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IRON DEFICIENCY ANAEMIA IN CKD

Standardising diagnosis and management

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Iron deficiency anaemia in chronic kidney disease: an overview

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Clinicians face many challenges when diagnosing and managing patients with this complication. Although national guidelines are available, their lack of consistency is causing confusion. This problem is compounded by the fragmented service provision available for this patient group, which is hindering interdisciplinary teamworking. Clearly, a new approach to this problem is needed

Chronic kidney disease (CKD) is a significant health burden with many complications. Anaemia is common even in the early stages of CKD and can have a significant impact on patients' morbidity and quality of life. There is some evidence to suggest anaemia in CKD is underdiagnosed and undertreated (Stack et al, 2018). The guidelines for the assessment and management of anaemia in patients with CKD are inconsistent and so can add to difficulties with management. Iron and erythropoiesis stimulating agents (ESAs) are the mainstay of treatment. Treatment with iron can be fraught with difficulties in relation to the route of administration, access to services and differences in service provision. Clear, unified guidelines and treatment pathways are needed to ensure patients with anaemia are assessed and treated appropriately, regardless of the CKD stage.

CHRONIC KIDNEY DISEASE

CKD is an abnormality in kidney structure or function that has been present for more than 3 months. This definition also includes the presence of indicators of kidney damage (proteinuria, haematuria, electrolyte disturbance due to tubular dysfunction, renal histological abnormalities, structural abnormalities or a history of kidney transplantation) or an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73m^2 on at least two occasions 90 days apart. The estimated prevalence of CKD in the UK is between 5% and 7% (Iwagami et al, 2017).

To further risk-stratify these patients, the severity of CKD is subdivided by eGFR and the level of albuminuria. Patients are classified as having stage G1, G2, G3a, G3b, G4, G5 CKD, based on eGFRs of ≥90, 60–89, 45–59, 30–44, 15–29 and 15 ml/min/1.73m^2 respectively, with a suffix of A1–A3 based on level of albuminuria (<3 mg/mmol, 3–30 mg/mmol and > 30 mg/mmol respectively) (Summary of Recommendations, 2013).

The National Institute for Health and Care Excellence (NICE) CKD guidelines have summarised when referral to nephrology should take place (NICE, 2015a). They advise that patients should be referred to nephrology if they have a GFR of less than 30ml/min/1.73m^2 with or without diabetes; if there is a sustained decrease in eGFR of ≥ 25% and a change in GFR category or a decline in GFR of 15 ml/min/1.73m^2 within a 12-month period. A referral may be also indicated if there are other indicators of kidney disease or a progressive decline in renal function at higher levels of GFR, Stable CKD stages G1–3 can be managed by primary care. Referral should be made in line with patient wishes and consideration of their comorbidities. The Renal Association advises that, in most cases, initial assessment of patients with CKD stage G3 should take place in primary care, with the aim of identifying those at risk of progressive renal decline (Renal Association, 2018),

Complications of CKD are multiple and heterogeneous. They include fluid overload, electrolyte disorders such as hyperkalaemia (elevated potassium level in blood), mineral bone disorders, metabolic acidosis (increased acid level in the body), hypertension, sexual dysfunction, dyslipidaemia (excess lipids in the blood) and anaemia.

ANAEMIA IN CHRONIC KIDNEY DISEASE

Anaemia is a common feature of CKD that increases in prevalence with worsening kidney function and affects nearly all patients with stage G5 CKD (Kidney Disease: Improving Global Outcomes (KDIGO), 2006). Typically, anaemia related to CKD is normocytic (normal sized red blood cells), normochromic (insufficient numbers but normal haemoglobin content of red blood cells) and hypoproliferative (inadequate bone marrow response) (Babitt and Lin, 2012). Iron deficiency is also common in patients with CKD. Iron deficiency anaemia (IDA) is usually microcytic (small red blood cells), hypochromic (reduced haemoglobin content of red blood cells) with a low ferritin. It is estimated that over half of patients with CKD stage G3 and G4 are iron deficient (Fishbane et al, 2009). An epidemiological study found that 17.4% of patients with CKD stage G3 were anaemic, rising to 50.3% of those with stage G4 CKD and 53.4% of those with CKD stage G5 (Stauffer and Fan, 2014). A large

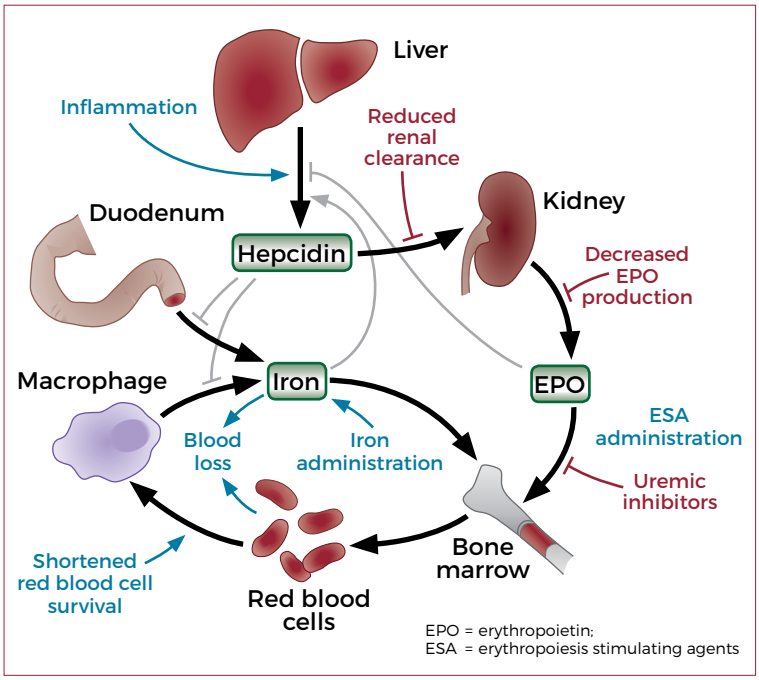

Figure 1. Pathophysiology of anaemia in chronic kidney disease (CKD). The black and grey arrows represent normal physiology; the red and blue arrows indicate the additional effects of CKD. (adapted from Babitt et al, 2012)

cross-sectional study of 112 215 patients found that the prevalence of anaemia was 15.3% in patients with CKD stage G3–5 and that the Hb level was <110 g/l in 3.8%, which is equivalent to over 108 000 of the population, based on 2001 census population figures (De Lusignan et al, 2005). The prevalence of anaemia will vary depending on the reference range used and the populations being studied.

CKD-related anaemia is associated with reduced quality of life, cardiovascular disease, increased hospitalisations and mortality (KDOQI, 2006). Fraenkel (2015) described the associations of anaemia of chronic disease with 'critical illness, obesity, aging, and kidney failure, as well as with the well-established associations of cancer, chronic infection, and autoimmune disease'.

AETIOLOGY AND PATHOPHYSIOLOGY OF ANAEMIA IN CKD

The aetiology of anaemia in CKD is thought to be multifactorial, with erythropoietin (EPO) deficiency, uraemia-induced inhibitors of erythropoiesis, shortened red cell survival, deficiencies in nutrients such as folate and vitamin B_{12} and disordered iron homeostasis all thought to play a role (Babitt and Lin, 2012).

Hepcidin is the main hormone controlling the homeostasis of iron within the body (Babitt and Lin, 2010); it has relatively recently been identified as a contributor to the iron deficiency commonly found in CKD patients. Excess hepcidin can also lead to impaired absorption of dietary iron and mobilisation of iron from existing body stores (Babitt and Lin, 2012).

Iron deficiency can be further subdefined into absolute iron deficiency anaemia and functional iron deficiency anaemia. Systemic iron homeostasis is maintained by the balance of iron absorption from diet and iron release from storage locations in the liver and reticuloendothelial macrophages (Babitt and Lin, 2012). Impaired iron absorption in the CKD population can lead to absolute iron deficiency. The use of erythropoietin stimulating agents (ESAs) in this population can stimulate erythropoiesis, thus depleting the circulating iron stores (Babitt and Lin, 2012). Babitt and Yin also described that functional iron deficiency is 'characterised by impaired iron release from body stores that is unable to meet the demand of erythropoiesis (also called reticuloendothelial blockade). These patients have low serum transferrin (a measure of circulating iron) and normal or high serum ferritin (a marker of body iron stores)' (Babitt and Yin, 2012). In patients with CKD, there is also a risk that anaemia may be exacerbated by the medications they are taking. Medication such as ACE-inhibitors/ARBS and immunosuppression can all contribute to anaemia.

Figure 1 shows a schematic representation of the various factors that contribute to anaemia in the CKD population (Babitt and Lin, 2012).

CLINICAL IMPACT OF ANAEMIA

The consequences of anaemia are significant. Anaemia leads to hypoxia, which gives rise to peripheral vasodilatation, thereby lowering blood pressure. This, in turn, activates the sympathetic and renin angiotensin aldosterone system (RAAS) to maintain the blood pressure. Stroke volume and heart rate increase, which, along with an activated RAAS, can cause renal ischaemia, fluid retention and increased plasma volume. This leads to increased cardiac load, which eventually progresses to heart failure. Chronic anaemia can also cause left ventricular hypertrophy (LVH), which can lead to myocardial fibrosis, cardiomyopathy and heart failure (Silverberg et al, 2001).

Patients with anaemia can have non-specific symptoms and signs such as tiredness and fatigue, shortness of breath, palpitations and skin pallor. Covic et al (2017) reviewed data from patients with CKD in continental Europe and the UK to quantify the impact of cardiovascular disease and anaemia in those with non-dialysis CKD (ND-CKD). They found that 61.4% of this population were anaemic. Within this cohort, there was a higher mean number of cardiovascular comorbidities,

which were associated with significant reductions in quality of life, work productivity and activity impairment. This was seen particularly in the patients with anaemia.

ASSESSMENT OF ANAEMIA IN CKD

Guidance on assessment and treatment of CKD-related anaemia is provided by NICE (incorporated in the Renal Association guidance) (NICE, 2015b) and KDIGO (Mikhail et al, 2017). There are variations between them. Guidance on screening and diagnosis is summarised in *Table 1*.

Low serum ferritin can be useful in diagnosing absolute iron deficiency. Normal or raised ferritin does not exclude iron deficiency, as this could be raised due to infection or inflammation (Mikhail et al, 2017). Other red cell indices and C-reactive protein (CRP) levels can be used to diagnose iron deficiency in anaemic patients with raised ferritin.

Both guidelines advise that CKD should be considered as the possible cause of anaemia when GFR is <60 ml/min/1.73m^2. However, it is more likely to be the cause when the GFR is <30 ml/min/1.73m^2 (Mikhail et al, 2017; KDIGO, 2012). New et al (2008) studied the prevalence of anaemia by CKD stage in the general diabetic population. They found that people with CKD stage G3 accounted for the largest proportion of people with anaemia (18%). This could mean that a significant number of people with early stage CKD are not known to nephrologists and are being under-treated for anaemia.

TREATMENT AND MONITORING OF IRON DEFICIENCY ANAEMIA IN ND-CKD

Both guidelines highlight similar key concepts in terms of screening and diagnosis of anaemia (*Table 2*). Once all other causes have been ruled out, and iron deficiency has been established, treatment depends on other factors such as:

- Severity of IDA/anaemia
- Previous response to treatment
- Side effects
- Availability of intravenous (IV) access
- Need to start ESA.

Other factors to take into account regarding route of administration are:

- Preferences of the patient or family/carers
- Nursing/administration costs
- Cost of local drug supply
- Provision of resuscitation facilities (advised when administering IV iron due to risk of anaphylaxis).

When giving IV iron, NICE advises a high-dose, low-frequency regimen be considered.

ORAL VERSUS IV IRON

The FIND-CKD study found that IV ferric carboxymaltose resulted in the target haemoglobin level being reached quicker compared with oral iron, and that ferritin and haemoglobin levels were similarly well maintained (Macdougall et al, 2014). It reported a delayed or reduced need for other treatments for anaemia, including ESA. There was no difference in cardiovascular or infectious events.

In a further analysis of the FIND-CKD data, Macdougall et al (2017) found that ND-CKD patients responded poorly to oral iron, with only 21.6% of anaemic patients seeing a rise in their Hb of 1 g/dL or more. Kalra et al (2016) also found that IV iron (iron isomaltoside) was more effective than oral iron in increasing haemoglobin in the ND-CKD population. In their randomised controlled trial, Pisani et al (2015) found that oral liposomal iron, although slower to raise haemoglobin, resulted in similar final haemoglobin levels to IV iron gluconate. When treatment was stopped, however, IV iron was found to maintain iron stores for longer than did oral iron. In addition, the oral

TABLE 1. SCREENING AND DIAGNOSIS OF ANAEMIA IN CKD BASED ON NICE AND KDIGO GUIDELINES

	NICE (2015b)/ Mikhail et al (2017)	KDIGO (2012)
Screening	Annually for chronic kidney disease (CKD) G3	Annually for CKD G3
	Twice a year for non-dialysis-chronic kidney disease (ND-CKD) G4–G5	Twice a year for ND-CKD G4–G5
Diagnosis	Investigate for cause if haemoglobin (Hb) < 110g/l or symptomatic	Hb < 130 g/l in males Hb < 120 g/l in females
	Do not check erythropoietin levels routinely	Do not check erythropoietin levels routinely
Further indices	Full blood count, red cell indices, white blood cells + differentials, platelets, reticulocyte count, transferrin saturation (TSATS) and ferritin	Full blood count, red cell indices, white blood cells + differentials, platelets, reticulocyte count, transferrin saturation (TSATS) and ferritin
	Also check: • % hypochromic red cells (HRC) or reticulocyte Hb (CHr) count or • C-reactive protein (CRP)	Also check: • B12 • Folate
	May need to check: • B12 • Folate • Haemolysis screen • Serum/urine electrophoresis • Serum-free lights chains • Bone marrow examination	

TABLE 2. TREATMENT AND MONITORING AS PER NICE AND KDIGO GUIDELINES

	NICE (2015b)/Mikhail et al (2017)	KDIGO (2012)
Iron treatment	Advises iron treatment if: ● % hypochromic red cells >6% ● Reticulocyte Hb (CHr) <29 pg ● Ferritin <100 ng/ml and TSATS <20%	1–3 month trial of oral iron if: ● Transferrin saturation (TSATS) ≤30% or ferritin ≤ 500 ng/ml
	Oral iron sufficient in non-dialysis-chronic kidney disease (ND-CKD) and peritoneal dialysis. Intravenous (IV) if intolerant or target haemoglobin (Hb) not reached in 3 months	Avoid IV iron during active infections
ESA treatment	Offer to patients who are likely to benefit in terms of quality of life and physical function, or who want to avoid blood transfusions, especially potential transplant recipients	Address treatable causes of anaemia before erythropoiesis stimulating agents (ESA) treatment
		As per NICE/Mikhail et al (2017)
		No specific target
Monitoring	Hb every 1–3 months when on ESA	TSATS and ferritin every 3 months
	Iron status every 1–3 months when on iron supplementation	
Target	Hb 100–120 g/l	No specific target

iron associated with a lower incidence of adverse events.

The safety profile of IV iron has been questioned. In 2013, the Medicine and Healthcare products Regulatory Agency (MHRA) released guidance on the administration of IV iron and advised that it should only be given in areas where the staff have been trained to manage anaphylactic and anaphylactoid reactions and resuscitation equipment is available (MHRA, 2014). Agarwal et al (2015) found that IV iron was associated with increased risk of serious adverse events, including cardiovascular and infectious episodes. However, Roger et al (2017) found, in a further analysis of the FIND-CKD study, that cardiac and infectious events were similar between the IV and oral iron groups, supporting the safety profile of IV iron.

Along with the CKD trials, there are several important studies in patients with heart failure that have led the European Society of Cardiology (ESC) and the Scottish Intercollegiate Guidelines Network (SIGN) to recommend the use of IV iron only in patients with iron deficiency anaemia and chronic heart failure (Ponikowski et al, 2016; SIGN, 2016). The FAIR-HF trial looked at patients with chronic heart failure with iron deficiency to determine the effect of IV iron repletion therapy using self-reported patient global assessment (Anker et al, 2009). The subsequent CONFIRM-HF study showed that treatment with IV iron led to an improvement in functional capacity, symptoms and quality of life, and may be associated with a reduced risk of hospitalisation due to an exacerbation of heart failure (Ponikowski et al, 2015). The IRONOUT-HF study found that oral iron supplementation did not lead an increase in exercise capacity in patients with heart failure and reduced ejection fraction (Lewis et al, 2017).

USE OF EYTHROPOIESIS-STIMULATING AGENTS

Along with iron treatment, ESAs are the mainstay of treatment for anaemia in CKD patients. ESAs should be commenced when all other causes of anaemia have been evaluated and treated and patients should be iron replete. However, the CHOIR study found that achieving a higher haemoglobin level with the use of ESAs was associated with a higher risk of death, hospitalisation for heart failure and myocardial infarction (Singh et al, 2006). In addition, patients in the higher haemoglobin target group were more likely to have more than one adverse event. Quality-of-life improvements were largely the same in the two groups. The TREAT study found that treatment with darbepoetin alfa in patients with diabetes, CKD and anaemia did not reduce the risk of death or cardiovascular events, but did increase the risk of stroke (Pfeffer et al, 2009). As result, it is advised that high-dose ESAs be used with extreme caution in this group of patients (Mikhail et al, 2017).

A meta-analysis comparing possible adverse events to ESA found that the higher the haemoglobin level achieved with this treatment in CKD patients, the higher the risk of stroke, hypertension, vascular access thrombosis, serious cardiovascular events and end stage renal disease; there was also a possible association with an increased risk of death (Palmer et al, 2010).

There is further concern about the use of ESAs and malignancy. The TREAT study found that, in patients with a history of cancer, the mortality was higher in the ESA-treated group (Pfeffer et al, 2009). Consequently, it is advised that ESA should be used with extreme caution in patients with a history of malignancy (especially active cancer with an anticipated cure) (Mikhail et al, 2017).

Some patients do not respond as expected to ESA treatment. ESA resistance is defined as 'failure to reach the target Hb level despite subcutaneous epoetin dose > 300 IU/kg/week or darbopoetin dose > 1.5 microgram/kg/week. Hyporesponsive patients who are iron replete

should be screened clinically and by investigations for other common causes of anaemia' (Mikhail et al, 2017). Rarely, anti-erythropoietin antibodies are formed, leading to pure red cell aplasia (PRCA) and ESA resistance. Immunosuppression is usually needed in these cases, although some respond to ESA cessation (Mikhail et al, 2017).

NOVEL AND EXPERIMENTAL APPROACHES

Novel treatments are being researched to improve the treatment options for CKD-associated anaemia. Zhong et al (2018) reviewed nine studies using hypoxia-inducible factor (HIF) stabilisers for the treatment of anaemia. The meta-analysis found that HIF-stabilisers were an effective treatment for anaemia in the ND-CKD population and were safe for short-term use. These novel treatments show promise; however, as yet none are approved for clinical use.

PRACTICAL CONSIDERATIONS AND CHALLENGES

There are multiple challenges to the effective and efficient diagnosis and treatment of CKD-related anaemia. There are many guidelines, but their advice differs on the diagnosis and treatment of anaemia. Multiple blood tests are required as part of the screening process and their interpretation is not always straightforward, especially as there are often confounding factors such as intercurrent infection (leading to raised ferritin, for instance).

When managing patients with CKD stage G3, various considerations need to be taken into account. Although many NHS hospital trusts have specialist nurses who manage IDA and administer IV iron, different specialties, such as gastroenterology, cardiology, haematology and preoperative assessment clinics, will have different care pathways. If there is little integration between these specialties, there will be various service and funding models operating within the same trust. Often, there is no overarching 'anaemia team' to coordinate anaemia management (of any cause) via a common pathway.

The elderly population with CKD can further challenge the management of anaemia. Nilsson-Ehle et al (2000) found that there was a significant decline in haemoglobin in healthy men aged 70–88 and a less-pronounced one in women. Using the World Health Organization (WHO) criteria to define anaemia, McCartney et al (2017) undertook a retrospective primary care-based study of people aged >65 years undergoing a full blood count in Oxfordshire. Of this population, 29.6% were anaemic, with the majority (82.4%) having a normocytic anaemia. Goddard et al (2011) discussed the continued lack of consensus on what level of anaemia requires further evaluation in an older population, and that the limited guidance available on the sequence of investigation could be contributing to the number of elderly people referred to renal anaemia services.

For many frail and elderly patients, care closer to their homes within the community could be of benefit. Caring for the needs of patients with long-term conditions should involve partnerships between primary care, secondary care and patients, rather than the NHS providing single, unconnected episodes of care. The Five Year Forward View describes 'how the health service needs to change, arguing for a more engaged relationship with patients, carers and citizens so that we can promote wellbeing and prevent ill-health' (NHS England, 2014). It puts forward a new model of healthcare that could see the emergence of the 'multispeciality community provider', whereby groups of GPs combine with nurses, hospital specialists and others to create integrated out-of hospital care or primary and acute care systems that combine general practice and hospital services. Community-based anaemia clinics could potentially improve the patient experience, but provisions would need to be implemented to support community health care providers with this.

Nurse-led community anaemia clinics could provide improved treatment for IDA for those with early stage CKD. Patients with CKD are often multi-morbid, leading to polypharmacy. There is a complex relationship between polypharmacy and non-adherence, which has cost and clinical implications (McKillop and Joy, 2013). Community-based nurses can be well placed to encourage patients to actively participate in treatment. Cancelo-Hidalgo et al (2013) found that the incidence of oral iron-related adverse events can be up to 47% and that adherence is a significant problem in iron administration programmes. The introduction of anaemia management protocols, inclusive of parenteral iron in community-based clinics with resuscitation facilities, could reduce the number who have a poor response to treatment. Furthermore, renal nurses can have a major impact on patient outcomes by improving patient education and concordance (Wish and Weigel, 2001).

CONCLUSION

There is a high prevalence of anaemia in the ND-CKD population. A large proportion of these patients are iron deficient. Anaemia can develop in the early stages of CKD and be unrecognised and undertreated (New et al, 2008), resulting in significant morbidity. Patients with early stage CKD are likely to be managed in the community, where there may be a lack of familiarity with the guidelines on the management of the condition and lack of access to necessary treatments such as IV iron or ESA. A streamlined and simplified approach is required, with primary and secondary care access to the required services.

CKD-related anaemia should be a diagnosis of exclusion and there should be prompt referral to specialist services, if required. A trial of oral iron should

be based on patient preference, previous tolerance and effects, and the need to avoid ESA treatment (previous stroke, malignancy). A review of IV iron services at local, regional and national levels should be undertaken, with an assessment of commissioning arrangements to streamline services and improve patient treatment and experience.

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The challenges of managing iron deficiency anaemia in chronic kidney disease: survey results

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An online survey, conducted via the *Journal of Kidney Care*, identified variations in knowledge about iron deficiency anaemia (IDA), as well as concerns about the ease with which national guidance on its management can be implemented. The results highlight the need to simplify and standardise recommendations on the management of IDA

Chronic kidney disease (CKD) is a relatively common long-term condition that is estimated to affect 5–7% of the population (Couser et al, 2011). It is more common in people with diabetes and hypertension, and affects an estimated 33% of those aged over 75 years (Public Health England, 2014). It increases the risk of cardiovascular disease (CVD) by twofold to fourfold, and people with stage 3a or 3b CKD are more likely to die from CVD than progress to kidney failure (Gansevoort et al, 2013).

People with stable CKD stages 3a and 3b are often managed by non-renal specialists or in primary care; those with CKD stages 4 and 5 are usually managed in renal centres.

Anaemia is a recognised complication affecting an estimated 15.4% of people with CKD, which becomes more common as kidney function worsens (Stauffer and Fan, 2014). Anaemia is more prevalent in CKD patients who also have diabetes; it is of greater severity and develops at earlier stages of CKD in diabetics compared with non-diabetics (Al-Khoury et al, 2006). It can exacerbate symptoms reported by patients with CKD such as fatigue and weakness, and contributes to the development of CVD (Macdougall, 2013). Anaemia in CKD may be caused by iron and/or erythropoietin deficiency. Iron deficiency anaemia (IDA) can be treated with iron supplementation but anecdotal reports from renal anaemia specialist nurses suggest that opportunities to recognise and treat it early may be missed. Treatment of erythropoietin deficiency in CKD is usually managed by renal centres.

Vifor Pharma is a pharmaceutical company that researches, develops and manufactures intravenous (IV) iron products. It aims to identify issues and generate solutions that will help improve renal anaemia management and, ultimately, patients' quality of life. The company believes that a better understanding of the challenges that are faced by health professionals is an essential precursor to the development of strategies for the early identification and treatment of IDA in non-dialysis CKD patients.

To investigate this, Vifor Pharma surveyed the readers of *Journal of Kidney Care* about their knowledge of and perceived challenges to the management of IDA in non-dialysis CKD patients.

TABLE 1. RESPONDENTS' ROLES

Role	Number
Primary care nurse	7
Hospital nurse	11
Specialist nurse	25
Nephrologist	5
Other (please specify)	
Dietitian	1
Former anaemia nurse specialist	1
Paramedic	2
Phlebotomist	1
Total	53

METHOD

Vifor Pharma developed a survey to evaluate health professionals' knowledge about the diagnosis, testing, management and treatment of IDA in non-dialysis CKD patients. The survey comprised 12 questions, based on feedback from clinicians and advisory boards. The initial draft was piloted on five nephrologists, five anaemia nurses and eight renal nurses for comment.

All questions had multiple-choice answers, but three also had the additional option to add free-text. It was anticipated that the survey would take less than 10 minutes to complete.

The survey was hosted on the *Journal of Kidney Care* website for 4 weeks in May–June 2018 and emailed to 5354 people who opted to receive emails from the journal. It was aimed at all health professionals who read *Journal of Kidney Care*, and it was hoped it would be completed by a spread of primary care clinicians, nurses, pharmacists and

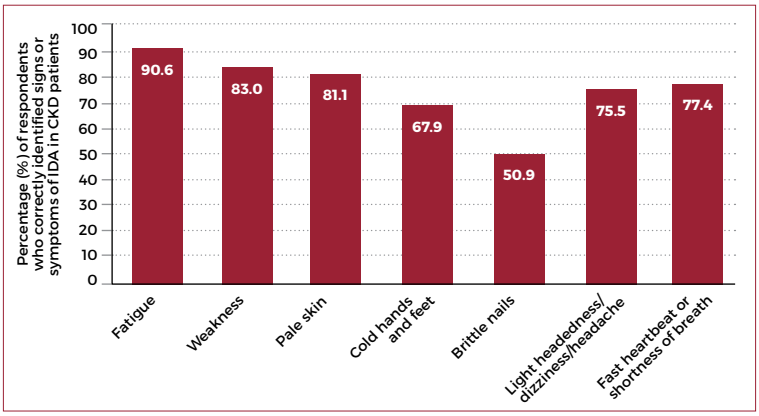

Figure 1. What are the signs and symptoms of IDA in CKD patients?

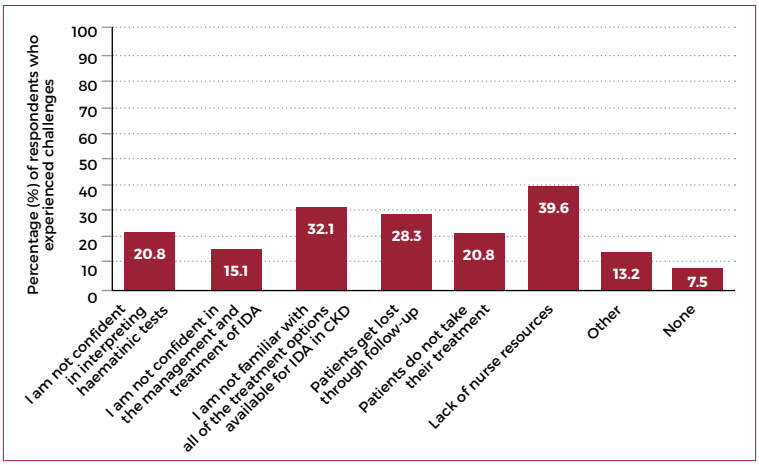

Figure 2. What are the challenges you experience in treating your IDA patients?

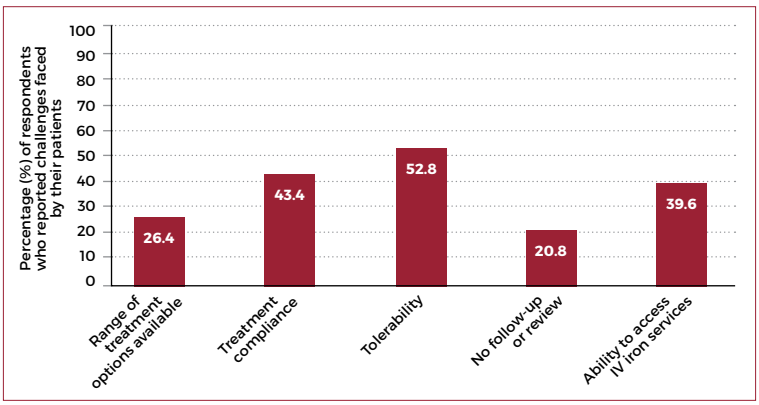

Figure 3. What challenges do your patients face with existing ID treatments?

nephrologists. There were no exclusion criteria, although it was clearly described as a renal anaemia survey, so would be likely to attract renal clinicians.

The survey was hosted on an online survey platform, surveygizmo. https://www.surveygizmo.com/

Responses were anonymised and submission of a completed survey was presumed to indicate consent.

RESULTS

RESPONSE

A total of 845 people opened the survey link, of whom 53 (6.3%) completed and submitted it. Respondents had a variety of job roles (*Table 1*). The majority were nurses (44/53, 83%), with almost half describing themselves as specialist nurses (25/53, 47%). As respondents were not asked for details about their role or specialty, it was not possible to determine whether the hospital and specialist nurses were renal nurses, or their renal specialty. Due to this and the small number of responses from nephrologists and primary care nurses, it was not appropriate to evaluate results for differences between roles.

KNOWLEDGE OF SYMPTOMS AND EXPERIENCE

Respondents were asked to tick which signs and symptoms in a list were indicative of IDA. Twenty-five respondents (47%) correctly ticked all of them as indicative of IDA. Two (4%) did not tick any. The most frequently correctly identified symptom of IDA was fatigue (selected by 48 (91%) respondents), and the least frequently correctly identified symptom was brittle nails (selected by 27 (51%) respondents). Full details are given in *Figure 1*.

Eighteen respondents (34%) encountered non-dialysis CKD patients with IDA on a daily basis and a further 18 (34%) encountered them weekly. The remaining respondents encountered non-dialysis CKD patients with IDA monthly (n=6, 11%) or rarely (n=11, 21%).

CHALLENGES FACED BY STAFF AND PATIENTS

Respondents were asked about the challenges faced by staff and patients when managing IDA in non-dialysis CKD patients. Four respondents (7.5%) reported that they did not experience any challenges in treating their IDA patients. Individual results are described below; full results are given in *Figures 2* and *3*.

Resources

The most frequently identified challenge facing staff treating IDA patients was lack of nurse resources (n=21; 40%), whereas for patients it was the ability to access IV iron services (n=21; 40%). Fourteen (26%) felt that the range of treatment options available was a challenge for patients. Other resources identified as impacting on IDA

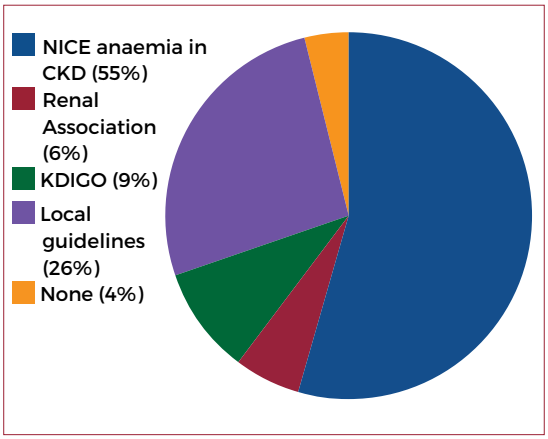

Figure 4. Which IDA guidelines do you mostly follow in CKD?

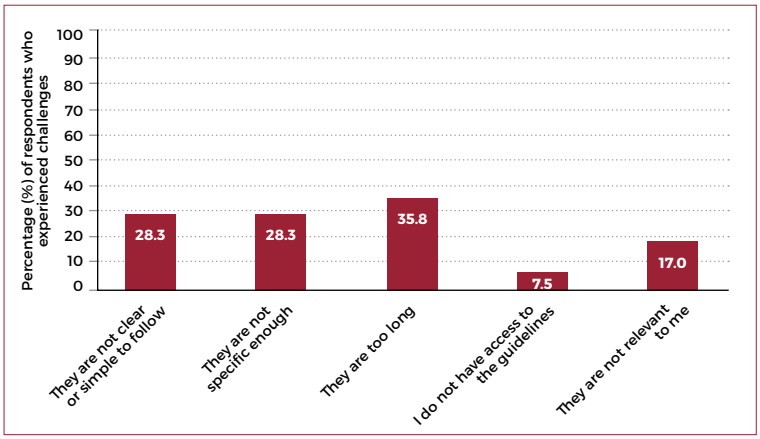

Figure 5. What challenges do you experience with current IDA guidelines in CKD?

management included lack of clinic time, clinic facilities and patient transport. Issues with follow-up were identified as a challenge for both staff (n=15, 28%) and patients (n=11, 21%).

Knowledge

Not being familiar with all treatment options available for IDA in CKD (n=17, 32%), not being confident when interpreting haematinic tests (n=11, 21%) and a lack of confidence in the management and treatment of IDA (n=8, 15%) were identified as challenges for some staff.

Adherence

Eleven respondents (21%) stated that patients not taking their treatments was a challenge for them. However, when asked about perceived patient challenges, tolerability to IDA treatments (n=28, 53%) and treatment compliance (n=23, 43%) were most frequently identified.

GUIDELINES FOR MANAGING IDA IN NON-DIALYSIS CKD PATIENTS

Respondents follow a variety of guidelines to manage IDA in CKD (*Figure 4*), with most following the National Institute for Health and Care Excellence (NICE) guideline on managing anaemia in CKD (n=29, 55%). More than a quarter follow a local guideline (n=14, 26%).

Some respondents experienced challenges with the current guidelines on IDA (*Figure 5*), reporting that they are too long (n=19, 36%), not specific enough (n=15, 28%) or not clear or simple to follow (n=15, 28%).

CARDIOVASCULAR DISEASE

Almost all respondents cared for CKD patients who also have CVD, with approximately half the sample (n=26, 49%) estimating that between 25% and 50% of their CKD patients also have CVD. Of the remainder, 13 respondents (25%) considered that 10–25% of their CKD patients had this disease, and 10 (19%) that over >50% had it. Despite regularly caring for CKD patients who also have CVD, three-quarters (n=40, 76%) were not aware of the European Society of Cardiology (ESC) and Scottish Intercollegiate Guidelines Network (SIGN) guidelines on treating iron deficiency in heart failure.

ONGOING MANAGEMENT OF IDA

There was variation in how often respondents thought CKD patients with IDA should be followed up: 27 (51%) thought this should be every 1–3 months, 10 (19%) thought monthly and 11 (21%) every 3–6 months (*Figure 6*).

Just over half of respondents (n=29, 55%) thought that anaemia nurses should be primarily responsible for ongoing management of IDA (*Figure 7*). Only a quarter thought that GPs (n=8, 15%) or community nurses (n=5, 9%) should be primarily responsible, although two respondents (4%) suggested that care should be shared between primary and secondary care. One respondent made an additional suggestion that patients should have more responsibility.

Thirty-three respondents (62%) would have liked further information or training on the management of patients with IDA.

DISCUSSION

This survey has revealed some important challenges faced by health professionals involved in the management of IDA in non-dialysis CKD patients.

Respondents' knowledge about signs and symptoms of IDA was variable, which might be related to the frequency with which each symptom occurs in IDA, but could also

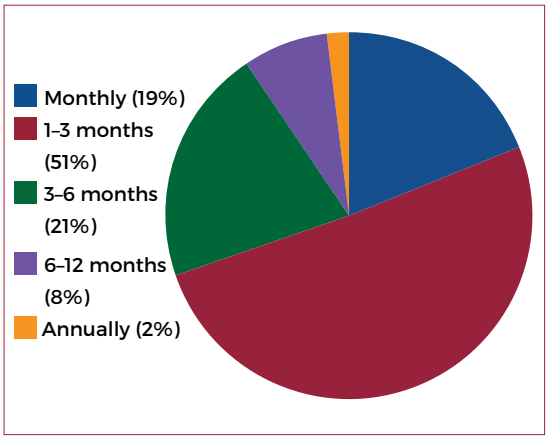

Figure 6. How often do you think CKD patients with IDA should be followed up?

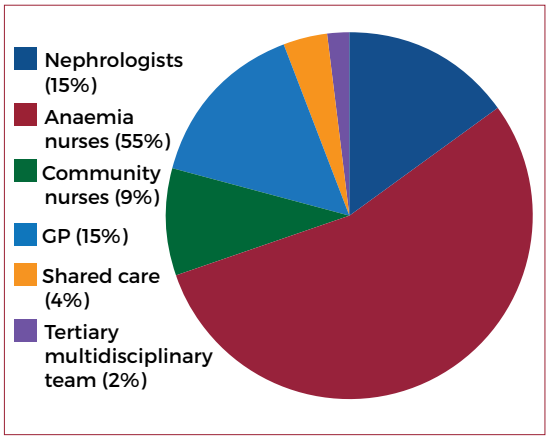

Figure 7. Who do you think should be primarily responsible for the ongoing management of IDA?

reflect the frequency with which staff encounter non-dialysis CKD patients with IDA. One-third of respondents encountered non-dialysis patients with IDA monthly or rarely, suggesting that this is not part of their everyday work. Some reported gaps in their knowledge or lack of confidence when managing IDA. Almost two-thirds said they would like further information or training. A variety of national and local guidelines provide recommendations on the identification and management of IDA, including those by NICE (2015a) and the Renal Association (2017). Some respondents found the guidelines cumbersome. Furthermore, the lack of consistency between them may increase confusion among non-renal clinicians, who may not encounter non-dialysis CKD patients with IDA on a regular basis. For example, NICE (2015b) recommend screening for anaemia when eGFR is <45 ml/min/1.73m^2, while the Renal Association recommends screening once eGFR is <60 ml/min/1.73m^2. IDA may develop before patients are referred to specialist renal centres, making awareness of the need for routine screening for anaemia in CKD stages 3a and 3b essential. Most respondents were not familiar with European Society of Cardiology guidelines on treating iron deficiency in heart failure (Ponikowski et al, 2016). As many CKD patients also have CVD disease and are at risk of heart failure, awareness of this should be promoted.

Tolerability and adherence to treatment with iron supplementation were identified as the biggest challenges for patients. Oral iron supplements are cheap and simple to administer but, as they often cause gastrointestinal upset (constipation or diarrhoea) and absorption is reduced in CKD, renal units routinely offer IV iron. It is important that patients are involved in decision-making to ensure appropriate treatment and better adherence. Oral iron supplementation may be preferred by some, but will not be tolerated by others, so IV iron should be available as an alternative. Resource issues such as a lack of nurses or clinic facilities were identified as the greatest challenges faced by respondents and some reported that it was difficult for their patients to access IV iron services. Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2013) requires that full resuscitation facilities be available when IV iron is administered, limiting the administration of IV iron in community settings. IV iron services are now generally provided in hospitals by haematology and renal services, and access from primary care is limited in some areas. Pathways should ensure that all patients can access IV iron services when appropriate.

More than half of respondents thought that anaemia nurses should be primarily responsible for the ongoing management of IDA, with only a quarter thinking that this is the role of GPs or community nurses. This suggests that IDA in non-dialysis CKD is often viewed as a specialist service despite the frequency with which it occurs, particularly in those with diabetes. Most renal units have renal anaemia specialist nurses who provide an expert anaemia service that includes administration of IV iron. However, CKD often occurs alongside other medical conditions, so consideration should be given on how non-renal specialists can best be supported in the identification and management of IDA. This may be particularly appropriate for patients with multiple medical problems, to avoid fragmentation of care and reduce hospital visits.

RECOMMENDATIONS

Simplifying the guidelines and making them consistent might improve their usability and reduce variation in

management. In particular, this would help health professionals who do not specialise in anaemia management to identify IDA, initiate treatment and guide referral to anaemia specialists when needed.

Innovative approaches to IV iron supplementation are needed to ensure the efficient use of resources. For example, closer collaboration between haematology and renal anaemia services could avoid the duplication of IV iron administration services on one site or allow patients to access an IV iron service closer to home.

Advice and helplines (for health professionals) and shared-care guidelines should be promoted to help non-renal specialists manage IDA in non-dialysis CKD patients, particularly those with multiple medical problems.

LIMITATIONS

A major limitation of this survey was the poor response rate, with only 6.3% of those who opened the link completing it. The reason for this is unclear, but may reflect the survey's focus on non-dialysis CKD, with those caring for dialysis and transplant patients not perceiving the survey to be relevant to them. More detail about the respondents' job roles would have increased understanding of whether different professional groups experience different challenges. Some of the questions might not have applied to respondents who rarely care for non-dialysis CKD patients with IDA, so it would have been useful to include 'not applicable' in the multiple-choice answers.

The survey was distributed via a renal journal so respondents were likely to have a renal focus. Further surveys should seek the views of primary care clinicians, including GPs, heart failure and diabetes clinicians, as they are often responsible for managing CKD stages 3a and 3b. Patients' views should also be sought, to increase understanding of their opinions about the risks and benefits of iron replacement treatments.

CONCLUSION

IDA is a common complication of chronic kidney disease and predisposes to the development of CVD. This survey identified some of the challenges to managing IDA in non-dialysis CKD patients, including gaps in knowledge and variations in access to IV iron services. More training and education may improve understanding and confidence in those who care for non-dialysis CKD patients with IDA less often, but easy access to specialist renal anaemia nursing advice should also be enabled. Simpler guidelines could facilitate earlier identification and better treatment of IDA by non-renal specialists, and a review of the provision of IV iron services would ensure equitable access. This could lead to improvements in quality of life and a reduction in long-term complications such as heart failure.

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An algorithm for the diagnosis and management of iron deficiency anaemia in chronic kidney disease

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The guidance on the management of iron deficiency anaemia in patients with chronic kidney disease has been described by some clinicians as cumbersome and confusing. This has led to the development of a simple and accessible algorithm, based on the same evidence. This article explains how the algorithm can be applied to practice

An online survey of clinicians' understanding of the diagnosis, treatment and monitoring of iron deficiency anaemia (IDA) identified wide variations in practice. It showed that, although many doctors and nurses use the National Institute for Health and Care (NICE) guidelines on anaemia and chronic kidney disease (CKD), many find them lengthy and not specific enough to assist with clinical decision-making.

The survey findings indicate there is an understanding and confidence gap in the identification and management of IDA in the earlier stages of CKD, more specifically stage 3 patients whose CKD is managed in primary care, rather than by the renal specialist team.

This algorithm (*Figure 1*) gives clear information on how to screen and identify IDA. It signposts readers about when to escalate and seek medical advice if the haemoglobin (Hb) is low and at what estimated glomerular filtration rate (eGFR) patients should be referred to nephrology for management of renal anaemia. This should help health professionals to identify and treat IDA earlier, potentially improving patients' quality of life and clinical outcomes.

The algorithm gives clear guidance on the blood indices that can be used to identify and measure IDA, and advises that oral iron should be the first-line choice for the management and prevention of IDA. It highlights the options for oral iron supplementation, along with the recommended dose for each brand. Advice is given on which medications are best avoided when taking oral iron, such as protein pump inhibitors (PPIs), which reduce the gastric acid levels and therefore impede iron absorption.

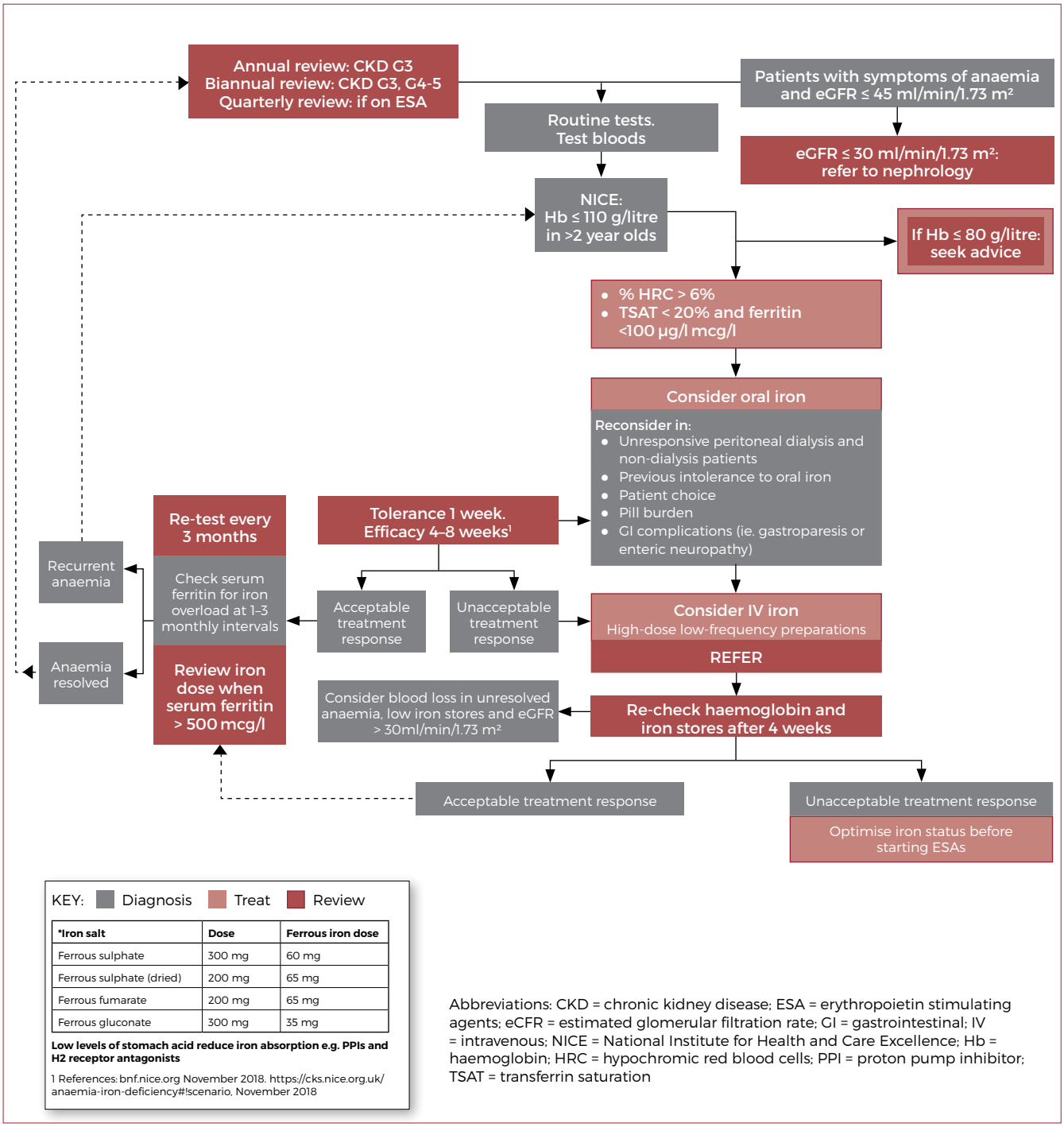
Clear information is also given on when to review the use of oral iron and consider the use of intravenous (IV) iron. Many patients with CKD are taking multiple medications, which can create a huge pill burden, and so may be reluctant to add another medication to their regimen. Those taking oral iron may also have gastrointestinal (GI) disturbances, which can lead to non-adherence to their medications and thus suboptimal management of their IDA.

The algorithm encourages referral to nephrology services for IV iron, when appropriate. This can be delivered in nurse-led anaemia clinics in the community, which may be closer to patients' homes. It also advises on the use of high-dose low-frequency IV iron, as this reduces the burden of repeated hospital visits. Guidance is given on the frequency with which the patient's response to iron should be monitored, and on how to ensure that patients are iron replete before commencing erythropoietin stimulating agents (ESAs). The process for ongoing monitoring and testing for IDA is clearly defined. GPs and community teams can then add a flag onto the patient's EMIS electronic GP record when his or her 3-monthly iron stores and Hb checks are due. Hopefully, this prompt will aid the early diagnosis of IDA and timely initiation of iron replacement, thereby minimising the physiological effects of ongoing anaemia on the patient and his or her quality of life.

EMBEDDING THE ALGORITHM IN PRACTICE

The algorithm can be applied in both primary and secondary care. It can be used as a framework for teaching sessions on the identification and management of IDA. This standardised approach should help avoid variations in practice and improve patient access to timely treatment.

The CKD service at a north west London trust delivers CKD and anaemia education sessions to GPs and practice nurses at GP practices and clinical commissioning group (CCG) events. This specialist team support has been positively received by these teams, who perhaps are less familiar with anaemia management. This approach has also helped GPs discuss renal or anaemia-related patient concerns. This education model has encouraged collaborative working across primary and secondary care and delivers a less fragmented plan of care to patients. Specialist CKD nurses regularly visit GP practices and undertake a joint review of patients on the practice CKD register. This supports GPs in the early identification of CKD and anaemia, appropriate and timely referral to secondary care and the development of individualised care plans. These education sessions have been positively evaluated by GPs and primary care teams and can assist greatly in enabling services to standardise their management of the long-term conditions.



*Iron salt	Dose	Ferrous iron dose
Ferrous sulphate	300 mg	60 mg
Ferrous sulphate (dried)	200 mg	65 mg
Ferrous fumarate	200 mg	65 mg
Ferrous gluconate	300 mg	35 mg

Low levels of stomach acid reduce iron absorption e.g. PPIs and H2 receptor antagonists

1 References: bnf.nice.org November 2018. https://cks.nice.org.uk/anaemia-iron-deficiency#!scenario, November 2018

Abbreviations: CKD = chronic kidney disease; ESA = erythropoietin stimulating agents; eCFR = estimated glomerular filtration rate; GI = gastrointestinal; IV = intravenous; NICE = National Institute for Health and Care Excellence; Hb = haemoglobin; HRC = hypochromic red blood cells; PPI = proton pump inhibitor; TSAT = transferrin saturation

Figure 1. Algorithm for the diagnosis and treatment of iron deficiency in non-dialysis chronic kidney disease patients

Ferinject® ▼(ferric carboxymaltose)

Prescribing Information – UK

For full prescribing information refer to the Summary of Product Characteristics (SmPC)

Active ingredient: Ferric carboxymaltose (50 mg/mL)
Presentation: Solution for injection/infusion. Available as a 2 mL vial (as 100 mg of iron), 10 mL vial (as 500 mg of iron) and 20 mL vial (as 1000 mg of iron).
Indication: Treatment of iron deficiency when oral iron preparations are ineffective or cannot be used. The diagnosis must be based on laboratory tests.
Dosage and Administration: The posology of Ferinject follows a stepwise approach:
Step 1: Determination of the iron need;
The individual iron need for repletion using Ferinject is determined based on the patient's body weight and haemoglobin (Hb) level. The table in the SmPC should be used to determine the iron need.
Step 2: Calculation and administration of the maximum individual iron dose(s);
Based on the iron need determined, the appropriate dose(s) of Ferinject should be administered:
A single Ferinject administration should not exceed:
• 15 mg iron/kg body weight (for administration by intravenous injection) or 20 mg iron/kg body weight (for administration by intravenous infusion)
The maximum recommended cumulative dose of Ferinject is 1000 mg of iron (20 mL Ferinject) per week.
Administration rates for intravenous injection:
For iron doses of 100 mg to 200 mg, there is no prescribed administration time. For doses >200 mg to 500 mg, Ferinject should be administered at a rate of 100 mg iron/min. For doses >500 mg to 1000 mg, the minimum administration time is 15 min.
Administration of intravenous drip infusion:
For iron doses of 100 mg to 200 mg, there is no prescribed administration time. For doses >200 mg to 500 mg, Ferinject should be administered in a minimum of 6 mins. For doses >500 mg to 1000 mg, the minimum administration time is 15 mins.
Ferinject must be diluted in 0.9% m/V NaCl but not diluted to concentrations less than 2 mg iron/mL.
Step 3: Post-iron repletion assessments
Contraindications: Hypersensitivity to Ferinject or any of its excipients. Known serious hypersensitivity to other parenteral iron products. Anaemia not attributed to iron deficiency. Iron overload or disturbances in utilisation of iron.
Special warnings and precautions: Parenterally administered iron preparations can cause potentially fatal anaphylactic/anaphylactoid reactions. The risk is enhanced for patients with known allergies, a history of severe asthma, eczema or other atopic allergy, and in patients with immune or inflammatory conditions. Ferinject should only be administered in the presence of staff trained to manage anaphylactic reactions where full resuscitation facilities are available (including 1:1000 adrenaline solution). Each patient should be observed for 30 minutes following administration. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. Careful monitoring of iron status is recommended to avoid iron overload. There is no safety data on the use of single doses of more than 200 mg iron in haemodialysis-dependent chronic kidney disease patients. Parenteral iron must be used with caution in case of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that treatment with Ferinject is stopped in patients with ongoing bacteraemia. In patients with chronic infection a benefit/risk evaluation has to be performed. Caution should be exercised to avoid paravenous leakage when administering Ferinject.
Special populations: The use of Ferinject has not been studied in children. A careful risk/benefit evaluation is required before use during pregnancy. Ferinject should not be used during pregnancy unless clearly necessary and should be confined to the second and third trimester.
Undesirable effects: Common (≥1/100 to <1/10): Hypophosphataemia, headache, dizziness, flushing, hypertension, nausea, injection/infusion site reactions. Please consult the SmPC in relation to other undesirable effects.
Legal category: POM
Price: pack of 5 x 2 ml = £81.18; pack of 5 x 10 ml = £405.88; pack of 1 x 20 ml = £154.23
MA Number: 15240/0002
Date of Authorisation: 19.07.2007
MA Holder: Vifor France, 100–101 Terrasse Boieldieu, Tour Franklin La Défense 8, 92042 Paris La Défense Cedex, France
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Date of revision: 03/17

Job bag number: UK/FER/16/
Date of preparation: 04/17

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Adverse events should also be reported to Vifor Pharma UK Ltd. Tel: +44 1276 853633