Current misconceptions in diagnosis and management of iron deficiency

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Abstract

The prevention and treatment of iron deficiency is a major public health goal. Challenges in the treatment of iron deficiency include finding and addressing the underlying cause and the selection of an iron replacement product which meets the needs of the patient. However, there are a number of non-evidence-based misconceptions regarding the diagnosis and management of iron deficiency, with or without anaemia, as well as inconsistency of terminology and lack of clear guidance on clinical pathways. In particular, the pathogenesis of iron deficiency is still frequently not addressed and iron not replaced, with indiscriminate red cell transfusion used as a default therapy. In our experience, this imprudent practice continues to be endorsed by non-evidence-based misconceptions. The intent of the authors is to provide a consensus that effectively challenges these misconceptions, and to highlight evidence-based alternatives for appropriate management (referred to as key points). We believe that this approach to the management of iron deficiency may be beneficial for both patients and healthcare systems. We stress that this paper solely presents the Authors' independent opinions. No pharmaceutical company funded or influenced the conception, development or writing of the manuscript.

Key words: iron deficiency, anaemia, oral iron, intravenous iron, misconceptions.

Introduction

Using World Health Organization (WHO) criteria for defining anaemia, data from 187 countries revealed a significant reduction in the prevalence of global anaemia from 40.2% in 1990 to 32.9% in 2010, with wide variations across regions[1]. Decreases in the prevalence of mild and moderate anaemia accounted for most of the reduction, while the prevalence of severe anaemia remained largely unchanged. Iron deficiency (ID) remains the most common cause of anaemia worldwide, accounting for about one half of all cases. Other common causes include infestations, congenital anaemias (e.g., haemoglobinopathies), and anaemia associated with chronic kidney disease (CKD), although, again, the proportion of cases resulting from specific causes varies widely across regions[1].

The prevention and treatment of ID is a major public health goal, especially in women, children, and individuals in low-income countries. Challenges in the treatment of ID include finding and addressing the underlying cause and the selection of an iron replacement product which meets the needs of the patient[2,3].

There are a number of non-evidence-based misconceptions regarding the diagnosis and management of ID, either with anaemia (IDA) or without anaemia (NAID), as well as inconsistency of terminology and lack of clear guidance on clinical pathways[4,5]. In particular, the pathogenesis of IDA is still frequently not addressed and iron not replaced, with indiscriminate red cell transfusion used as a default therapy. In our experience, this imprudent practice continues to be endorsed by non-evidence-based misconceptions.

Methodology

Following the methodology used in previous publications[5,6], the corresponding Author (MM) invited co-Authors to participate and drafted a preliminary list of misconceptions on the diagnosis and management of IDA and NAID (based on the current practice of the Authors, who are actively working in the field of

anaemia, both in Europe and the USA). The intent of the Authors was to provide a consensus that effectively challenges these misconceptions, and to highlight what we collectively consider should be appropriate management (referred to as key points). We stress that this paper solely contains the Authors' independent opinions. No pharmaceutical company funded or influenced the conception, development or writing of the manuscript.

Misconception #1

Iron status can be easily evaluated and normal ferritin concentrations exclude iron deficiency

Appropriate assessment of iron status and definitions of ID are paramount when prescribing iron supplementation. In the early stages of ID, haematopoiesis is not affected. As iron stores diminish further, the red cells become microcytic (mean corpuscular volume <80 μL) and then hypochromic (mean corpuscular haemoglobin <28 pg). Greater red cell distribution width (RDW>15, anisocytosis) and thrombocytosis can be also observed on blood counts of patients with ID. The peripheral blood smear (slide) may show microcytosis, hypochromia, anisocytosis and poikilocytosis. Although often overlooked, a corrected reticulocyte count is necessary for the classification of anaemia. The reticulocyte production index (RPI) is calculated according to the formula:

RPI= ([% reticulocytes] × [haematocrit/45]) × 0.5

(a RPI >2 is not compatible with IDA[3]).

Serum ferritin is the most frequently used laboratory test for evaluating iron stores. Although there may be some variability in normal ranges between laboratories, generally ferritin values between 30-300 ng/mL are regarded as normal[2,7]. A serum ferritin level <30 ng/mL is the most sensitive (92%) and specific (98%) cut-off level for the identification of absolute ID, with or without anaemia[8], but most clinical laboratories still use lower cut-off levels (<15-25 ng/mL)[9]. Thus, it is generally believed that serum ferritin values within the "normal range" exclude the presence of ID, but ferritin is an acute-phase reactant and its levels are profoundly affected by inflammation.

Transferrin saturation (TSAT) assesses the iron that is available for tissues and a low TSAT (<16-20%) further indicates insufficient iron supply to support normal erythropoiesis[2,7]. In the presence of inflammation (e.g., C-reactive protein >5 mg/L) and/or TSAT <20%, serum ferritin levels between 30 and 100 ng/mL suggest absolute ID, whereas ferritin levels >100 ng/mL argue against concurrent ID and usually indicate iron sequestration, as seen in anaemia of chronic inflammation[2,6,7].

Other tests, such as increased hypochromic red cells (HYPO >5%, Advia; Siemens Healthineers, Erlangen, Germany), low haemoglobin density (LHD >4%; Beckman-Coulter, Brea, California, CA, USA) and low reticulocyte haemoglobin content (CHr <29 pg, Advia, Siemens; Ret-HE <25 pg, Sysmex Corporation-Global, Kobe, Japan), are the best-established variables for the identification of absolute ID in this setting, which if present should be treated with iron supplementation[6,7,10-13]. Red blood cell size factor (RSF, Beckman-Coulter) is a parameter derived from the square root of the product of the mean corpuscular volume of erythrocytes and reticulocytes. RSF shows good correlation with CHr, with slightly better sensitivity and identical specificity for the detection of iron-restricted erythropoiesis; a RSF value <88% denotes ID[14]. All these tests have limitations in terms of sample stability or appropriate equipment availability. However, if available, they could potentially save money, time and confusion. The ratio of serum transferrin receptor to the log of ferritin (sTfr/log Ft >2; also called ferritin index), may have a role if red cell and reticulocyte parameters are unavailable[11].

Several guidelines have issued recommendation for iron supplementation based on these diagnostic parameters. The European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel disease (ECCO Guidelines), recommend iron supplementation, preferably intravenous (IV), for patients with ferritin levels <30 ng/mL or <100 ng/mL and TSAT <20%[15]. These definitions are also supported by guidelines on anaemia management in surgical patients[16,17].

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on anaemia management in CKD define absolute ID by ferritin <100 ng/mL and TSAT <20%. If an increase in haemoglobin concentration without starting treatment with an erythropoiesis-stimulating agent (ESA) is desired, these guidelines suggest iron therapy (either IV or oral) if TSAT <25% and ferritin is <200 ng/mL in CKD patients not undergoing dialysis and <300 ng/mL in those undergoing dialysis[18]. For CKD patients on ESA treatment with TSAT ≤30% and ferritin ≤500 ng/mL, they also suggest iron therapy if an increase in haemoglobin concentration or a decrease in ESA dose is desired[18].

Similarly, for patients with symptomatic chronic heart failure, the European Society of Cardiology guidelines define ID by serum ferritin <100 ng/mL, or ferritin between 100-299 ng/mL and TSAT <20%, and consider the administration of ferric carboxymaltose (FCM) in order to alleviate symptoms, and improve exercise capacity and quality of life[19,20].

In contrast, some guidelines for the management of cancer-related anaemia recommend administration of IV iron even at ferritin concentrations as high as 500 or 800 ng/mL, if the TSAT is <40% in an ESA-unresponsive patient[21-23].

Key points

- Uncomplicated iron deficiency can be diagnosed by assessing standard iron parameters, such as serum ferritin and transferrin saturation.
- A low serum ferritin concentration (<30 ng/mL) is diagnostic for absolute iron deficiency, independently of any other parameter.
- In the setting of inflammation, serum ferritin levels between 30 and 100 ng/mL strongly suggest absolute iron deficiency.
- In the setting of inflammation with normal-to-elevated ferritin levels (>100 ng/mL), assessments of haemoglobinisation of red cells (hypochromic red cells, low haemoglobin density) and reticulocytes (reticulocyte haemoglobin content, red blood cell size factor) are useful parameters for identifying the presence of iron-restricted erythropoiesis. The ferritin index may have a role if the above mentioned red cell and reticulocyte parameters are unavailable.
- In the setting of inflammation, ferritin levels within or even above the normal range do not exclude the presence of iron-restricted erythropoiesis and patients may still benefit from iron supplementation. However, at present no upper limit of ferritin can be universally proposed with certainty. When available, physicians should refer to specific guidelines[18-23]. Nonetheless, the level of evidence supporting the proposed ferritin cut-offs is generally low.

Misconception #2

Non-anaemic iron deficiency does not require any intervention

A normal haemoglobin level does not exclude ID. Individuals with normal body iron stores must lose a large portion of body iron before the haemoglobin falls below the laboratory definition of anaemia (generally, haemoglobin <13 g/dL for men, and <12 g/dL in non-pregnant women). In fact, the WHO recognises that "mild anaemia" (haemoglobin ≥11 g/dL - <12/13 g/dL) is a misnomer, as ID is already advanced by the time anaemia is detected, and has consequences even when no anaemia is clinically apparent[9].

Non-anaemic patients with reduced or absent iron stores (NAID) may have symptoms such as fatigue or reduced exercise tolerance (iron is required for optimal mitochondrial function essential for respiration and energy production)[24]. Most current guidelines do not recommend routine testing of iron parameters in the absence of anaemia. As a result NAID is invariably diagnosed in the laboratory[25] when physicians are proactive. However, the benefit of oral or IV iron replacement for NAID-associated fatigue has been demonstrated in menstruating women, runners and blood donors[26-34].

NAID is frequent in pregnancy and can adversely affect both the mother (increased risk of preterm delivery, Caesarean delivery and transfusion) and the neonate (increased risk of low APGAR score at 5 minutes, intensive care admission, delayed growth and development and an increase in behavioural problems that persist up to 10 years after iron repletion)[35,36]. As total iron needs during pregnancy may exceed 1,000 mg, daily or alternate day iron supplementation (30-60 mg/day) during pregnancy may avoid preterm anaemia and minimise the probability of ID in the neonate[37,38].

NAID is also prevalent among patients with gastro-intestinal pathologies such as inflammatory bowel disease, gastric bypass, coeliac disease, *Helicobacter pylori* infection, and atrophic gastritis. In addition to the appropriate treatment for the underlying disease (e.g., gluten-free diet or antibiotics for *Helicobacter pylori* eradication), these patients may benefit from iron supplementation[39,40].

In patients with cancer or inflammatory bowel disease, NAID may induce secondary thrombocytosis (platelet count ≥350,000/μL), which has been identified as an independent risk factor for thromboembolic events[41,42]. In experimental studies, ID alters megakaryopoiesis and platelet phenotype independently of thrombopoietin, through a mechanism mediated by increased expression of hypoxia-induced factor 2α[43,44]. The correction of ID lowers platelet counts and platelet activation in patients with CKD, cancer and inflammatory bowel disease-associated secondary thrombocytosis, and might contribute to reduce the risk of thromboembolic events[45-48]. Further investigation should clarify whether ID is a preventable cause of thrombosis, especially in the elderly.

In congestive heart failure, NAID was independently associated with compromised physical performance and quality of life, and an increase of all-cause and cardiovascular mortality; treatment of NAID with IV iron may improve functional status within four weeks, and these improvements are maintained after 24 weeks and 52 weeks[20].

In observational studies of patients undergoing abdominal or cardiac surgery, pre-operative NAID has been associated with poor outcomes (increased rates of post-operative infections, transfusion, fatigue)[49,50]. Although it is presently unknown whether pre-operative correction of NAID may offset the excess of risk of post-operative complications, guidelines recommend peri-operative iron supplementation for patients with NAID[16,17].

Beyond iron therapy, interventions to find the source of blood or iron loss (e.g., gastro-intestinal investigation) are also necessary in these individuals, especially men and non-menstruating women with

new-onset, absolute ID (ferritin <30 ng/mL)[3,17]. Patients with microcytosis due to NAID should be evaluated for chronic hypoxaemia, myeloproliferative disease (e.g. polycythaemia *rubra vera*), or another cause of increased red cell production (increased iron use). Iron replacement may cause a surge in haemoglobin that could induce hyperviscosity in this subgroup[6].

In a healthy adult, 1 ng/mL of serum ferritin reflects approximately 8 mg of stored iron, whereas 200-250 mg of iron is required to raise the haemoglobin concentration by 1 g/dL[51]. In patients experiencing peri-operative blood loss leading to a haemoglobin drop ≥3 g/dL, a pre-operative ferritin <100 ng/mL may reflect inadequate (low) iron stores to sustain erythropoiesis for recovering their basal haemoglobin levels and maintain normal iron stores (ferritin ≥30 ng/mL)[16,17,52].

In major orthopaedic surgery, the pre-operative administration of ferrous sulphate and vitamins (B_{12} and folate) increased serum ferritin and transferrin saturation and reduced transfusion rate[53,54]. However, adherence to iron supplementation was 67%, and adverse drug reactions were present in 52% of patients[55]. IV iron administration (e.g., 500 mg) should be considered if there is <4 weeks until surgery or the patient cannot tolerate oral iron[6,7,56]. In orthopaedic and cardiac surgery, peri-operative IV iron may reduce transfusion rates; it preserves iron stores and hastens the recovery from post-operative anaemia[57-60].

Key points

- Iron stores should be replaced with oral or intravenous iron in most patients with non-anaemic iron deficiency to improve symptoms and/or avoid the development of iron-deficiency anaemia.
- Patients with low iron stores (ferritin < 100 ng/mL) undergoing surgery with a high risk of developing severe post-operative anaemia may benefit from peri-operative oral or IV iron supplementation.
- It is imperative to find the source of decreased iron, such as reduced uptake, increased iron loss, or increased iron use, in both iron-deficiency anaemia and non-anaemic iron deficiency. Patients should be proactively treated while these searches are ongoing.

Misconception #3

Oral iron is "always" efficacious if patients tolerate high daily doses

The mainstay therapy for ID is oral iron which is effective, readily available, safe, and inexpensive (especially for low-resource countries). Oral iron avoids the need for venous access and infusion monitoring, and eliminates the risk of infusion reactions. It is, however, time-consuming and requires months of treatment to correct anaemia and replenish iron stores.

There is a huge variety of formulations of ferrous salts (sulphate, gluconate, fumarate, etc.) and ferric complexes (amino acids, polysaccharide, ovo-albumin, etc.) which are available as tablets, elixirs or solutions. There is no evidence that one iron salt formulation is more effective or has fewer side effects than another, as long as they are taken[61]. However, as they are poorly absorbed, the use enteric-coated formulations should be avoided[62]. Data from randomised controlled trials indicate that non-salt-based oral iron formulations, such as ferrous bis-glycinate chelate, ferric maltol or sucrosomial iron, may represent an alternative option for patients with intolerance of iron salts or those on maintenance therapy with IV iron, though more studies are needed[63-67].

Oral iron is usually prescribed at a high dose (100-200 mg elemental iron) to be taken one to three times a day. Up to 70% of patients on oral iron (especially ferrous sulphate) report gastrointestinal side effects, due to exposure to unabsorbed iron, which ultimately reduces tolerance and adherence to treatment[68].

However, lower-dosage iron supplements can be effective for treating ID and are associated with fewer gastrointestinal side effects. In non-anaemic young women with plasma ferritin levels <20 ng/mL, providing lower dosages (40-60 mg elemental iron) and avoiding twice-daily dosing was found to maximise fractional absorption due to the reduced effect of absorbed iron on hepcidin release[69].

Whether these data also apply to IDA is not known. Anaemia-induced hypoxia and erythropoietin production down-regulate hepcidin expression[70], and this may counterbalance the stimulatory effect of iron, allowing the use of higher oral iron doses. In a randomised study, 90 patients with IDA (average age 85 years) received 15 mg, 50 mg or 150 mg of elemental iron per day. At two months, there were no between-group differences in the levels of haemoglobin or ferritin. Haemoglobin increased 1.4 g/dL in the three groups, but adverse effects were significantly more common with higher doses[71]. In an observational study of patients with inflammatory bowel disease with mild-to-moderate anaemia, oral iron treatment (100 mg/day) was effective and well tolerated by most patients, did not exacerbate the symptoms of the underlying inflammatory bowel disease, and was associated with a relative improvement in quality of life[72]. Based on these findings a new paradigm for low-dose, alternate-day iron may be prudent.

There are a number of commonly used medications (tetracycline, antacids, proton pump inhibitors, H_2 antagonists, etc.) which reduce the absorption of iron salts. It is recommended that oral iron be taken 12 hours apart from these drugs. The intake of iron salts together with food also reduces absorption of iron, but increases

the tolerance. Should the patient develop intolerance of iron salts, switching to another oral iron formulation or to IV iron may be appropriate[3,62].

Key points
- Patients with mild-to-moderate iron-deficiency anaemia may benefit from oral iron therapy provided that there is tolerance of and no contraindications to oral iron.
- Low daily doses (e.g., 50 mg) or moderate doses (e.g., 100 mg) every other day may increase both tolerance and efficacy of oral iron supplementation.
- Once anaemia is corrected, oral iron supplementation should be continued for at least 3 months to replenish iron stores.

Misconception #4

The use of intravenous iron should be restricted to severe cases of anaemia

Severe IDA presenting with alarming symptoms, such as haemodynamic instability, or risk criteria, such as coronary heart disease, should be treated with red blood cell transfusion using the minimal amount necessary to achieve clinical stability. Adhering to patient-adapted restrictive transfusion criteria and transfusing one unit at the time, with post-transfusion reassessment, is strongly recommended by the majority of guidelines[22,73-75].

Red blood cell transfusion produces a rapid, albeit transient, rise in haemoglobin, increasing oxygen-carrying capacity. However, severe IDA will recur unless the cause is identified and addressed, if possible. After haemodynamic stability has been achieved with transfusion, additional iron supplementation should be considered with the IV route preferred.

IV iron has been demonstrated to be superior to oral iron in a number of clinical settings[76-81]. Furthermore, IV iron is a necessity when oral iron cannot be taken or is ineffective, such as in the presence of inflammation or on-going blood loss. Its avoidance is not only counterproductive but potentially harmful, and limiting its use will dramatically increase ESA usage as well as red blood cell transfusions with their associated complications[82]. Unlike ESA, IV iron does not increase haemoglobin concentrations beyond recommended levels, but it has been reported to reduce ID-induced secondary thrombocytosis, which may contribute to lowering the risk of thromboembolic complications[41,45-47,83]. The use of IV iron formulations which allow infusion of high doses of iron (1,000 mg or more), such as low molecular weight iron dextran (LMW ID), FCM, or iron isomaltoside-1000 (ISM), in a short time (15-60 minutes), offers added convenience to both physicians and patients[84,85].

Key points
- For patients with severe iron-deficiency anaemia, administration of intravenous iron is the replacement therapy of choice.
- In the settings of intolerance of, or refractoriness to oral iron, active bleeding, inflammatory conditions, erythropoiesis-stimulating agent treatment, or need for a rapid recovery of haemoglobin, switching to intravenous iron therapy is appropriate for managing mild-to-moderate anaemia.
- The use of intravenous iron formulations that allow nearly full iron replacement in one or two infusions is preferred for most patients.
- When offering intravenous iron therapy to people not receiving haemodialysis, consider high-dose, low frequency intravenous iron as the treatment of choice for adults and young people when trying to achieve iron repletion.

Misconception #5

There is no need for re-assessment after iron repletion with intravenous iron

A full response to IV iron administration can take up to six-eight weeks. Patients experience an improvement of well-being within a few days, the reticulocyte count rises in one week, and haemoglobin increments are seen in one or two weeks. Depending on the severity of anaemia, normal levels will be reached in most patients in one or two months. Therefore, after initial IV iron repletion and depending on underlying co-morbidities, a reassessment of both response and iron status is prudent as further iron supplementation is often required (oral or IV)[15,62,86].

Generally, reassessment should be performed no earlier than four-six weeks after treatment to allow adequate time for erythropoiesis and iron utilisation, and to avoid interference of IV iron with assays of iron status (standard laboratory methods do not discriminate between transferrin-bound iron, compound-bound iron and labile iron)[62].

When there is chronic ongoing blood loss or participation in a pre-operative haemoglobin optimisation programme more frequents visits may be required to evaluate the response and establish an effective iron dose. Recently Theusinger *et al.*[87] reported on the results of a pragmatic approach to pre-operative anaemia management in major orthopaedic surgery (2009-2011; n=6,721). If there were no contraindications, patients presenting with a haemoglobin <13 g/dL received 1,000 mg IV iron and 40,000 IU recombinant human erythropoietin (rHuEPO) subcutaneously, and were reassessed two weeks later. Those whose haemoglobin remained <13 g/dL received a second dose of IV iron and rHuEPO.

All treated patients presented with normal haemoglobin levels (≥13 g/dL) on the day of surgery.

If haemoglobin and iron status do not normalize, the cause for this failure should be carefully determined[62,88]. Patients at risk of recurrent ID, such as those with cancer, CKD, chronic heart failure, inflammatory bowel disease, history of gastric bypass, heavy menstrual bleeding, hereditary haemorrhagic telangiectasia, malabsorption, or any condition in which active blood loss exceeds absorptive capacity, should be assessed at frequent intervals to determine whether maintenance iron supplementation is indicated[15,62,86,89-92].

Key points

- The haematological response to intravenous iron should be assessed, and the need for further iron supplementation established, six to eight weeks after initial iron repletion.
- Lack of response to intravenous iron should be appropriately investigated.
- Patients responding to initial intravenous iron therapy but at risk of the iron deficiency recurring should be periodically reassessed and/or receive maintenance oral or intravenous iron supplementation.

Misconception #6

All intravenous iron formulations are alike

Currently, six IV iron formulations are available for clinical use worldwide: ferric gluconate (FG), iron sucrose (IS), low molecular weight iron dextran (LMWID), ferric carboxymaltose (FCM), iron isomaltoside-1000 (ISM), and ferumoxytol (FXT) (Table I).

For the approved indications and at recommended doses, all the available IV iron formulations are essentially equal in terms of safety and efficacy[82,93]. This statement only applies to original IV iron formulations. In dialysis-dependent (DD)-CKD patients, the switch from the originator IS to an IS similar led to higher iron and ESA doses required and incurred and increased total anaemia treatment costs; this situation reverted after a switch back to the originator IS[94,95]. The European Medicines Agency states that current scientific knowledge and regulatory experience for characterisation of nano-sized colloidal IV iron preparations indicate that quality characterisation, on its own, would not provide sufficient assurance of the similarity between the two products, even if the quality tests performed show similarity. In the context of such iron-based preparations, a "weight of evidence

Table I - Characteristics of different intravenous iron formulations.

	Iron gluconate[6]	Iron sucrose[7]	LMWID[8]	Ferric carboxymaltose[9]	Iron isomaltoside 1000[10]	Ferumoxytol[11]
Brand name	***Ferrlecit®***	***Venofer®***	***Cosmofer® INFeD®***	***Ferinject® Injectafer®***	***Monofer® Monoferro®***	***FeraHeme® Rienso®***
Molecular weight (kDa)	289-440	30-60	165	150	150	750
Labile iron (% injected dose)[1]	3.3	3.5	2.0	0.6	1.0	0.8
Maximal single dose (mg)	125	200	20 mg/kg	20 mg/kg (max 1,000 mg)	20 mg/kg	510
Infusion time for 1,000 mg (min)[2]	720	300	180*	45	45	90
Product cost per 1,000 mg (€)[3]	-	112	103	192	192	162[4]
Administration cost per 1,000 mg (€)[5]	554	231	139	35	35	70
Total cost per 1,000 mg dose (€)	-	342	242	227	227	232

1) Jahn MR, *et al*. Eur J Pharm Biopharm 2011; **78**: 480-91.
2) Includes 30 min post-infusion observation.
3) Quintana-Díaz M, *et al* . Blood Transfus 2017; **15**: 438-46.
4) British National Formulary BNF68, September 2014 - March 2015. BMJ Group and the Royal Pharmaceutical Society of Great Britain, London, 2014.
5) Includes infusion time cost and post-infusion time (30 min) cost at day-hospital (€ 277/6 hours; € 0.77/min), according to official prices for healthcare services in the Autonomous Community of Madrid (Spain).
6) Ferrlecit summary of product characteristics. Available at: http://www.products.sanofi-aventis.us/ferrlecit/ferrlecit.pdf; Accessed on 18/01/2017.
7) Venofer summary of product characteristics. Available at: http://www.luitpold.com/documents/22.pdf. Accessed on 18/01/2017.
8) LMWID, low molecular weight iron dextran; Cosmofer summary of product characteristics. Available at:http://www.cosmofer.com/product/cosmofer-spc/cosmofer-spc.aspx. Accessed on 18/01/2017.
9) Ferinject summary of product characteristics. Available at: http://www.ferinject.co.uk/smpc/. Accessed on 18/01/2017.
10) Monofer summary of product characteristics. Available at: http://www.monofer.com/spc.aspx; Accessed on 18/01/2017.
11) FeraHeme summary of product characteristics. Available at: http://www.feraheme.com/pdfs/Feraheme_Prescribing_Information.pdf. Accessed on 18/01/2017.

* Although it is not an approved dosing by the USA Food and Drug Administration or European Medicines Agency, Auerbach *et al.* (Am J Hematol 2011; **86**: 860) did not observed any serious adverse events in over 5,000 administration of LMWID at doses of 1,000 mg in 250 mL of normal saline over 1 hour (estimated total cost per 1,000 mg dose in Spain € 173).

approach" including data from quality, non-clinical and human pharmacokinetic studies is required[96].

There are remarkable differences in originator compound structures which may greatly influence feasibility and cost of treatment courses (acquisition cost, number of doses, and infusion time)[97,98]. FCM is the IV iron formulation for which there is the highest level of clinical evidence, and is currently the only one recommended in the European guidelines for the management of ID in heart failure[19]. However, there is no published evidence suggesting a clinical advantage of one formulation over another.

Acquisition costs for different IV iron formulations could be subject to purchasing agreements among hospitals, health-care providers, distributors and manufacturers. Thus, they may vary widely between and within countries. As shown in Table I, in Spain, the acquisition costs of LMWID, FCM and ISM are considerably higher than that of IS (FG and FXT are not available). As iron is strongly bound to carbohydrates in these IV formulations, the amount of labile iron available is very low, thus allowing rapid administration of large single doses. Current evidence does not support a benefit for therapeutic doses exceeding 1,000 to 1,500 mg[3,62]. All this facilitates full iron replacement, with fewer visits necessary, resulting in reduced administration costs. These advantages may outweigh the higher acquisition costs of such iron formulations, and result in significantly lower total costs[99-103]. Estimated total costs for FXT are similar to those for LMWID, FCM and ISM, whereas those for FG and IS are significantly higher (Table I). In the USA, centres are paid $ 68 for an hour in the chair for IV iron and $ 41 for 15 minutes. Acquisition costs for 1,000 mg IV iron are significantly higher in the United States of America than in Europe.

The European Medicines Agency recommends close monitoring for signs of hypersensitivity during and for at least 30 minutes after every administration of an IV iron product[104]. The guidelines for risk minimisation and management of hypersensitivity reactions to IV iron also suggest observation/monitoring every 15 minutes during the infusion and for 30 minutes after its completion, especially for patients at risk such as those who have had a previous adverse reaction to IV iron or have more than one drug allergy, a history of severe atopy, pre-existing severe respiratory or cardiac disease, or are taking beta-blockers or angiotensin-converting enzyme inhibitors[105]. In contrast, since IV iron delivery should not be associated with a severe delayed reaction, the KDIGO Controversies Conference considered that there is no physiological basis to recommend that patients should be observed for 30 minutes after an infusion of IV iron has been completed[106].

With regards to dose, data from some trials comparing IV iron administration at "lower dose" (IS) with "higher dose" (FCM, ISM, FXT)[107-110] showed a higher proportion of patients with a haemoglobin increase ≥2 g/dL from baseline at any time of the study and/or a shorter time to get such an increase with higher dose IV iron. Biochemical iron parameters improved both faster and quantitatively more with higher dose IV iron, compared to lower dose[107-113].

Key points

- There are structural differences between intravenous compounds which greatly influence feasibility and cost of treatment courses.
- Intravenous iron formulations allowing higher dose administration are more convenient both for the patient (fewer venous punctures, less time off work, etc.) and the healthcare system (fewer visits to day hospital, less ambulance transport, etc.). These advantages outweigh higher acquisition costs, and result in significantly lower total costs of treatment.

Misconception #7

Intravenous iron is associated with a high risk of anaphylaxis

A report from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) stated that all IV iron medicines are associated with a small risk of causing allergic reactions which can be life-threatening if not treated promptly, but the benefits of IV iron exceed its risks provided that adequate measures are taken to minimise such reactions. The CHMP report also added that "data on the risk of hypersensitivity comes mainly from post-marketing spontaneous reports and the total number of life-threatening and fatal events reported is low" and "although the data show a clear association of intravenous iron medicines and hypersensitivity reactions, the data cannot be used to detect any differences in the safety profile of the different iron medicines"[104]. High-molecular weight iron dextran, which produced hypersensitivity reactions more frequently than any other IV iron formulation, is no longer available, and was not addressed in this manuscript. Overall, the currently available formulations are much safer, with estimated serious adverse events rates of <1:250,000 administrations.

These conclusions were recently called in question by a publication from the Food and Drug Administration in the USA. Wang *et al.*[114] retrospectively reviewed a large cohort of new users of IV iron (n=688,183), enrolled in the United States of America fee-for-service Medicare programme from January 2003 to December 2013, to compare the risk of anaphylaxis among marketed IV iron products. The overall incidence was low, but a higher risk of anaphylaxis was found for iron dextran

compounds when compared to non-iron dextran (FG, IS, and FXT) (68/100,000 *vs* 24/100,000; p<0.001).

However, this could be an overestimation as high-molecular weight iron dextran was included, which is known to be associated with a higher risk of adverse reactions and was still available during the conduct of the study. Only Medicare patients were involved (with a mean age >70 years), so the majority of subjects who receive IV iron were not studied. These include patients with heavy uterine bleeding, pregnancy, after bariatric surgery and inflammatory bowel disease. Consequently, the population studied was not representative of patients receiving IV iron[115]. There are no data available for FCM or ISM in the USA. A recent evaluation suggests that adverse reactions are less common with newer formulations[93].

Similarly, although the USA Food and Drug Administration's Adverse Event Reporting System database is a valuable resource for reporting suspected allergic/anaphylactic reactions, it does not allow conclusions to be drawn about absolute risks and/or relative risks among IV iron products[116].

Subtracting the risk of anaphylaxis from the combined risk of anaphylaxis or death, enabled the risk of death to be estimated (see Wang *et al*., 2015, supplementary files)[114]. Interestingly, the risk of death on the date of first administration for incident IV iron users was an order of magnitude lower for iron dextran (0.8/100,000) than for IS (6.1/100,000), FG (6.4/100,000) or FXT (3.7/100,000). These data effectively contradict their conclusions.

We deem that the risk profile of IV iron therapy should also be compared to the risk of death and serious adverse events resulting from transfusion therapy. In fact, although haemovigilance and progress are improving the safety of transfusions with regards to infectious risks, the risks of death and non-infectious SAE (as estimated from Serious Hazards Of Transfusion [SHOT] data in 2012) are one in 322,580 and one in 21,413 components issued, respectively[117].

An incompletely understood side effect is fibroblast growth factor-23-induced hypophosphataemia which seems to affect patients receiving some IV iron preparations more than others (especially with FCM). IV iron induces an increase of biologically active, intact fibroblast-growth factor 23 that reduces renal phosphate absorption, leading to hypophosphatemia which may persist for up to six months. Generally, hypophosphataemia is of no clinical significance, although it may present with symptoms which are similar to those produced by anaemia, and there are case reports of patients requiring enteral and parenteral replacement therapy for some time after administration[118-121]. However, phosphate levels do not need to be checked routinely unless significant malnutrition is present[3,62].

In conclusion, although we believe that IV iron rarely causes serious adverse effects, it would be imprudent to ignore the history of reported life-threatening events. A recent excellent monograph on the management of hypersensitivity reactions to IV iron[105] supports our conclusions but cautions physicians to have immediately available the necessary therapeutic modalities to handle life-threatening hypersensitivity reactions. These authors also developed an excellent algorithm which provides intelligent recommendations to avoid unnecessary interventions while guiding clinicians on how to handle the extremely rare but serious events. The proposed algorithm is similar to that in the KDIGO Controversies document[106]. In this algorithm, anti-histamines have no role as pre-medication or part of the treatment paradigm.

Key points

- All intravenous iron formulations are essentially equally safe and efficacious.
- All intravenous iron medicines carry a very low risk of causing allergic reactions which can be life-threatening if not treated promptly.
- Physicians should have immediately available the necessary therapeutic modalities to handle life-threatening hypersensitivity reactions and follow a well-designed algorithm.

Misconception #8

Premedication reduces infusion reactions during intravenous iron administration

Many clinicians are still reluctant to use IV iron due to concerns about anaphylaxis, although true life-threatening allergic reactions are exceedingly rare and vastly overestimated[93,106]. Early formulations of high molecular weight iron dextran were associated with occurrences of anaphylaxis and even death, whereas newer formulations are much safer with severe adverse events vanishingly rare. Nonetheless, minor infusion reactions still occur and are often misinterpreted as serious adverse events[122].

Premedication with antihistamines (diphenhydramine) was reported to have caused the majority of perceived reactions to IV iron in one large cohort[123]. Antihistamines can cause somnolence, diaphoresis, hypotension and tachycardia which can be erroneously attributed to the administered iron. Tryptase levels, a marker of mast cell degranulation, are virtually always normal and consequently the use of premedication with antihistamines should not be advised[124].

All iron formulations can be associated with acute chest and back tightness, without accompanying hypotension, tachypnoea, tachycardia, wheezing, stridor or periorbital oedema[106,125,126]. Although the cause has not been clearly elucidated, these reactions

are consistent with minor reactions to labile free iron[106]. A novel postulate as a potential aetiology is activation of the complement system (the so-called, complement activation-related pseudo allergic, CARPA), and may be more serious[105].

Normally, reactions to "free" or "labile" iron abate spontaneously without any therapy and rarely recur with re-challenge. If symptoms recur, switching to another IV formulation is appropriate. Thus, aggressively treating non-allergic infusion reactions with diphenhydramine or vasopressors should be avoided as it may convert this mild reaction into a more serious adverse event. It is also important to be mindful that these infusion reactions should not be misinterpreted as hypersensitivity, as the European Medicines Agency stated that "intravenous iron containing products must also not be used in patients with serious hypersensitivity to other parenteral iron products" [104].

The reactions are more frequent in those with allergic diatheses[82]. Patients with asthma or more than one drug allergy, who are at slightly increased risk of an allergic or infusion reaction, may benefit from pre-medication with steroids or H_2 blockers prior to administration of IV iron[127]. For those with inflammatory arthritis a short course of prednisone (1 mg/kg/day orally for 4 days) may prevent a flare[128,129].

A few patients will experience self-limited arthralgia and myalgia the day after iron infusions. These reactions abate without therapy, leaving no sequelae, but administration of non-steroidal anti-inflammatory medications may shorten their duration[62].

When these recommendations are borne in mind, the administration of IV iron is a safe procedure, being much safer than most physicians realise.

Key points

- Premedication with antihistamines does not prevent infusion reactions and should be proscribed.
- Aggressive management of non-allergic infusion reactions with diphenhydramine and other therapies may convert a mild reaction into a more serious adverse event.
- Patients with asthma or drug allergies should be routinely pre-medicated with methylprednisolone or hydrocortisone prior to intravenous iron infusion.
- Non-steroid anti-inflammatory drugs may be useful for treating post-infusion arthralgia or myalgia if there are no contraindications

Misconception # 9

Intravenous iron may increase the risks of infection and oxidative stress

Current information on the relationship between IV iron and infection, and between IV iron and oxidative stress, deserves special consideration. However, we should differentiate between short-term IV iron administration (usually given as one or two large doses) and long-term IV iron therapy (as is the case for patients with CKD).

Elemental iron is an essential growth factor for bacteria, with many species expressing iron transport proteins that compete with transferrin, and it has long been suggested that patients with iron overload are at increased risk of infection[130]. In a systematic review and meta-analysis evaluating the efficacy and safety of IV iron, Litton *et al.*[131] reported that IV iron resulted in a significant increase in mean haemoglobin concentration (6.5 g/L; 95% CI [confidence interval]: 5.1-7.9 g/L), a reduction of transfusion risk (relative risk 0.74; 95% CI: 0.62-0.88), and no significant difference in mortality or serious adverse events compared with oral iron or no iron supplementation, but IV iron was associated with a significant increase in risk of infection of 1.33 (95% CI: 1.10-1.64). However, the conclusions of this meta-analysis are undermined by study limitations (search strategy was incomplete, infection was not a predefined endpoint in many studies, a dose-response relationship was not found), and are somewhat contradictory to most other published studies[132].

A more recent meta-analysis of 103 trials published between 1965 and 2013 (including 19,253 treated patients: 10,390 with IV iron, 4,044 with oral iron, 1,329 with no iron, 3,335 with placebo, and 155 with intramuscular iron) concluded that IV iron therapy was not associated with an increased risk of serious adverse events (relative risk: 1.04; 95% CI: 0.93-1.17) or infection (relative risk: 0.96; 95% CI: 0.63-1.46), when compared with oral or intramuscular iron, no iron or placebo[79]. In large observational studies, peri-operative IV iron reduced transfusion rates and did not have negative effect on rates of infection and 30-day mortality in surgical patients. In contrast, red cell transfusions deliver haem and labile iron, which support bacterial growth more readily[135]. Despite the absence of definitive clinical data, it seems sensible to avoid IV iron administration in the setting of acute infection[52].

Regarding patients on long-term IV iron therapy, one study of 117,050 DD-CKD patients reported that bolus dosing, when compared to maintenance dosing, was associated with a higher risk of infection-related hospital admissions, as well as infection-related mortality. However, maintenance or low-dose iron dosing was not associated with a higher risk of infection-related hospitalisation or mortality outcomes when compared with no iron[136]. Similarly, a small single-centre trial in non-dialysed CKD patients, showed a higher rate of cardiovascular events and infections requiring hospital admission in the group receiving IV iron[137]. In contrast, in the largest and longest trial (FIND-CKD, n=626)

ever conducted evaluating IV *vs* oral iron in anaemic, non-dialysed CKD patients with ID and not receiving ESA therapy, MacDougall *et al.*[138] did not find any difference in infection rates between patients receiving higher dose FCM (500-1,000 mg/4 weeks), lower dose FCM (200 mg/4 weeks) or oral ferrous sulphate (200 mg/day) during the 56-week follow-up (3.9%, 3.3%, and 3.8%, respectively).

A recent meta-analysis of 24 trials on IV *vs* oral iron supplementation in CKD patients (13 trials including 2,369 patients with CKD stages 3 to 5 and 11 including 818 patients with CKD stage 5D) showed similar rates of mortality, serious adverse events and any adverse events. Nevertheless, IV iron replacement was associated with a higher risk of hypotension (relative risk: 3.71; 95% CI: 1.74-7.94) and fewer gastrointestinal adverse events (relative risk: 0.43; 95% CI: 0.28-0.67)[139].

The available evidence relating IV iron administration to oxidative stress leading to atherogenesis and vascular remodelling is indirect, and there is little to no evidence that IV iron adversely affects survival in patients with DD-CKD, as most data come from observational, retrospective studies. In a cohort of 58,058 DD-CKD patients, IV iron doses greater than 400 mg/month were associated with higher cardiovascular death rates[140], whereas a larger retrospective study on DD-CKD patients showed no association between large doses of iron and short-term cardiovascular morbidity and mortality[141]. In the FIND-CKD study the incidences of cardiac events were identical across all three groups (high-dose FCM, low-dose FCM, and oral iron)[138]. In patients with congestive heart failure, who may also present with CKD, ID was independently associated with cardiovascular mortality, while IV iron therapy improved functional status[20].

The conclusion should be that "too much iron is bad" for CKD patients, but further large clinical studies are needed. The on-going Proactive IV irOn Therapy in haemodiALysis (PIVOTAL) (EudraCT Number: 2013-002267-25) trial is a four-year trial and will involve over 2,000 patients from 50 renal units in the UK. This is the largest renal clinical trial ever undertaken comparing a high-dose *vs* a low-dose IV iron regimen. Hard end-points include the risk of death, myocardial infarction, stroke, heart failure, and infections. Changes in laboratory parameters, quality-of-life and ESA requirements will also be monitored. It is hoped that the PIVOTAL results will fill many gaps in our knowledge on IV iron therapy in CKD patients[142].

Key points

- Data from meta-analyses and large observational studies indicated that short-term intravenous iron therapy was not associated with an increased risk of infection when compared to oral iron or no iron.
- In dialysis-dependent patients with chronic kidney disease on long-term intravenous iron maintenance therapy, low-dose iron dosing was not associated with a higher risk of infection-related hospital admissions or mortality outcomes when compared with no iron.
- In non dialysis-dependent patients with chronic kidney disease on long-term intravenous iron maintenance therapy, neither lower nor higher iron dosing seems to be associated with a higher risk of infection when compared with oral iron.
- There is no convincing evidence that intravenous iron administration induces significant oxidative stress leading to cardiovascular morbidity and mortality.

Misconception #10

No adjuvant iron is needed with erythropoiesis-stimulating agent treatment if the ferritin level is normal

ESA increase erythropoiesis in a dose-dependent fashion, although their stimulatory effect may be reduced by inflammation[143]. Iron does not directly stimulate erythropoiesis, but an adequate supply to the bone marrow is indispensable for building up haemoglobin. Inflammation-induced hepcidin synthesis leads to sequestration of iron, thus decreasing iron mobilisation from stores. ESA increase intestinal iron absorption, and decrease hepcidin synthesis (through the stimulation of erythroferrone release by erythroblasts) facilitating iron mobilisation. Functional ID refers to insufficient mobilisation of iron from stores to meet the increased demands imposed by high-dose ESA, even in the presence of normal iron stores. Importantly, insufficient iron supply during ESA treatment leads to thrombocytosis[1,7,47].

Administration of ESA is indicated for iron-replete patients who are anaemic due to CKD or chemotherapy[18,22,106]. ESA are also used to optimise pre-operative haemoglobin levels in patients scheduled for major surgery in which moderate-to-high blood loss is expected. Assessment of iron status and correction of ID are mandatory before starting ESA therapy[144,145]. In the presence of functional ID, adjuvant iron therapy improves the haemoglobin response to ESA[73,146,147].

A systematic Cochrane review of studies of cancer and chemotherapy-associated anaemia, including eight randomised controlled trials comparing ESA plus iron *vs* ESAs alone in 2,087 participants (12 comparisons), showed that addition of IV iron to ESA produces a faster and superior haematopoietic response, reduces the risk of red blood cell transfusions, improves haemoglobin levels, and appears to be well tolerated, in comparison with oral iron salts or no iron[148]. In addition, a randomised controlled trial of 67 anaemic onco-

haematological patients not receiving chemotherapy (40% functional ID), and supported with rHuEPO beta and oral iron or IV iron sucrose, showed that rHuEPO plus IV iron resulted in an 11% overall cost savings compared to ESA without iron supplementation (€ 2,178/patient/year). This reduction in overall cost was largely driven by reduced rHuEPO dosages (saving of € 3,829/patient/year), irrespective of the cost incurred for IV iron supplementation (€ 1,654/patient/year)[149,150].

It is recommended that iron supplementation is started immediately in all iron-deficient cancer patients prior to them receiving an ESA. For those hypo-responsive to ESA with functional ID, the addition of IV, and not oral iron, is recommended. Whereas there are no guidelines on dosing, the new European Society for Medical Oncology/European Organisation for Research and Treatment of Cancer (ESMO/EORTC) guidelines recommend 1,000 mg IV iron to be given together with the initiation of ESA[151]. However, a small trial found similar efficacy but better tolerance of oral sucrosomial iron (30 mg/day) compared to IV iron (FG, 125 mg/week) in 64 anaemic cancer patients without absolute or functional ID, scheduled to receive chemotherapy and darbepoetin alfa for eight weeks[66]. Thus, newer oral iron formulations may prevent functional ID in some subgroups of patients, such as those with cancer or CKD[152,153], although further studies are warranted.

It must be borne in mind that the joint guideline from the American Society of Clinical Oncology and the American Society of Hematology (ASCO-ASH) recommend using ESA therapy with great caution in patients with active malignancy, particularly when cure is the anticipated outcome[154]. The Medicines and Healthcare Products Regulatory Agency (MHRA) advised that ESA should not be given to patients with cancer who do not fulfil the criteria in the authorised cancer indications, and that patients should be monitored closely to ensure that the lowest approved dose of ESA is used to adequately control of symptoms of anaemia[155].

In the TREAT study on CKD patients with diabetes, there was an increased risk of stroke in the high-dose ESA group (hazard ratio: 1.92; 95% CI: 1.38-2.68) and venous thrombo-embolic events occurred significantly more frequently in the high haemoglobin arm (2.0%) compared to the placebo arm (1.1%, p=0.02)[156]. A meta-analysis of ESA use in CKD found that targeting higher haemoglobin levels in CKD increases risks of stroke, hypertension, and vascular access thrombosis and probably increases risks of death, serious cardiovascular events, and end-stage renal disease[157]. Relative thrombocytosis induced by ESA in the presence of functional ID was a possible explanation for the increased thrombotic risk[158].

In CKD patients, adjuvant IV iron has long been recognised to improve haematological response and to reduce the dose of ESA required (KDIGO). Additionally, in the FIND-CKD trial, IV FCM targeting a ferritin of 400-600 ng/mL quickly reached and maintained haemoglobin level, and delayed and/or reduced the need for other anaemia management including ESA[138].

In the setting of orthopaedic surgery, a large randomised controlled trial demonstrated that the administration of four doses of an ESA (rHuEPO 40,000 IU plus oral iron, starting three weeks prior to the scheduled procedure) decreased transfusion rates in patients undergoing lower limb arthroplasty or spinal surgery[159]. In contrast, in a more recent study with a similar design, rHuEPO was found to significantly reduce the number of patients requiring allogeneic blood transfusion but not the number of allogeneic units transfused, at unacceptably high costs (€ 7,300 per avoided transfusion)[160], calling into question the routine use of four doses of rHuEPO. Data from several studies suggest that one or two doses of rHuEPO could be sufficient to reach a target haemoglobin level ≥13 g/dL, especially when co-adjuvant IV iron is administered[87,161,162]. These results suggest a possible role for iron supplementation as monotherapy. Three small trials have shown that administration of iron without ESA in women receiving chemotherapy prevented a haemoglobin fall during treatment cycles and led to a significant reduction of transfusion requirements[163-165]. A large observational study in anaemic cancer patients receiving iron indicated that patients with baseline haemoglobin levels up to 11.0 g/dL and a serum ferritin level ≤500 ng/mL had an increase in haemoglobin and a reduction in the need for blood transfusions[166]. Additionally, in patients with gastrointestinal cancer (mostly colorectal cancer) scheduled for potentially curative surgery, pre-operative administration of IV iron improved haemoglobin levels and reduced transfusion requirements and/or time spent in hospital[167-170]. Therefore, iron supplementation as monotherapy is recommended for ID cancer patients who cannot receive ESA[73].

Key points

- Assessment of iron status and correction of iron deficiency are mandatory before starting erythropoietin-stimulating agent therapy.
- Functional iron deficiency should be corrected with intravenous iron.
- Addition of intravenous iron to erythropoiesis-stimulating agents leads to a faster and superior hematopoietic response, reduces the risk of red blood cell transfusions, is well tolerated, and reduces overall treatment costs when compared to oral iron salts or no iron.

- In chronic kidney disease and cancer-associated anaemia, monotherapy with intravenous iron may result in increased haemoglobin, reduced needs for blood transfusions, and delayed and/or reduced needs for erythropoiesis-stimulating agents, the latter of which may increase the risk of cancer recurrence.

Disclosure of conflict of interests

MM has received industry-supplied funding for consultancies, lectures and/or travel from Pharmacosmos, Vifor Pharma, Zambon and NutraPharma, and is member of the Editorial Boards of Revista Española de Anestesiología y Reanimación and Blood Transfusion; MB has received has received a fee from Alexion and support, for staff and drugs as part of a trial, from Pharmacosmos; FG has received funding for consultancies, lectures and/or travel from Pharmacosmos, Vifor Pharma, Abbvie, Janssen, Takeda and MSD previously, and is member of the Editorial Boards of Journal of Crohn's and Colitis and Gastroenterología y Hepatología; GML is the Editor-in-Chief of Blood Transfusion and this manuscript has undergone additional external review as a result; SB has received honoraria for lecturing and research funding for an investigator-led study from Pharmacosmos, and funding from Vifor Pharma to attend the EDTA 2017; MC has received industry-supplied funding for consultancies, lectures and/or travel from Vifor Pharma, and Zambon; AS received research grants from CSL Behring, Gauss Surgical, Masimo and HbO_2 Therapeutics; he has also received honoraria from CSL Behring, Masimo and Merck, and acted as a consultant for CSL Behring, Gauss Surgical, Masimo Corporation and Vifor Pharma; MA has received funding for research and/or honoraria from Pharmacosmos, AMAG Pharmaceuticals and Luitpold Pharmaceuticals Inc; SG-Rand JP have nothing to declare.

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Arrived: 24 April 2017 - Revision accepted: 30 June 2017
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