has finished [14].

Recognition of HSRs to iv iron

Acute HSRs to iron infusions, as to other iv drugs, are best classified as mild, moderate or severe/life-threatening (or anaphylactic) on the basis of symptoms, signs and clinical observations (Fig 1) [41,42]. Mild reactions can progress rapidly through moderate to severe ones; severe HSRs can also occur very rapidly without progression through the milder syndromes.

A further mild acute adverse reaction has been described by Fishbane [43,44]. This occurs in about 1/100 patients given intravenous drugs and is characterized by transient flushing, joint pains and truncal myalgia. Its pathogenesis is unknown, but symptoms tend to abate spontaneously over a few minutes and do not usually recur on re-challenge.

Management of HSRs to iv iron

Management of an HSR to iv iron depends on its severity and is outlined in Fig 1; each step will not be detailed here, but in every instance of an HSR, the iron infusion should be stopped immediately and recommenced, after at least 15 minutes, *only* in patients with mild and spontaneously improved HSRs. There is scanty formal evidence relating to management of HSRs occurring specifically during iron infusions and the recommendations made in Fig 1 are drawn from other contexts in which iv drugs are given [45-50].

The selection of individual drugs for treatment of HSRs, and their doses and routes of administration, varies according to local practice. However, it is worth noting that iv antihistamines are no longer favoured as their side effects (tachycardia, hypotension, somnolence) may mimic mild HSRs or make them appear more severe than they actually are [51]

If an HSR occurs, it is important that after it has resolved it is carefully documented so that a future treatment strategy can be drawn up. Factors that need to be recorded include the severity of the attack (mild, moderate, severe) and its course; any previous administration of iv iron preparations (including their dates, doses and infusion rates); identified risk factors; the interventions made and the response to them; whether the patient was discharged home or

transferred to intensive care; and that the responsible clinician and the local drug regulatory authorities were informed of the event [48].

Conclusions

Iron deficiency anemia is common world-wide, and its causes cross all medical specialties. Most patients respond well to treatment with oral iron preparations. For those not doing so, and for those who are intolerant of oral iron or who are severely anemic, iv iron offers an excellent alternative, so long as it is given in the appropriate dose, in a safe clinical environment and with due recognition of the occasionally severe adverse reactions that it can evoke.

Many people with iron deficiency anemia receive inappropriate, too little, or even no treatment for their condition; it is hoped that application of some of the points from this pragmatic review will help practitioners prescribe and administer the right treatment for their patients safely and effectively.

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Table 1. Blood film and iron indices in iron deficiency anemia and anemia of chronic disease.

	Normal range (precise values vary between laboratories)	**Iron deficiency anemia**	**Anemia of chronic disease**
Serum iron	11-32 µmol/l	Low	Low
Ferritin	22-560 pmol/l	Low**	Normal or raised
Transferrin	1.88 – 3.41 g/L	High	Low
Transferrin saturation	20-50%	Low	Normal
Total iron binding capacity	45-82 µmol/l	High	Low or normal
Red cell morphology	MCV 80-95 fl MCHC 30-34 gHb/100ml	Microcytic, hypochromic *	Normocytic or microcytic, normochromic

*Microcytosis and hypochromasia can also be present in thalassaemia and sideroblastic anemia. **Ferritin is an acute phase protein and can be raised in the presence of iron deficiency, for example in renal failure, hyperthyroidism, poorly controlled diabetes mellitus and inflammatory disease such as inflammatory bowel disease

Table 2. WHO definition of anemia (adapted from ref [2])

Age	**Hb (g/dl)**
Children (6 months – 5 years)	<11.0
Children (5-11 years)	<11.5
Children (12-13 years)	<12.0
Pregnant women	<11.0
Non-pregnant women	<12.0
Men	<13.0

Table 3. Simplified method for estimating cumulative iron dose (adapted from ref [37])

Hb g/dl	Body weight 35 kg to <70 kg	Body weight ≥70 kg*
<10 g/dl	1,500 mg	2,000 mg
≥10 g/dl	1,000 mg	1,500 mg

*ideal body weight is used in overweight patients, and actual weight in underweight people.

Figure 1. Outline of recognition and treatment of hypersensitivity reactions to iv iron (from ref [15] with permission)

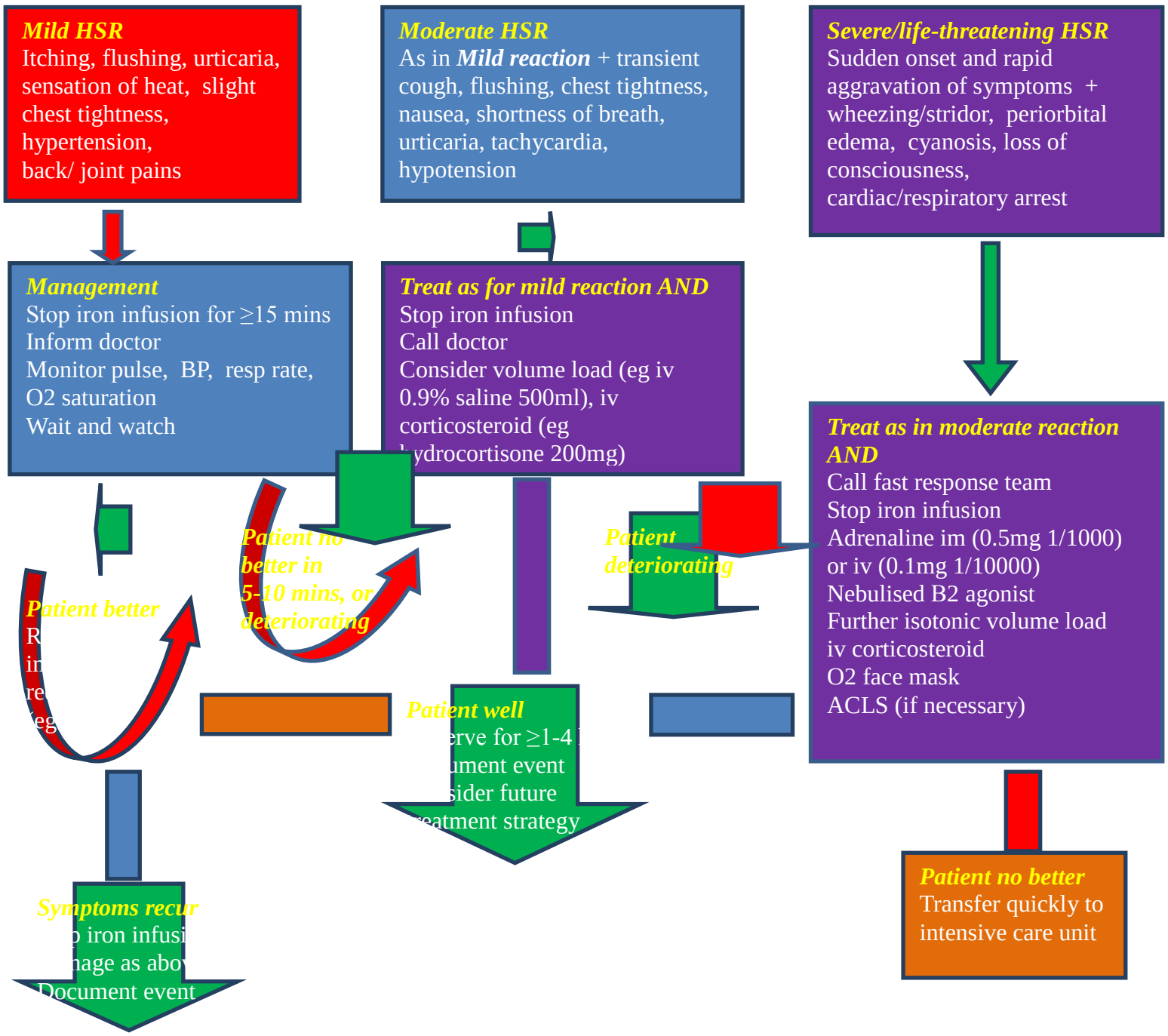

Figure 2. Algorithm for management of iron deficiency anemia