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ORIGINAL ARTICLE

Management of iron deficiency in patients admitted to hospital: time for a rethink of treatment principles

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Abstract

Background: Iron deficiency is very common in patients admitted to hospital. Its management is changing with new insights into iron absorption and therapeutic options.

Aims: The aims of this study were to develop guidelines for the correction of iron deficiency in patients admitted to hospital and to compare these with current practice.

Methods: Based on current published evidence, guidelines were developed. All patients in whom iron deficiency was detected during hospital admission over a 2.5 year period were retrospectively studied. Their management was compared with that of the guidelines developed.

Results: Three clinical scenarios were identified—(A) urgent attention to haemoglobin required: blood transfusion followed by i.v. iron recommended, (B) Semiurgent iron repletion: i.v. iron recommended and (C) non-urgent iron repletion: oral or i.v. repletion recommended. A total of 119 patients was identified, age 18–99 (median 77) years, 29% men, and haemoglobin 33–130 (87) g/L. Of 66 given blood transfusion, 17 had subsequent i.v. iron, 25 oral iron and 24 no other form of iron repletion. Of the other 53, nine had i.v. iron, 32 oral iron and 12 had no treatment. Fifty-five per cent of patients were managed according to the proposed guidelines and this occurred less frequently (9%) in those presenting with cardiovascular problems than in those with anaemia, gastrointestinal bleeding or other medical problems (all >60%; $P < 0.0001$, Fisher's exact test).

Conclusion: Current management is haphazard, with underutilization of i.v. iron and failure to initiate any regimen for iron repletion being common. It may be time for a change in approach to repletion of iron in ill patients.

Introduction

Iron deficiency is a common problem recognized in patients admitted to hospital. Iron-deficiency anaemia itself may be the primary reason for admission, it may be a complication of a condition such as inflammatory bowel disease, or iron deficiency with or without anaemia may be an incidental finding in a patient admitted for other reasons. The clinical response to the identification of iron deficiency is to define and treat its cause and to replete iron stores. Repletion of iron stores is clinically important because it can provide a welcome relief of symptoms of anaemia, such as tiredness, easy fatigue and shortness of breath,[1] and can relieve unwanted strain on the heart in the setting of cardiac failure and ischaemic heart disease.[2–4] Correction of iron deficiency when the haemoglobin remains in the normal range may also be important in improving tiredness and mental concentration.[5] For these

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reasons, it is recommended that all patients with iron deficiency should receive iron supplementation.

Published guidelines indicate that oral supplementation is the regimen of choice and that parenteral iron should be used 'when there is an intolerance to at least two oral preparations or non-compliance'.[6] The basis for such a strategy has a poor evidence base. Hence, guidelines are based more on perceptions of safety and efficacy of different strategies than the results of comparative studies. Furthermore, the application of such a strategy might not be appropriate in specific clinical settings, such as for the patient admitted to hospital where iron deficiency is pathogenically important to the primary problem or in association with chronic inflammation such as inflammatory bowel disease.

Guidelines and practice often differ, but how patients admitted to hospital and found to have iron deficiency are treated is not known. Furthermore, concerns voiced regarding the relative neglect in undertreating iron deficiency in specific conditions raise issues of whether published guidelines are still applicable in many situations.[7] This study, therefore, aimed to develop guidelines for the correction of iron deficiency in patients admitted to hospital based on the best evidence currently available and to compare these with current practice in a general hospital in the outer suburbs of Melbourne.

Methods

Development of guidelines

Using PubMed and cross-referencing, published reports pertaining to strategies in the correction of iron deficiency, including efficacy and safety, and to the importance of anaemia and its correction in many clinical scenarios, were identified. A table of the efficacy and safety of different strategies of iron replacement was compiled. Clinical presentations were stratified according to the importance of the iron deficiency to the clinical situation. Practice guidelines for the correction of the iron deficiency were then constructed according to the clinical categories.

Audit of current practice

Patients admitted to Maroondah Hospital from January 2002 to June 2004 with an ICD10 code of iron-deficiency anaemia were identified from the medical record database. Patients were eligible for study if they had appropriate haematological investigation and serum iron studies measured and recorded in the case notes. Patients were included if they had iron deficiency defined by a serum ferritin <100 mg/L (see criteria outlined below).[8] A presumptive diagnosis of iron-deficiency anaemia was not accepted based on low haemoglobin and mean corpuscular volume alone if iron studies were not carried out or did not support that diagnosis.

Patients' case notes were reviewed and demographic data, admission diagnosis, associated conditions, laboratory results, treatment regimens and complications were recorded. Patients were divided into two groups: those with unequivocal iron deficiency where the serum ferritin was <20 μg/L and those with equivocal iron deficiency, as defined by serum ferritin between 20 and 100 μg/L and with a transferrin saturation <20%. The patients were then classified into one of three categories of clinical scenario defined below and their management compared with that of the guidelines developed.

Proportions were compared using Fisher's exact test. A P value less than or equal to 0.05 was considered statistically significant.

Results

Development of guidelines

Two aspects were examined – the relative benefits and risks associated with therapeutic options and the stratification of clinical scenarios.

Comparison of therapeutic options

The three options in managing iron deficiency in the inpatient are blood transfusion, oral iron or parenteral iron. Blood transfusion is a method of rapidly increasing the haemoglobin in situations where anaemia is a threat to life. The indications for transfusion and its risks are well documented.[9] It is not considered primarily an iron replacement therapy.

A comparison of the methods for iron supplementation available in Australia is shown in Table 1. Oral iron is available in most countries in the form of ferrous salts (sulfate, gluconate and fumarate), as tablets, slow-release formulations and elixirs. Iron polymaltose, ferric maltilol and haeme polypeptide are available in limited countries (not Australia). Ferrous salts are cheap, simple and safe to use, with the exception of slow-release formulations in patients with oesophageal or intestinal stenosis, where lodging of the tablet can cause local ulceration. The risks of severe adverse effects are small but there is theoretical, experimental and some clinical evidence that it might exacerbate intestinal inflammation via free oxygen radical production.[10,11] Oral iron enables effective iron repletion in patients who have normal iron absorption but generally at least 3 months of therapy is required to achieve this. However, its efficacy may be impaired by three factors:

- *Side-effects are very common*. Prospective studies have reported incidences of 10–40% and comprise most

Table 1 Comparison of oral iron with the two available forms of i.v. iron

Issue	Oral	i.v.	
		Iron polymaltose	Iron sucrose
Ability to replete iron stores	Reduced when: Reduced absorption – anaemia of chronic disease, coeliac disease Continuing iron loss	Assured	Assured
Speed of repletion of iron stores	Requires prolonged therapy, 3 months	Rapid, one infusion	3–5 weeks (5–10 infusions, 100–200 mg each, weekly or twice weekly)
Adherence to therapy	One in four chance of non-adherence No check on adherence	Assured	Clinically obvious by attendance
Frequency of side-effects	Up to 40%	'Infrequent'†	0.5–1%†
Risks	Exacerbation of intestinal inflammation	Anaphylaxis – rate uncertain (?<0.1%)	Anaphylaxis <0.005%
	Localized gastrointestinal ulceration if stenosis or motility disturbance (slow-release iron preparation)	Skin staining if leakage	Skin staining if leakage
	Black faeces – may be misinterpreted; preclude colonoscoy	Exacerbation of inflammatory arthritis	
Cost	Cheap +	More expensive +++	Expensive ++++
	Drug costs only	Drugs costs (including premedication), pharmacy charge, disposables, bed charge	Drugs costs, pharmacy charge, disposables, ± bed charge
Convenience	Simple, easy	Carried out during admission	Initial infusion carried out during admission but requires repeat infusions. One to two/week for up to 5 weeks
	Preparations purchased over the counter	Premedication optional No need for ongoing tablet taking	No need for premedication No need for ongoing tablet taking

†Manufacturer's product information.

commonly diarrhoea, epigastric discomfort, nausea, severe abdominal pain and vomiting.[12–14] Adherence to oral iron therapy is low, with up to one in four not taking the therapy in prospective studies, presumably because of side-effects.[13]

- *Multiple factors interfere with its absorption.* Concomitant ingestion with food and some medications, such as proton pump inhibitors, may impair iron absorption, but judicious timing of its ingestion and/or the use of concomitant acidification with ascorbic acid can generally overcome these.[15] More concerning is the effect of chronic inflammation itself on intestinal absorption because acute phase responses increase hepcidin secretion by the liver with subsequent reduction in intestinal absorption.[16,17]
- *The level of ongoing loss of iron can outstrip absorption of iron from the gastrointestinal tract.* In situations, such as that which potentially occurs in inflammatory bowel disease, positive iron balance might not be achieved even if absorption of iron was efficient.[7] Indeed, 25% of patients with inflammatory bowel disease failed to replete iron stores despite apparent adherence to therapy.[13]

Iron when given i.m. requires several potentially painful, deep injections (to avoid skin discoloration) and seems inappropriate for the inpatient and will not be considered further. There are currently two preparations of i.v. iron available in Australia – iron polymaltose usually used as a single total dose iron infusion, and iron sucrose, of which up to 300 mg can be safely given at one infusion.[18] Iron gluconate is also available in some countries in Europe and USA. The high risk of life-threatening anaphylactic reactions (0.61%) with iron dextran led to its withdrawal from the market.[19] As there have been no large series reported for the use of iron polymaltose, the risk of anaphylaxis cannot be definitively determined. However, small series, such as 62 patients with chronic renal failure,[20] 50 pregnant women[21] and a three-hospital retrospective review of adverse effects of 380 infusions of i.v. iron polymaltose,[22] showed no episodes of anaphylaxis and no serious adverse events. Reviews of tens of thousands of infusions with iron sucrose in the setting of chronic renal disease,[23] obstetrics[24,25] or inflammatory bowel disease[1,26] have consistently shown excellent tolerability and no episodes of anaphylaxis.

However, the rate of 'serious anaphylaxis hypersensitivity' has been reported to be 0.002% with iron sucrose and the 'hypersensitivity rate' has been reported to be 0.0005%.[27]

The efficacy of oral and i.v. iron has been compared in observational studies and in randomized controlled trials in four settings: chronic renal diseases, obstetrics, inflammatory bowel disease and autologous blood transfusions.

- *Chronic renal disease.* In patients with chronic renal failure, i.v. iron therapy was more efficacious than oral iron, without increased mortality and morbidity when used in accordance with clinical practice guidelines.[28–30] The i.v. iron may also be efficacious where oral iron had failed.[30]
- *Obstetrics.* Three studies have shown i.v. iron to be superior to oral iron during pregnancy. In the first, i.v. iron polymaltose resulted in higher levels and rates of increased haemoglobin as well as significantly higher levels of iron stores than did oral iron fumarate.[21] Similarly, in the second study, i.v. iron sucrose achieved better tolerance and higher mean haemoglobin and ferritin levels than did oral ferrous sulfate.[24] In the third study, i.v. iron repleted iron stores superiorly to oral iron but there was no difference in haemoglobin levels.[31]
- *Inflammatory bowel disease.* In a study of 59 patients, i.v. iron sucrose induced a clinically significant elevation of haemoglobin in 91% within 12 weeks without toxicity.[26] Furthermore, in a randomized controlled trial of patients with Crohn's disease, response to i.v. iron alone had twice the effect on haemoglobin levels as did erythropoietin combined with oral iron.[32]
- *Autologous blood transfusion.* The i.v. iron sucrose permitted more units of blood to be donated than did oral iron supplements in a randomized study[33] and had a greater benefit than oral iron when combined with erythropoietin.[14] However, no benefit was observed when iron deficiency was not present.[34]

In summary, evidence indicates that i.v. iron is more efficacious than oral iron in iron deficiency associated with increased need and reduced absorption of iron. It normalizes haemoglobin faster and more reliably than oral iron, which commonly induces side-effects, has poor patient adherence and may not replete iron stores even when taken at recommended dosage. There is no recognizable increase in risk with i.v. iron polymaltose (as a total dose infusion) or iron sucrose (at maximum 300 mg per infusion).

Stratification of clinical scenarios

Patients admitted to hospital and found to have iron deficiency were categorized into three clinical scenarios and these are outlined in Table 2. The first scenario (A) is that there may be associated life-threatening anaemia and/or ongoing large volume blood loss, in which cases blood transfusion is required to urgently raise the haemoglobin level. The second scenario (B) is that the iron deficiency is of immediate relevance to the disease process or symptoms of presenting illness and its correction is likely to improve the clinical problem. Anaemia is of particular importance in the presence of compromised

Table 2 Proposed guidelines for iron replacement therapy in patients admitted to hospital

Scenario	Details	Examples	Treatment proposed
A. Urgent attention to haemoglobin	Life-threatening anaemia and/or presence of ongoing large volume blood loss	• Severe anaemia • Anaemia and heart failure • Anaemia and unstable angina • Acute on chronic blood loss	Blood transfusion + subsequent iron replacement therapy as per scenario B
B. Semi-urgent iron repletion	Iron deficiency is of immediate relevance to the disease process or symptoms of presenting illness, and its correction likely to improve the clinical problem	• Severe iron-deficiency anaemia • Increased cardiac workload might be poorly tolerated, heart failure, ischaemic heart disease • Ongoing loss of iron and/or poor iron absorption (inflammatory bowel disease, other chronic inflammatory or malignant conditions, chronic renal failure) • Black stools unwanted (recent melaena, require colonoscopy) • Require surgery associated with potential blood loss	i.v. iron
C. Non-urgent iron repletion	Incidental iron deficiency noted in patients with other conditions that would not be compromised by the presence of iron deficiency		Oral or i.v. iron according to individual situation (e.g., patient preference, efficiency of iron absorption)

cardiac function or perfusion.[2–4] The effect of iron deficiency in patients with inflammatory bowel disease[1] or in pregnant mothers[25] may also be considerable and published reports abound with the importance of correcting iron deficiency effectively in chronic renal failure.[23] Likewise, patients soon to undergo surgery with a risk of blood loss who are found to be iron deficient should benefit from semi-urgent iron repletion to improve their recuperative abilities postoperatively.[35] The black stools associated with oral iron also impair the ability to interpret stools after an upper gastrointestinal bleed and are detrimental to the quality of colonoscopy because of the absorption of light. The third scenario (C) is one where iron deficiency is noted incidentally in patients with other conditions that would not be compromised by its presence.

Treatment guidelines

Table 2 outlines suggested treatment approaches for the three scenarios based on the discussion above. In scenarios A and B, i.v. iron is indicated based on the certainty and rapidity of iron repletion and the low risk of inducing adverse effects in sick patients. In non-urgent situations (scenario C), the choice of iron replacement therapy rests with different issues. The cheap and simple approach of oral iron would often be appropriate and i.v. iron used if not tolerated or successful.

Audit of current practice

Over the 2-year period, 267 patients had been classified as iron deficient but only 119 (45%) met the inclusion criteria. The remaining 148 patients were excluded for various reasons including insufficient data, lack of iron studies, severe macrocytosis, haematological malignancy and a serum ferritin >100 μg/L.

Iron studies divided the group into the categories of unequivocal iron deficiency and equivocal iron deficiency approximately equally. Demographic information, summary data of key haematological and biochemical tests and the admitting problem are outlined in Table 3. The admitting problem was classified into five groups – anaemia, cardiovascular causes (comprising ischaemic heart disease and cardiac failure), gastrointestinal bleeding (overt or occult), miscellaneous medical causes and surgical/orthopaedic causes. Patients were admitted under the care of

Table 3 Demographics, results of investigations, admission diagnoses and treatment given for iron deficiency

		Iron deficiency	
	Whole group	Unequivocal†	Equivocal‡
Number	119	69	50
Age (years): median age (range)	77 (18–99)	72 (18–95)	81 (25–99)
Sex			
Women	85 (71%)	50 (73%)	35 (70%)
Men	34 (29%)	19 (28%)	15 (30%)
Haemoglobin (g/L): median (range)	87 (33–130)	82 (33–125)	89 (50–130)
MCV (fL): median (range)	76 (52–96)	72 (52–92)	82 (64–96)
Ferritin (μg/L): median (range)	15 (1–95)	9 (1–20)	44 (21–95)
Transferrin saturation (%): median (range)	6 (2–36)	4 (2–36)	10 (2–20)
Admission diagnosis			
Anaemia	24 (20%)	22 (32%)	2 (4%)
Cardiovascular causes	23 (19%)	15 (21%)	8 (16%)
Gastrointestinal bleed	13 (11%)	6 (9%)	7 (14%)
Other medical causes	53 (45%)	23 (33%)	30 (60%)
Surgical/orthopaedic	6 (4%)	3 (4%)	3 (6%)
Treatment			
Blood transfusion only	24 (20%)	16 (23%)	9 (18%)
Blood and iron infusion	17 (14%)	12 (17%)	5 (10%)
Blood and oral iron	25 (21%)	14 (20%)	10 (20%)
Iron infusion only	9 (8%)	5 (7%)	4 (8%)
Oral iron only	32 (27%)	17 (25%)	15 (30%)
No treatment given	12 (10%)	5 (7%)	7 (14%)

†Serum ferritin ≤20 μg/L.

‡Serum ferritin 21–100 μg/L, transferrin saturation <20%.

General Medical Units for all but gastrointestinal bleeding (under the care of the Gastroenterology Unit) and surgical causes. For patients with cardiac problems, the Cardiology Unit contributed to management on a consultative basis.

Of the 50 patients with equivocal iron deficiency, 30 were admitted with miscellaneous medical causes. Of these, nine had infective causes including urinary tract infection, pneumonia and cellulitis, five had exacerbation of chronic obstructive airways disease with possible lung infection, one had stroke and the remaining 15 had miscellaneous problems such as syncope, fall, general debility and difficulty coping at home. Only three patients in this group and one with unequivocal iron deficiency had haemoglobin levels within stated normal range (women >110 g/L, men >120 g/L).

The treatment given to patients specifically for iron deficiency and/or anaemia while inpatients or on discharge from the hospital is also shown in Table 1. Blood transfusions were given to the majority of patients (55%); 26% of these patients were also given a total dose iron infusion (iron polymaltose) and 38% were prescribed oral iron. The remaining 36% received no further iron supplementation during admission or on discharge. Twenty-two per cent of all patients received an iron infusion and none had ongoing oral iron therapy. Oral iron was the only therapy offered in 27% and no treatment at all was instituted in 10% of patients. There were no significant differences in the treatment offered to patients with unequivocal iron deficiency compared with those with equivocal iron deficiency (data not shown).

Complications of the therapy were uncommon. Fluid overload and pulmonary oedema complicated blood transfusion in four patients, one admitted with gastrointestinal bleeding and three with cardiovascular causes. Iron infusions were given following premedication with corticosteroids and antihistamine. They were associated with mild reactions in two patients – urticaria in one and a febrile reaction in the other – but the iron infusion could be completed at a slower rate in both. None of the patients treated with oral iron had problems documented while an inpatient.

Comparison with proposed treatment guidelines

Patients were retrospectively classified into one of the three clinical scenarios defined in the proposed guidelines shown in Table 2. The classification according to admitting problem is shown in Figure 1. The distribution of scenarios differed according to the admitting problem, with patients in scenario A mainly presenting with anaemia or gastrointestinal bleeding and scenario B being more common in patients with cardiovascular or surgical causes.

Overall, 55% of patients were managed according to the proposed guidelines. As shown in Figure 2, there was a marked difference in results across the admitting problems. Only 9% of patients with cardiovascular problems were managed according to the guidelines in contrast to more than 60% presenting with anaemia, gastrointestinal bleeding and other medical problems ($P < 0.0001$ for all, Fisher's exact test). The results were similar if the subgroup with low serum ferritin were analysed alone (Fig. 2).

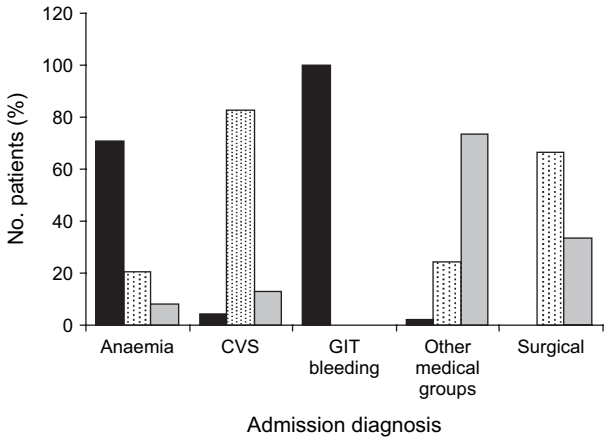

Figure 1 Classification of patients with different admission problems into clinical scenarios (■) A, (⁝⁝) B and (▨) C, according to the guidelines outlined in Table 2. CVS, cardiovascular problems; GIT, gastrointestinal bleeding.

Discussion

Iron deficiency is common, especially in a population admitted to hospital, because the median age is older and many admitting conditions are associated with blood loss and/or reduced absorption.[36] This was confirmed in

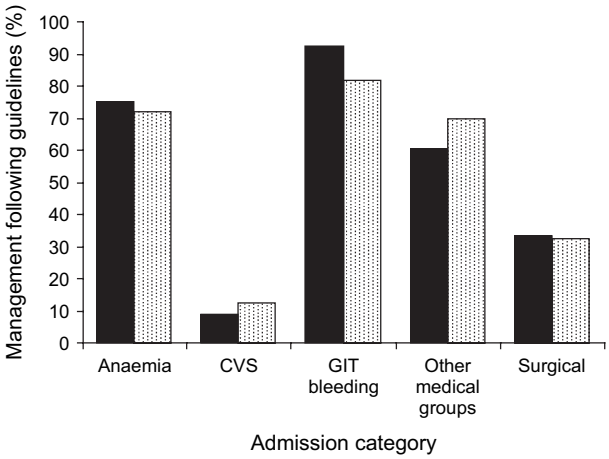

Figure 2 Proportions of iron-deficient patients, classified by the admitting problem, who were managed according to the guidelines shown in Table 2. The proportion of patients in the cardiovascular (CVS) group was significantly less than that in the anaemia, gastrointestinal (GIT) bleeding and other medical groups (all $P < 0.0001$; Fisher's exact test). ■, all; ⁝⁝, ferritin <20 mg/L.

this study carried out at a community hospital with 309 beds, in which 119 patients with definite or equivocal iron deficiency were identified over a 2.5-year period, in addition to many other patients with likely iron deficiency but without confirmatory diagnostic tests carried out during the relevant admission. Previous studies have found shortcomings in the rate of recognition of iron deficiency, particularly in the elderly population, and its subsequent investigation. However, the practice of iron replacement therapy has seldom been scrutinized.[37] The current audit of practice indicates considerable heterogeneity in the approaches taken.

The question arises whether such heterogeneity of management actually matters. The results clearly indicate that it is a serious problem because 27% of patients were discharged from hospital without a plan of iron replacement management being instituted, even when the iron deficiency was appropriately recognized. Similar findings were reported 27 years ago.[37] The application of guidelines for management is one way of tackling deficiencies of clinical management so that performance can be better judged. Published guidelines and management principles outlined in textbooks are, however, at odds with current evidence.[6] For these reasons, simple guidelines based on published evidence and logical extrapolation were devised in this study.

Applying these guidelines to the audited population indicated heterogeneity of approach according to the organ system underlying the primary reasons for admission. Thus, gastroenterological problems were often managed as per the guidelines, whereas cardiological problems were not. The divergence is not surprising as iron deficiency is a core business for the gastroenterologist and not the cardiologist. However, the importance of effective management of anaemia in patients with cardiac disease has received considerable attention. Correction of anaemia using erythropoietin and i.v. iron reduces mortality and length of stay in hospital.[2–4]

The reasons why the proposed guidelines differ from previous ones deserve further attention. Four major factors have dictated a need to change approach.

- The understanding of iron absorption has advanced considerably in recent years. The key role for hepcidin, an acute phase reactant, in reducing iron absorption in chronic inflammatory conditions has altered the notion stated widely (e.g., Goddard *et al.*[6]) that reduced iron absorption is seldom an issue in iron deficiency.[16,17] It offers a more reasonable explanation for the frequency of iron deficiency in chronic inflammatory conditions and for the poor response to oral iron often observed.
- Anaemia of chronic disease has previously been considered unresponsive to iron supplementation and requires therapy with erythropoietin. Although this might be true of oral iron, several studies have shown response to i.v. iron alone.[30,38,39] Thus, 'functional iron deficiency' associated with chronic inflammation and other severe illnesses, where iron stores may not be low but iron release for biological processes is inhibited, may be overcome in many patients by i.v. iron therapy.[40]
- Comparative studies in specific situations, such as pregnancy, chronic renal failure and inflammatory bowel disease, have indicated that there are differences in the efficacy between oral and i.v. delivery of iron.
- Safety issues that previously hindered the use of i.v. iron, particularly the chance of anaphylactic reaction that was associated with the now withdrawn iron dextran, are no longer valid with current preparations. Concerns regarding the effects of free radical formation or free iron in the circulation, increased susceptibility to infection and risk of cardiovascular disease remain theoretical and are poorly supported.[23]

In conclusion, the current audit of the management of iron deficiency in patients being admitted to hospital indicates haphazard management resulting in the failure to address iron replacement therapy in one in four of those patients. Recent evidence indicates that more aggressive iron replacement using the i.v. route should be applied at least in patients where the iron deficiency is an important potential contributor to mortality and/or morbidity. The guidelines produced might permit a starting point of debate as to whether general opinion and practice in treatment approach should change.

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