Anaemia management in people with chronic kidney disease

NICE guideline
Draft for consultation, November 2014

If you wish to comment on this version of the guideline, please be aware that all the supporting information and evidence for the 2015 recommendations is contained in the full version of the 2015 guideline. Evidence for the 2006 and 2011 recommendations are in the full version of the 2006 and 2011 guidelines, respectively.
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Introduction

Anaemia is defined internationally as a state in which the quality or quantity of circulating red blood cells is below normal. Blood haemoglobin (Hb) concentration serves as the key indicator for anaemia because it can be measured directly and has an international standard. A major cause of anaemia of chronic kidney disease (CKD) is a reduction in erythropoietin production due to kidney damage. Erythropoietin stimulates the bone marrow to produce red blood cells, and it is produced by the kidney in response to low tissue oxygen levels.

Possible adverse effects of anaemia include reduced oxygen use, increased cardiac output, left ventricular hypertrophy, reduced cognition and concentration, reduced libido and reduced immune responsiveness.

The guideline development group for this 2015 update considered the evidence in several areas that provide challenges for clinicians managing the anaemia of CKD. Recombinant human erythropoietin (also called EPO, an erythropoietic stimulating agent or ESA) for treating anaemia of CKD is an important tool in managing the condition. But some CKD patients with anaemia who are offered an ESA are ‘ESA resistant’ – that is, their condition consistently fails to respond to the ESA treatment. These patients often receive large doses of ESA, sometimes with blood transfusion, with limited benefits and at significant cost to the NHS. Many CKD patients with anaemia receiving an ESA are admitted with an intercurrent illness – such as pneumonia – which may temporarily render them acutely hyporesponsive to that ESA. There is uncertainty about the management of these groups of patients, and these areas were considered in the update. The update once again highlighted the often limited trial evidence in nephrology, compared with other specialities.

Over the past decade attention has shifted to the role and management of iron deficiency in anaemia of CKD. In CKD patients there is often a complex inflammatory state that makes it difficult to diagnose iron deficiency when using its standard markers, such as serum iron, serum total iron binding
capacity or ferritin. In recent years evidence has been published on newer markers of iron deficiency and intravenous iron preparations. In this 2015 update, the guideline development group reassessed the diagnosis and management of iron deficiency in CKD, and made several recommendations in these areas.

This guideline covers the management of anaemia in adults, children and young people with a clinical diagnosis of anaemia associated with CKD. It does not cover people with anaemia not principally caused by CKD. All parts of the care pathway are covered in the guideline.

**Medicines**

The guideline will assume that prescribers will use a medicine’s summary of product characteristics to inform decisions made with individual patients.

This guideline recommends some medicines for indications for which they do not have a UK marketing authorisation at the date of publication, if there is good evidence to support that use. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or those with authority to give consent on their behalf) should provide informed consent, which should be documented. See the General Medical Council’s [Prescribing guidance: prescribing unlicensed medicines](#) for further information. Where recommendations have been made for the use of medicines outside their licensed indications (‘off-label use’), these medicines are marked with a footnote in the recommendations.
Patient-centred care

This guideline offers best practice advice on the care of people with anaemia of CKD.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If the patient is under 16, their family or carers should also be given information and support to help the child or young person to make decisions about their treatment. Healthcare professionals should follow the Department of Health’s advice on consent. If someone does not have capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

If a young person is moving between paediatric and adult services, care should be planned and managed according to the best practice guidance described in the Department of Health’s Transition: getting it right for young people.

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with anaemia of CKD. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.
Strength of recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Guideline Development Group is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also ‘Patient-centred care’).

**Interventions that must (or must not) be used**

We usually use ‘must’ or ‘must not’ only if there is a legal duty to apply the recommendation. Occasionally we use ‘must’ (or ‘must not’) if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

**Interventions that should (or should not) be used – a ‘strong’ recommendation**

We use ‘offer’ (and similar words such as ‘refer’ or ‘advise’) when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, ‘Do not offer…’) when we are confident that an intervention will not be of benefit for most patients.

**Interventions that could be used**

We use ‘consider’ when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to
have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

**Recommendation wording in guideline updates**

NICE began using this approach to denote the strength of recommendations in guidelines that started development after publication of the 2009 version of ‘The guidelines manual’ (January 2009). This does not apply to any recommendations shaded in grey and ending [year of original publication] (see ‘Update information’ box below for details about how recommendations are labelled). In particular, for recommendations labelled [2015], the word ‘consider’ may not necessarily be used to denote the strength of the recommendation.
Update information

This guidance is an update of NICE clinical guideline 114 (published February 2011) and will replace it.

New recommendations have been added for the diagnosis and management of people with anaemia of CKD.

You are invited to comment on the new and updated recommendations in this guideline. These are marked as:

- [new 2015] if the evidence has been reviewed and the recommendation has been added or updated.

You are also invited to comment on recommendations that NICE proposes to delete from the 2011 guideline, because either the evidence has been reviewed and the recommendations have been updated, or NICE has updated other relevant guidance and has replaced the original recommendations. Appendix A sets out these recommendations and includes details of replacement recommendations. Where there is no replacement recommendation, an explanation for the proposed deletion is given.

Where recommendations are shaded in grey and end [2006] or [2011], the evidence has not been reviewed since the respective guideline. We will not be able to accept comments on these recommendations. Yellow shading in these recommendations indicates wording changes that have been made for the purposes of clarification only.

Where recommendations are shaded in grey and end [2006, amended 2015], the evidence has not been reviewed but changes have been made to the recommendation wording that change the meaning (for example, because of equalities duties or a change in the availability of drugs, or incorporated guidance has been updated). These changes are marked with yellow shading, and explanations of the reasons for the changes are given in appendix A for information. We will not be able to accept comments on these
recommendations.

The original NICE guideline and supporting documents are available here.
Key priorities for implementation

The following recommendations have been identified as priorities for implementation. The full list of recommendations is in section 1.

Diagnostic evaluation and assessment of anaemia

- Carry out testing to diagnose iron deficiency and determine potential responsiveness to iron therapy and long-term iron requirements at least once every 3 months (monthly for people receiving haemodialysis).
  - Use percentage of hypochromic red blood cells (% HRC; more than 6%) (only if processing of blood sample on the same day is possible).
  - If using percentage of hypochromic red blood cells is not possible, use reticulocyte haemoglobin content (CHr; less than 29 pg) or equivalent tests – for example, reticulocyte haemoglobin equivalent.
  - If these tests are not available or the person has thalassaemia or thalassaemia trait, use a combination of transferrin saturation (less than 20%) and serum ferritin measurement (less than 100 micrograms/litre). [new 2015] [1.1.3]

- Do not use transferrin saturation or serum ferritin measurement alone to assess iron deficiency status in people with anaemia of CKD. [new 2015] [1.1.4]

Assessment and optimisation of erythropoiesis

Benefits of treatment with ESAs

- Offer treatment with ESAs to people with anaemia of CKD who are likely to benefit in terms of quality of life and physical function. [2006] [1.3.1]

Optimal Hb levels

- The correction to normal levels of Hb with ESAs is not usually recommended in people with anaemia of CKD.
  - Typically maintain the aspirational Hb range between 100 and 120 g/litre for adults, young people and children aged 2 years and older, and
between 95 and 115 g/litre for children younger than 2 years of age, reflecting the lower normal range in that age group.

- To keep the Hb level within the aspirational range, do not wait until Hb levels are outside the aspirational range before adjusting treatment (for example, take action when Hb levels are within 5 g/litre of the range’s limits). [2011] [1.3.11]

ESAs: monitoring iron status during treatment

- Offer iron therapy to people receiving ESA maintenance therapy to keep their¹:
  - percentage hypochromic red cells (% HRC) less than 6% (unless serum ferritin is greater than 800 micrograms/litre)
  - reticulocyte haemoglobin count or equivalent tests above 29 pg (unless serum ferritin is greater than 800 micrograms/litre)
  - transferrin saturation level above 20% and serum ferritin level above 100 micrograms/litre (unless serum ferritin is greater than 800 micrograms/litre).

Levels should be monitored every month in people receiving haemodialysis and every 3 months in people receiving pre-dialysis or peritoneal dialysis. [new 2015] [1.3.20]

Iron therapy for adults and children who are iron deficient, before ESAs and not on haemodialysis

- Offer iron therapy to people² with anaemia of CKD before discussing ESA therapy. For people who are not receiving haemodialysis, consider a trial of oral iron before offering intravenous iron therapy. [new 2015] [1.3.21]

- In people with anaemia of CKD who are not receiving haemodialysis and who are intolerant to oral iron, offer intravenous iron therapy³ before discussing ESA therapy. [new 2015] [1.3.22]

¹ See recommendation 1.1.3 for tests of choice to determine iron deficiency.
² At the time of publication (May, 2015), intravenous iron did not have a UK marketing authorisation for use in children and young people for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council’s Prescribing guidance: prescribing unlicensed medicines for further information.
Iron therapy for people who are iron deficient and receiving ESAs

- Offer intravenous iron therapy to adults who are receiving ESA therapy, and to children\(^3\) who are receiving ESA therapy and haemodialysis, after a discussion about the risks and benefits of treatment options. Take into account the person’s choice. \[new\ 2015\] [1.3.24]

- In children with anaemia of CKD who are receiving ESA therapy but not haemodialysis, consider oral iron before intravenous iron therapy\(^3\). If the child is intolerant to oral iron or haemoglobin target levels are not reached within 3 months (see recommendation 1.3.11), offer intravenous iron therapy. \[new\ 2015\] [1.3.26]

- When offering intravenous iron therapy to adults, consider high-dose low-frequency\(^4\) intravenous iron as the treatment of choice when trying to achieve iron repletion. Take into account all of the following:
  - preferences of the person with anaemia of CKD and their family or carers
  - nursing and administration costs
  - cost of local drug supply
  - provision of resuscitation facilities.

Intravenous iron administered at a low dose and high frequency\(^5\) may be more appropriate for all children\(^3\) and for adults who are having in-centre dialysis. \[new\ 2015\] [1.3.27]

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\(^3\) At the time of publication (May, 2015), intravenous iron did not have a UK marketing authorisation for use in children and young people for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council’s \Prescribing guidance: prescribing unlicensed medicines\ for further information.

\(^4\) The GDG considered this to be a maximum of 2 infusions in adults, with a minimum of 500 mg of iron in each infusion.

\(^5\) The GDG considered this to be more than 2 infusions in adults, of between 100 and 200 mg of iron in each infusion.
1 Recommendations

The following guidance is based on the best available evidence. The full guideline [hyperlink to be added for final publication] gives details of the methods and the evidence used to develop the guidance.

1.1 Diagnostic evaluation and assessment of anaemia

Diagnostic role of Hb levels

1.1.1 Consider investigating and managing anaemia in people with CKD if:

- their Hb level falls to 110g/litre or less (or 105 g/litre or less if younger than 2 years) or
- they develop symptoms attributable to anaemia (such as tiredness, shortness of breath, lethargy and palpitations). [2011]

Diagnostic role of glomerular filtration rate

1.1.2 An estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73m² should trigger investigation into whether anaemia is due to CKD. When the eGFR is greater than or equal to 60 ml/min/1.73m² the anaemia is more likely to be related to other causes. [2006]

Diagnostic tests to determine iron status and predicting response to iron therapy

1.1.3 Carry out testing to diagnose iron deficiency and determine potential responsiveness to iron therapy and long-term iron requirements at least once every 3 months (monthly for people receiving haemodialysis).

- Use percentage of hypochromic red blood cells (% HRC; more than 6%) (only if processing of blood sample on the same day is possible).
• If using percentage of hypochromic red blood cells is not possible, use reticulocyte haemoglobin content (less than 29 pg) or equivalent tests – for example, reticulocyte haemoglobin equivalent.

• If these tests are not available or the person has thalassaemia or thalassaemia trait, use a combination of transferrin saturation (less than 20%) and serum ferritin measurement (less than 100 micrograms/litre). [new 2015]

1.1.4 Do not use transferrin saturation or serum ferritin measurement alone to assess iron deficiency status in people with anaemia of CKD. [new 2015]

Measurement of erythropoietin

1.1.5 Do not routinely consider measurement of erythropoietin levels for the diagnosis or management of anaemia in people with anaemia of CKD. [2006]

1.2 Management of anaemia

Initiation of ESA therapy in iron-deficient patients

1.2.1 ESA therapy should not be initiated in the presence of absolute iron deficiency without also managing the iron deficiency. [2006]

Maximum iron levels in people with anaemia of CKD

1.2.2 In people treated with iron, serum ferritin levels should not rise above 800 micrograms/litre. In order to prevent this, review the dose of iron when serum ferritin levels reach 500 micrograms/litre. [2006]

Clinical utility of ESA therapy in iron-replete patients

1.2.3 The pros and cons of a trial of anaemia management should be discussed between the clinician, the person with anaemia of CKD, and their families and carers if applicable. [2006]
1.2.4 ESAs need not be administered where the presence of comorbidities, or the prognosis, is likely to negate the benefits of correcting the anaemia. [2006]

1.2.5 Initiate a trial of anaemia correction when there is uncertainty over whether the presence of comorbidities, or the prognosis, would negate benefit from correcting the anaemia with ESAs. [2006]

1.2.6 Where a trial of ESA therapy has been performed, assess the effectiveness of the trial after an agreed interval. Where appropriate, a mutual decision should be agreed between the clinician, the person with anaemia of CKD and their families and carers on whether or not to continue ESA therapy. [2006]

1.2.7 Review all people started on ESA therapy after an agreed interval in order to decide whether or not to continue using ESAs. [2006]

Nutritional supplements

1.2.8 Supplements of vitamin C, folic acid or carnitine should not be prescribed as adjuvants specifically for the treatment of anaemia of CKD. [2006]

Androgens

1.2.9 In people with anaemia of CKD, androgens should not be used to treat the anaemia. [2006]

Hyperparathyroidism

1.2.10 In people with anaemia of CKD, treat clinically relevant hyperparathyroidism to improve the management of the anaemia. [2006]

Patient-centred care: ESAs

1.2.11 Give people offered ESA therapy and their GPs information about why ESA therapy is required, how it works and what benefits and side effects may be experienced. [2006]
1.2.12 When managing the treatment of people with anaemia of CKD, there should be agreed protocols defining roles and responsibilities of healthcare professionals in primary and secondary care. [2006]

1.2.13 Inform people receiving ESA therapy about the importance of concordance with therapy and the consequences of poor concordance. [2006]

1.2.14 When prescribing ESA therapy, take into account patient preferences about supervised- or self-administration, dose frequency, pain on injection, method of supplying ESA and storage. [2006]

1.2.15 In order for people to self-administer their ESA in a way that is clinically effective and safe, make arrangements to provide ready, reasonable and uninterrupted access to supplies. [2006]

Patient education programmes

1.2.16 Offer culturally and age-appropriate patient education programmes to all people diagnosed with anaemia of CKD (and their families and carers). These should be repeated as requested, and according to the changing circumstances of the patient. They should include the following key areas:

- Practical information about how anaemia of CKD is managed.
- Knowledge (for example, about symptoms, iron management, causes of anaemia, associated medications, phases of treatment).
- Professional support (for example, contact information, community services, continuity of care, monitoring, feedback on progress of results).
- Lifestyle (for example, diet, physical exercise, maintaining normality, meeting other patients).
- Adaptation to chronic disease (for example, previous information and expectations, resolution of symptoms). [2006]
1.3 Assessment and optimisation of erythropoiesis

Benefits of treatment with ESAs

1.3.1 Offer treatment with ESAs to people with anaemia of CKD who are likely to benefit in terms of quality of life and physical function. [2006]

Blood transfusions

1.3.2 Avoid blood transfusions where possible in people with anaemia of CKD in whom kidney transplant is a treatment option. [2006]

1.3.3 In people with anaemia of CKD, there may be situations where a transfusion is indicated clinically. In these cases, follow the relevant haematology guidelines. [2006, amended 2015]

Comparisons of ESAs

1.3.4 Discuss the choice of ESA with the person with anaemia of CKD when initiating treatment and at subsequent review, taking into consideration the patient's dialysis status, the route of administration and the local availability of ESAs. There is no evidence to distinguish between ESAs in terms of efficacy. [2006]

Coordinating care

1.3.5 People with anaemia of CKD should have access to a designated contact person or persons who have principal responsibility for their anaemia management and who have skills in the following activities:

- Monitoring and managing a caseload of patients in line with locally agreed protocols.
- Providing information, education and support to empower patients and their families and carers to participate in their care.
- Coordinating an anaemia service for people with CKD, working between secondary and primary care and providing a single
point of contact, to ensure patients receive a seamless service of
the highest standard.

- Prescribing medicines related to anaemia management and
  monitoring their effectiveness. [2006]

Providing ESAs

1.3.6 ESA therapy should be clinically effective, consistent and safe in
people with anaemia of CKD. To achieve this, the prescriber and
patient should agree a plan that is patient-centred and includes:

  - continuity of drug supply
  - flexibility of where the drug is delivered and administered
  - the lifestyle and preferences of the patient
  - cost of drug supply
  - desire for self-care where appropriate
  - regular review of the plan in light of changing needs. [2006]

ESAs: optimal route of administration

1.3.7 The person with anaemia of CKD and the prescriber should agree
(and revise as appropriate) the route of administration of ESAs,
taking into account the following factors:

  - patient population (for example, haemodialysis patients)
  - pain of injection
  - frequency of administration
  - the lifestyle and preferences of the patient
  - efficacy (for example, subcutaneous versus intravenous
    administration, or long-acting versus short-acting preparations)
  - cost of drug supply. [2006]

1.3.8 The prescriber should take into account that when using short-
acting ESAs, subcutaneous injection allows the use of lower doses
of drugs than intravenous administration. [2006]
ESAs: dose and frequency

1.3.9 When correcting anaemia of CKD, the dose and frequency of ESA should be:

- determined by the duration of action and route of administration of the ESA
- adjusted to keep the rate of Hb increase between 10 and 20 g/litre/month. [2006]

Optimal Hb levels

1.3.10 When determining individual aspirational Hb ranges for people with anaemia of CKD, take into account:

- patient preferences
- symptoms and comorbidities
- the required treatment. [2011]

1.3.11 The correction to normal levels of Hb with ESAs is not usually recommended in people with anaemia of CKD.

- Typically maintain the aspirational Hb range between 100 and 120 g/litre for adults, young people and children aged 2 years and older, and between 95 and 115 g/litre for children younger than 2 years of age, reflecting the lower normal range in that age group.
- To keep the Hb level within the aspirational range, do not wait until Hb levels are outside the aspirational range before adjusting treatment (for example, take action when Hb levels are within 5 g/litre of the range’s limits). [2011]
1.3.12 Consider accepting Hb levels below the agreed aspirational range if:

- high doses\(^6\) of ESAs are required to achieve the aspirational range or
- the aspirational range is not achieved despite escalating ESA doses. [2011]

1.3.13 Consider accepting Hb levels above the agreed aspirational range when:

- these develop with iron therapy alone or
- these develop with low doses of ESAs or
- it is thought that the person might benefit (for example, if they have a physically demanding job) or
- the absolute risk of cerebrovascular disease is thought to be low. [2011]

1.3.14 Age alone should not be a determinant for treatment of anaemia of CKD. [2006]

**Adjusting ESA treatment**

1.3.15 Optimise iron status before or coincident with the initiation of ESA administration and during maintenance treatment with ESAs\(^7\). [2006, amended 2011]

1.3.16 Use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin type II receptor antagonists is not precluded, but if they are used, an increase in ESA therapy should be considered. [2006]

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\(^6\) > 175 IU/kg/week for haemodialysis population; > 125 IU/kg/week for peritoneal dialysis population; > 100 IU/kg/week for non-dialysis population (Data provided by the National Renal Registry and GDG expert opinion).

\(^7\) Amended to clarify that iron status should be monitored during ESA maintenance treatment (see 1.3.20).
1.3.17 Take into account Hb measurements when determining the dose and frequency of ESA administration.

- Investigate the cause of an unexpected change in Hb level (that is, intercurrent illness, bleeding) to enable intervention and optimise iron status.\(^8\)
- Increase or decrease ESA dose and/or frequency when Hb measurements fall outside action thresholds (usually below 105 g/litre or above 115 g/litre), or for example when the rate of change of Hb suggests an established trend (for example, greater than 10 g/litre/month). [2006, amended 2011]

**Treating iron deficiency: correction**

1.3.18 Ensure that people with anaemia of CKD who are receiving ESAs are given iron therapy to achieve:\(^9\)

- percentage hypochromic red blood cells less than 6% (unless ferritin is greater than 800 micrograms/litre)
- reticulocyte haemoglobin count or equivalent tests above 29 pg (unless serum ferritin is greater than 800 micrograms/litre).

If the above tests are not available, iron therapy should maintain transferrin saturation greater than 20% and serum ferritin level greater than 100 micrograms/litre (unless serum ferritin is greater than 800 micrograms/litre).

Most patients will need 600–1000 mg of iron for adults or equivalent doses for children,\(^10\) in a single or divided dose depending on the preparation. Iron should be administered in a setting with appropriate facilities and healthcare staff. [new 2015]

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\(^8\) Amended to show iron status should be optimised following an unexpected change in Hb level.

\(^9\) See 1.1.3 for tests of choice to determine iron deficiency.

\(^10\) At the time of publication (May, 2015), intravenous iron did not have a UK marketing authorisation for use in children and young people for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
Treating iron deficiency: maintenance

1.3.19 Once percentage hypochromic red blood cells are less than 6%, reticulocyte haemoglobin count or equivalent tests above 29 pg, or transferrin saturation is greater than 20% and serum ferritin level is greater than 100 micrograms/litre, offer people with anaemia of CKD who are receiving ESAs maintenance iron.

The dosing regimen will depend on modality, for example haemodialysis patients will need the equivalent of 50–60 mg intravenous iron per week (or an equivalent dose in children\textsuperscript{11} of 1 mg/kg/week). [new 2015]

ESAs: monitoring iron status during treatment

1.3.20 Offer iron therapy to people\textsuperscript{11} receiving ESA maintenance therapy to keep their\textsuperscript{12}:

- percentage hypochromic red cells (% HRC) less than 6% (unless serum ferritin is greater than 800 micrograms/litre)
- reticulocyte haemoglobin count or equivalent tests above 29 pg (unless serum ferritin is greater than 800 micrograms/litre)
- transferrin saturation level above 20% and serum ferritin level above 100 micrograms/litre (unless serum ferritin is greater than 800 micrograms/litre).

Levels should be monitored every month in people receiving haemodialysis and every 3 months in people receiving pre-dialysis or peritoneal dialysis. [new 2015]

Iron therapy for adults and children who are iron deficient, before ESAs and not on haemodialysis

1.3.21 Offer iron therapy to people\textsuperscript{11} with anaemia of CKD before discussing ESA therapy. For people who are not receiving

\textsuperscript{11} At the time of publication (May, 2015), intravenous iron did not have a UK marketing authorisation for use in children and young people for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council’s Prescribing guidance: prescribing unlicensed medicines for further information.

\textsuperscript{12} See 1.1.3 for tests of choice to determine iron deficiency.
haemodialysis, consider a trial of oral iron before offering intravenous iron therapy. [new 2015]

1.3.22 In people with anaemia of CKD who are not receiving haemodialysis and who are intolerant to oral iron, offer intravenous iron therapy\(^{13}\) before discussing ESA therapy. [new 2015]

**Iron therapy for adults and children who are iron deficient, before ESAs and who are on haemodialysis**

1.3.23 For people who are receiving haemodialysis, offer intravenous iron therapy\(^{13}\) before discussing ESA therapy. [new 2015]

**Iron therapy for people who are iron deficient and receiving ESAs**

1.3.24 Offer intravenous iron therapy to adults who are receiving ESA therapy, and to children\(^{13}\) who are receiving ESA therapy and haemodialysis, after a discussion about the risks and benefits of treatment options. Take into account the person’s choice. [new 2015]

1.3.25 Offer oral iron therapy to people who are receiving ESA therapy and:

- in whom intravenous iron therapy is contraindicated or
- who choose not to have intravenous iron therapy after discussion about the efficacy of oral and intravenous iron therapy. [new 2015]

1.3.26 In children with anaemia of CKD who are receiving ESA therapy but not haemodialysis, consider oral iron before intravenous iron therapy\(^{13}\). If the child is intolerant to oral iron or haemoglobin target levels are not reached within 3 months (see recommendation 1.3.11), offer intravenous iron therapy. [new 2015]

\(^{13}\) At the time of publication (May, 2015), intravenous iron did not have a UK marketing authorisation for use in children and young people for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council’s **Prescribing guidance: prescribing unlicensed medicines** for further information.
1.3.27 When offering intravenous iron therapy to adults, consider high-dose low-frequency\textsuperscript{14} intravenous iron as the treatment of choice when trying to achieve iron repletion. Take into account all of the following:

- preferences of the person with anaemia of CKD and their family or carers
- nursing and administration costs
- cost of local drug supply
- provision of resuscitation facilities.

Intravenous iron administered at a low dose and high frequency\textsuperscript{15} may be more appropriate for all children\textsuperscript{16} and for adults who are having in-centre dialysis. [\textbf{new 2015}]

### 1.4 Monitoring treatment of anaemia of CKD

#### Monitoring iron status

1.4.1 People with anaemia of CKD should not have iron levels checked earlier than 1 week after receiving intravenous iron. The length of time to monitoring of iron status is dependent on the product used and the amount of iron given. [\textbf{2006}]

1.4.2 Routine monitoring of iron stores to prevent iron overload using serum ferritin should be at intervals of 3 months. [\textbf{2006, amended 2015}]

\textsuperscript{14} The GDG considered this to be a maximum of 2 infusions in adults, with a minimum of 500 mg of iron in each infusion.

\textsuperscript{15} The GDG considered this to be more than 2 infusions in adults, of between 100 and 200 mg of iron in each infusion.

\textsuperscript{16} At the time of publication (May, 2015), intravenous iron did not have a UK marketing authorisation for use in children and young people for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's \textit{Prescribing guidance: prescribing unlicensed medicines} for further information.
Monitoring Hb levels

1.4.3 In people with anaemia of CKD, monitor Hb:

- every 2–4 weeks in the induction phase of ESA therapy
- every 1–3 months in the maintenance phase of ESA therapy
- more actively after an ESA dose adjustment
- in a clinical setting chosen in discussion with the patient, taking into consideration their convenience and local healthcare systems. [2006]

Detecting ESA resistance

1.4.4 After other causes of anaemia, such as intercurrent illness or chronic blood loss have been excluded, people with anaemia of CKD should be considered resistant to ESAs when:

- an aspirational Hb range is not achieved despite treatment with 300 IU/kg/week or more of subcutaneous epoetin or 450 IU/kg/week or more of intravenous epoetin or 1.5 micrograms/kg/week of darbepoetin, or
- there is a continued need for the administration of high doses of ESAs to maintain the aspirational Hb range. [2006]

1.4.5 In people with CKD, pure red cell aplasia (PRCA) is indicated by a low reticulocyte count, together with anaemia and the presence of neutralising antibodies. Confirm PRCA by the presence of anti-erythropoietin antibodies together with a lack of pro-erythroid progenitor cells in the bone marrow. [2006]

1.4.6 In people with anaemia of CKD, aluminium toxicity should be considered as a potential cause of a reduced response to ESAs after other causes, such as intercurrent illness and chronic blood loss, have been excluded. [2006]
Managing ESA resistance

1.4.7 In haemodialysis patients with anaemia of CKD in whom aluminium toxicity is suspected, perform a desferrioxamine test and review the patient's management accordingly. [2006]

1.4.8 Consider specialist referral for ESA-induced PRCA. [2006, amended 2011]

Role of blood transfusion in managing ESA resistance

1.4.9 Consider referring people with ESA resistance to a haematology service, particularly if an underlying haematological disorder is suspected. [new 2015]

1.4.10 Evaluate and discuss the risks and benefits of red cell transfusion with the person or, where appropriate, with their family or carers. [new 2015]

1.4.11 Take into account the person’s symptoms, quality of life, underlying conditions and the chance of a future successful transplant, in addition to haemoglobin levels, when thinking about the need for red cell transfusion. [new 2015]

1.4.12 Review the rate of red cell transfusion and consider a trial period of stopping ESA in people who have ESA resistance (typically on haemodialysis and on high-dose ESA) and are having frequent transfusions when:

- all reversible causes of ESA resistance have been taken into account and excluded and
- the person’s condition is otherwise ‘stable’ (without intercurrent illness such as infection) and
- the person is receiving adequate dialysis.

Review the rate of red cell transfusion between 1 and 3 months after stopping ESA therapy. If the rate of transfusion has increased, consider restarting ESA therapy. [new 2015]
2 Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future. The Guideline Development Group’s full set of research recommendations is detailed in the full guideline.

2.1 Management of anaemia of CKD with concurrent illness

What is the optimal management (in terms of clinical and cost effectiveness) of anaemia of CKD in patients who are receiving ESAs and have a significant concurrent acute infectious illness?

Why this is important

Chronic kidney disease is a risk factor for mortality in patients who develop acute illness. Acute illness in CKD patients is associated with development, or worsening, of anaemia.

The anaemia of end stage renal disease is managed primarily with ESAs and intravenous iron. When CKD patients develop acute illness, their anaemia becomes difficult to control. Acute inflammatory response usually renders patients hypo-responsive to treatments for anaemia. In addition, intravenous iron might promote bacterial infection. Many patients may end up having a blood transfusion – in part because of the lack of established guidelines on the management of anaemia in CKD patients with acute illness. Little is known about the relative safety of transfusion compared with parenteral iron therapy, with or without ESA therapy.

There is a need for long-term observational studies, as well as prospective randomised controlled trials to compare the effectiveness and safety of treating anaemia in acutely ill CKD patients with parenteral iron, erythropoiesis stimulation agents, blood transfusion or a combination of the 3 different therapies. A large epidemiological or cohort study is needed with a control group (for example, patients admitted to hospital as an emergency with an acute illness, but without anaemia). The study should be adequately powered
to detect factors predictive of important end points such as patient survival, deterioration of renal function, the need to initiate renal replacement therapy and prolonged hospital stay.

2.2 Treatment of ESA resistance

In people with chronic ESA-resistant anaemia of CKD, what is the clinical and cost effectiveness of treating with high-dose ESA compared with blood transfusion?

Why this is important
People with ESA hyporesponsiveness show evidence of increased morbidity and mortality compared with those who respond well to ESA therapy. Poor response to ESA therapy during the haemodialysis treatment period is thought to be associated with worse post-transplant long-term outcomes, including increased all-cause death and higher risk of graft failure. Little is known about the potential risks of maintaining people with CKD on high doses of ESA therapy while they are waiting for a transplant. It is unclear whether high-dose ESA should be continued in people with ESA resistance in an attempt to limit the number of blood transfusions, or whether people should stop ESA treatment and be treated with transfusions alone. The adverse effects differ between the strategies and are likely to have implications for both cost and quality of life.

Further research is needed to understand the clinical and cost-effectiveness of these 2 strategies. Long-term prospective observational or matched case-controlled studies are needed to assess the relative safety of large-dose ESA versus no ESA, with or without blood transfusions, on long-term patient and graft survival.

2.3 Treatment of ESA resistance in dialysis patients

What is the most effective type of intervention to treat dialysis patients with ESA-resistant anaemia?
Why this is important

5% to 10% of patients with end-stage renal disease show resistance to ESAs. ESA hyporesponsiveness in chronic haemodialysis patients may be associated with increased morbidity and mortality. In addition, pre-transplantation ESA hyporesponsiveness is thought to be associated with increased kidney allograft failure and patient mortality. Studies have shown that immunosuppressants, anti-oxidants, anti-cytokine therapies and high-flux membranes vary in how much they improve responsiveness to ESA therapy, but all the studies used a small sample size. There is inadequate evidence identified from available literature to inform recommending any intervention to improve ESA responsiveness.

Adequately powered randomised controlled trials are needed to establish the safety and efficacy of interventions to improve responsiveness to ESA therapy.

2.4 Iron therapies for conservative care of anaemia of CKD

What is the clinical and cost effectiveness of different iron therapies for people with anaemia of CKD opting for conservative care (defined in relation to dialysis)?

Why this is important

Conservative care for end-stage renal disease aims to provide control of symptoms, with an emphasis on maintaining the person’s quality of life. Anaemia management is a key element of conservative care. People opting for conservative care may prefer to receive treatment closer to home rather than in hospital, even if the treatments available in hospital are more effective. It is important to take into account quality of life and patient choice, as well as medical risks and benefits, when deciding on an anaemia treatment plan. Further research is needed into the clinical and cost-effectiveness of different iron therapies for people opting for conservative care.
2.5 Target haemoglobin levels in conservative management of anaemia of CKD

In people with anaemia of CKD opting for conservative management, what is the clinical and cost effectiveness of treating to differing target haemoglobin levels?

Why this is important
Most studies of ESA therapy involved people who differ considerably from those opting for conservative management. Trial evidence relates to people who tend to be younger, with fewer comorbidities. There are many people, mainly elderly in their later seventies and eighties, who opt for conservative management of CKD instead of dialysis. They often have several comorbidities. They will usually be treated with an ESA in accordance with guidelines for anaemia management in CKD, with the standard haemoglobin target range, although there is little information on the best haemoglobin target level for this relatively older, less active group of people. A 'usual' haemoglobin target level might reduce their anaemia symptoms. However, a lower target level might have no adverse impact on their health-related quality of life, while reducing the need for healthcare interventions that impair quality of life. A 'lower than usual' or 'permissive' haemoglobin target level might reduce the need for intravenous iron, ESA and hospital or clinic appointments. A trial is needed to compare a 'usual' haemoglobin target with a 'permissive' haemoglobin target.

3 Other information

3.1 Scope and how this guideline was developed

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover.
How this guideline was developed

NICE commissioned the National Clinical Guideline Centre to develop this guideline. The Centre established a Guideline Development Group (see section 4), which reviewed the evidence and developed the recommendations.

The methods and processes for developing NICE clinical guidelines are described in the guidelines manual.

3.2 Related NICE guidance

Details are correct at the time of consultation on the guideline (November 2014). Further information is available on the NICE website.

Published

General

- Patient experience in adult NHS services (2012) NICE guideline 138
- Medicines adherence (2009) NICE guideline 76

Condition-specific

- Chronic kidney disease (2014) NICE guideline 182
- Acute kidney injury (2013) NICE guideline 169
- Peritoneal dialysis (2011) NICE guideline 125
- Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia (2008) NICE technology appraisal guidance 142
- Guidance on home compared with hospital haemodialysis for patients with end-stage renal failure (2002) NICE technology appraisal guidance 48

Under development

NICE is developing the following guidance:

- Transfusion. NICE guideline. Publication expected October 2015.
4 The Guideline Development Group, National Collaborating Centre and NICE project team

4.1 Guideline Development Group

The Guideline Development Group members listed are those for the 2015 update. For the composition of previous Guideline Development Groups, see the full guideline.

Christopher Brown
Highly Specialist Clinical Lead Pharmacist for Nephrology, Abertawe Bro Morgannwg University Health Board, Swansea

Roy Connell
Clinical Nurse Specialist, Children’s Renal and Urology Unit, Nottingham University Hospitals

Jan Cooper
Patient and carer member, Kidney Research UK and Kidney Patients Association West Midlands Renal Network

Mark Devonald
Consultant Nephrologist, Nottingham University Hospitals

Belinda Dring
Anaemia Nurse Specialist and project lead – Renal and Transplant Unit, Nottingham University Hospitals

Damian Fogarty
Senior Lecturer and Consultant Nephrologist, Queen’s University Belfast and Chairman, United Kingdom Renal Registry

Kathryn Griffiths
General Practitioner, Unity Health, York

Ashraf Mikhail
Consultant Renal Physician, Morriston Hospital, Swansea
Nicholas Palmer  
Patient and carer member, National Kidney Federation

Mark Prentice  
Advance Renal Nurse Practitioner, James Paget University Hospital, Great Yarmouth

Laura Ratcliffe  
Department of Physiology and Pharmacology, University of Bristol

Suzanne Stephens  
Consultant Paediatric Nephrologist, Birmingham Children’s Hospital

Mark Thomas (Chair)  
Consultant Physician and Nephrologist, Heart of England NHS Foundation Trust

Wayne Thomas  
Consultant Haematologist, Derriford Hospital, Plymouth

4.2 National Clinical Guideline Centre

Susan Latchem  
Operations Director

Smita Padhi  
Senior Research Fellow

Jessica Glen  
Research Fellow

Grace Marsden (until May 2014)  
Senior Health Economist

David Wonderling (from May 2014)  
Head of Health Economics

Saoussen Ftouh (until April 2014)  
Project Manager
4.3  **NICE project team**

Sarah Willett  
Guideline Lead  

Martin Allaby  
Clinical Adviser  

Louise Shires  
Guideline Commissioning Manager  

Joy Carvill  
Guideline Coordinator  

Beth Shaw  
Technical Lead  

Paul Crosland  
Health Economist  

Annette Mead  
Editor  

4.4  **Declarations of interests**

The following members of the Guideline Development Group made declarations of interests. All other members of the Group stated that they had no interests to declare.
<table>
<thead>
<tr>
<th>Member</th>
<th>Interest declared</th>
<th>Type of interest</th>
<th>Decision taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mark Thomas (Chair)</td>
<td>Local investigator for an Amgen sponsored trial of fortnightly versus monthly Darbepoetin dosing in CKD. This has resulted in standard trial fees paid into the departmental Research Fund for research nurse, physician and other costs. The last invoice was paid in May 2012. He has been UK Chief investigator for this multinational study, a role that is nominal as it has not required any work or resulted in any payment.</td>
<td>Non-personal, non-specific pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Mark Thomas (Chair)</td>
<td>Local investigator for a Vifor sponsored RCT of intravenous Ferinject (ferric carboxymaltose) versus oral iron therapy in treatment of iron deficiency of CKD (the FIND-CKD study). This has resulted in standard trial fees paid into the departmental Research Fund for research nurse, physician and other costs.</td>
<td>Non-personal, specific pecuniary</td>
<td>Passed responsibility for the trial to a colleague</td>
</tr>
<tr>
<td>Mark Thomas (Chair)</td>
<td>Attended a meeting at the 'Birmingham Nephology Club', sponsored by Amgen, which included a meal, on 03/07/2014.</td>
<td>Personal, non-specific pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Roy Connell</td>
<td>Organised the paediatric nephrology nurses conference (March 2014) at which Amgen contributed to the cost of hosting the education day.</td>
<td>Non-personal, non-specific, pecuniary</td>
<td>Declare and participate</td>
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<tr>
<td>Mark Devonald</td>
<td>He was sponsored by Janssen to attend the American Society of Nephrology meeting in November 2012.</td>
<td>Personal, non-specific pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Mark Devonald</td>
<td>He is the organiser of the Nottingham acute kidney injury course which received unrestricted educational grants from MSD, Amgen, Boehringer Ingleheim and Shire.</td>
<td>Non-personal, non-specific pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Mark Devonald</td>
<td>He is organising an AKI</td>
<td>Non-</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Name</td>
<td>Description</td>
<td>Personal, non-specific, pecuniary</td>
<td>Participate</td>
</tr>
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</tr>
<tr>
<td>Belinda Dring</td>
<td>Course which is sponsored by Amgen who manufacture ESAs. The funding is specifically for the course and he will not be receiving any money.</td>
<td>Personal, non-specific, pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Belinda Dring</td>
<td>Between October 2012 and March 2013: she has undertaken consultancy work for Takeda providing 2 teaching sessions on renal anaemia and processes to negotiate tariff to the sales team. She has also had sponsorship from Janssen-Cilag to attend BRS. She is also an executive member of ANSA.</td>
<td>Personal, non-specific, pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Belinda Dring</td>
<td>Has been asked to co-write an article for the Nursing times on CKD – publication due at the end of the 2014. Received a payment.</td>
<td>Personal, non-specific, pecuniary</td>
<td>Declare and participate</td>
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<tr>
<td>Damian Fogarty</td>
<td>He has previously delivered educational lectures for various pharmaceutical companies on the epidemiology and generic management of CKD and diabetic nephropathy. These were paid by modest honoraria to him directly and were delivered largely to GPs but occasionally related medicine and surgical specialties such as diabetes and vascular surgery for instance. He has also been invited to consultancy and advisory boards on an ad hoc basis usually once per annum. These were also paid by modest honoraria to him directly.</td>
<td>Personal, non-specific, pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Damian Fogarty</td>
<td>He attended an investigators meeting for the PIVOTAL trial of i.v. iron. This was for Belfast to participate as a recruitment centre.</td>
<td>Non-personal, non-specific, pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Kathryn Griffiths</td>
<td>25/9/13 Speaker at meeting in Birmingham on Atrial Fibrillation. Fee and travel expenses paid by Omnium</td>
<td>Personal, non-specific, pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Medical Meetings. 26/9/13 Speaker at BMJ Masterclass in Manchester with fee and travel paid by BMJ Education. 2/10/13 Speaker at Meeting in Bradford on Anticoagulation Choices for AF. Travel and fee paid by Leeds University Pharmacy Course.</td>
<td>Kathryn Griffiths 7/9/13 Speaker at Meeting on Atrial Fibrillation arranged by EH Medical Meetings. But sponsored by Bayer. Fee paid to CVGP the Society for GP with an interest in Cardiovascular disease. 8/10/13 Speaker at primary care meeting on Atrial Fibrillation. Fee paid to Unity Health by Boehringer Ingelheim.</td>
<td>Kathryn Griffiths 14/9/13 Speaker at CVGP meeting in Cambridge sponsored by CVGP and accommodation provided by CVGP 14/10/13 Attended Northern Lights Meeting of CVGP which was sponsored by Pfizer but paid for own refreshments and travel</td>
<td>Kathryn Griffiths I attended the ACC in Washington 28–31 March 2014 and my travel and accommodation were funded by Boehringer Ingelheim</td>
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</tr>
<tr>
<td>Kathryn Griffiths</td>
<td>Non-personal, non-specific, pecuniary interest</td>
<td>Declare and participate</td>
<td>Personal, non-specific, non-pecuniary</td>
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<tr>
<td>Ashraf Mikhail</td>
<td>Principle investigator of the PHARMACOSMOS ‘Quality of life after IV iron in CK patients’ Phase III study due to start in Jan 2015, after guideline development. Principle investigator of the Astellas ‘HIF for anaemia in dialysis patients’ Phase III study due to start in March 2015.</td>
<td>Personal, specific, pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Nicholas Palmer</td>
<td>Attended a Baxter sponsored home dialysis round table discussion in October 2012. His hotel accommodation was paid for and he received a small fee. He also attended World Kidney Day event in March 2013 at Sanofi to provide information on CKD and AKI. His expenses were paid. He attended a Fresenius sponsored discussion on commissioning in March/April 2013. He was paid a small fee for attending.</td>
<td>Personal, non-specific, pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Nicholas Palmer</td>
<td>Attended a holiday dialysis conference in Barcelona sponsored by Diaverum. He gave a talk at this event. The company paid for his accommodation, lunch and dinner.</td>
<td>Personal, non-specific, pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Nicholas Palmer</td>
<td>Attended Sanofi global meeting in Dubrovnik at the end of March/April and presented “A patients journey with CKD”. Expenses/transport and hotel were paid for.</td>
<td>Personal, non-specific, pecuniary</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Suzanne Stephens</td>
<td>Her husband is an adult haematologist and has been on advisory Boehringer Ingleheim for work on Dabigatran and has given a talk for Pfizer regarding Apixaban.</td>
<td>Non-specific, family</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Wayne Thomas</td>
<td>Invited speaker at Sysmex</td>
<td>Personal,</td>
<td>Declare and participate</td>
</tr>
<tr>
<td>Annual User Meeting. Accommodation and transport paid, but not paid to speak. Subject will be on FID in professional capacity - already written paper (2013).</td>
<td>non-specific, pecuniary</td>
<td>participate</td>
<td></td>
</tr>
</tbody>
</table>
Appendix A: Recommendations from NICE clinical guideline 114 (2011) that have been deleted or changed

Recommendations to be deleted
The table shows recommendations from 2011 that NICE proposes deleting in the 2015 update. The right-hand column gives the replacement recommendation, or explains the reason for the deletion if there is no replacement recommendation.
<table>
<thead>
<tr>
<th>Recommendation in 2011 guideline</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin levels may be used to assess iron deficiency in people with CKD. Because serum ferritin is an acute-phase reactant and frequently raised in CKD, the diagnostic cut-off value should be interpreted differently to non-CKD patients. [2006] (1.1.3.1)</td>
<td>Serum ferritin is now recommended for assessment of iron overload only and not for diagnosis of iron deficiency. Recommendation replaced by: Do not use transferrin saturation or serum ferritin measurement alone to assess iron deficiency status in people with anaemia of CKD. [new 2015] (1.1.4)</td>
</tr>
<tr>
<td>Iron-deficiency anaemia should be diagnosed in people with stage 5 CKD with a ferritin level of less than 100 micrograms/l. Considered in people with stage 3 and 4 CKD if the ferritin level is less than 100 micrograms/l. [2006] (1.1.3.2)</td>
<td>Serum ferritin is now recommended for assessment of iron overload only and not for diagnosis of iron deficiency. Replaced by new recommendations: Carry out testing to diagnose iron deficiency and determine potential responsiveness to iron therapy and long-term iron requirements at least once every 3 months (monthly for people receiving haemodialysis). - Use percentage of hypochromic red blood cells (% HRC; more than 6%) (only if processing of blood sample on the same day is possible). - If using percentage of hypochromic red blood cells is not possible, use reticulocyte haemoglobin content (CHr; less than 29 pg) or equivalent tests – for example, reticulocyte haemoglobin equivalent. - If these tests are not available or the person has thalassaemia or thalassaemia trait, use a combination of transferrin saturation (less than 20%) and serum ferritin measurement (less than 100 micrograms/litre). [new 2015] (1.1.3)</td>
</tr>
<tr>
<td>In people with CKD who have serum ferritin levels greater than 100 micrograms/l, functional iron deficiency (and hence, those patients who are most likely to benefit from intravenous iron therapy) should be defined by: - percentage of hypochromic red cells greater than 6%, where the test is available or</td>
<td>The evidence base for 1.1.3.3 has been superseded by new evidence. Serum ferritin is now recommended for assessment of iron overload only and not for diagnosis of iron deficiency. This recommendation is replaced by the following recommendations which provide new guidance on the tests used to determine the potential responsiveness to iron therapy:</td>
</tr>
</tbody>
</table>

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17 Stages of chronic kidney disease
- transferrin saturation less than 20%, when the measurement of the percentage of hypochromic red cells is unavailable. [2006] (1.1.3.3)

| - Carry out testing to diagnose iron deficiency and determine potential responsiveness to iron therapy and long-term iron requirements at least once every 3 months (monthly for people receiving haemodialysis).   
| - Use percentage of hypochromic red blood cells (% HRC; more than 6%) (only if processing of blood sample on the same day is possible).   
| - If using percentage of hypochromic red blood cells is not possible, use reticulocyte haemoglobin content (CHr; less than 29 pg) or equivalent tests – for example, reticulocyte haemoglobin equivalent.   
| - If these tests are not available or the person has thalassaemia or thalassaemia trait, use a combination of transferrin saturation (less than 20%) and serum ferritin measurement (less than 100 micrograms/litre). [new 2015] (1.1.3)

Do not use transferrin saturation or serum ferritin measurement alone to assess iron deficiency status in people with anaemia of CKD. [new 2015] (1.1.4)

| In people with functional iron deficiency, iron supplements should be given concurrently when initiating ESA therapy. [2006] (1.2.1.2) |
| Superseded by new recommendations. New evidence has allowed guidance on the type of iron supplements to be recommended:   
| Offer iron therapy to people with anaemia of CKD before discussing ESA therapy. For people who are not receiving haemodialysis, consider a trial of oral iron before offering intravenous iron therapy. [new 2015] (1.3.21) |

In people with anaemia of CKD who are not receiving haemodialysis and who are intolerant of oral iron, offer intravenous iron therapy before discussing ESA therapy. [new 2015] (1.3.22)

For people who are receiving haemodialysis, offer intravenous iron therapy before discussing ESA therapy. [new 2015] (1.3.23)

Offer intravenous iron therapy to adults

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18 At the time of publication (May, 2015), intravenous iron did not have a UK marketing authorisation for use in children and young people for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
| People with anaemia of CKD who are receiving ESAs should be given iron therapy to maintain: | Based on new evidence, serum ferritin is now recommended for assessment of iron overload only and not for diagnosis of iron deficiency: |
| - serum ferritin level greater than 200 micrograms/l | Ensure that people with anaemia of CKD who are receiving ESAs are given iron therapy to achieve: |
| - transferrin saturation greater than 20% (unless ferritin is greater than 800 micrograms/l) | - percentage hypochromic red blood cells less than 6% (unless ferritin is greater than 800 micrograms/l). |
| - percentage hypochromic red blood cells less than 6% (unless ferritin is greater than 800 micrograms/l). | - reticulocyte haemoglobin count or equivalent tests above 29 pg (unless serum ferritin is greater than 800 micrograms/litre). |
| Most patients will require 600–1000 mg of iron for adults or equivalent doses for children, in a single or divided dose depending on the preparation. Patients with functional iron deficiency should be treated with intravenous iron. Peritoneal dialysis and non-dialysis patients who do not respond to oral iron will require intravenous iron. In appropriate circumstances, iron treatment can also be administered in the community. **[2006]** (1.3.10.1) | If the above tests are not available, iron therapy should maintain transferrin saturation greater than 20% and serum ferritin level greater than 100 micrograms/litre (unless serum ferritin is greater than 800 micrograms/litre). Most patients will need 600–1000 mg of iron for adults or equivalent doses for children, in a single or divided dose depending on the preparation. Iron should be administered in a setting with appropriate facilities and healthcare staff. **[new 2015]** (1.3.18) |

In non-dialysis patients with anaemia of CKD in whom there is evidence of absolute or functional iron deficiency, this should be corrected before deciding whether ESA therapy is necessary. **[2006]** (1.3.10.2)  

New evidence has allowed guidance on the type of iron supplements to be recommended. This recommendation is superseded by the following recommendation:  

Offer iron therapy to people with anaemia of CKD before discussing ESA therapy. For people who are not receiving haemodialysis, consider a trial of oral iron before offering intravenous iron therapy. **[new 2015]** (1.3.21)  

Once ferritin levels are greater than 200 micrograms/l, and the percentage

---

19 At the time of publication (May, 2015), intravenous iron did not have a UK marketing authorisation for use in children and young people for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council’s Prescribing guidance: prescribing unlicensed medicines for further information.

20 See 1.1.3 for tests of choice to determine iron deficiency.
hypochromic red cells is less than 6% or transferrin saturation is greater than 20%, people with anaemia of CKD who are receiving ESAs should be given maintenance iron. The dosing regimen will depend on modality, for example haemodialysis patients will require the equivalent of 50–60 mg intravenous iron per week (or an equivalent dose in children of 1 mg/kg/week). Peritoneal dialysis and non-dialysis patients who do not respond to oral iron will require intravenous iron. [2006] (1.3.11.1)

<table>
<thead>
<tr>
<th>People receiving ESA maintenance therapy should be given iron supplements to keep their:</th>
<th>Based on new evidence, serum ferritin is now recommended for assessment of iron overload only and not for diagnosis of iron deficiency. The evidence base for 1.3.12.1 has been superseded by new evidence: Offer iron therapy to people receiving ESA maintenance therapy to keep their:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- serum ferritin levels between 200 and 500 micrograms/l in both haemodialysis and non-haemodialysis patients, and either - transferrin saturation level above 20% (unless ferritin is greater than 800 micrograms/l) or - percentage hypochromic red cells (%HRC) less than 6% (unless ferritin is greater than 800 micrograms/l)</td>
<td>- percentage hypochromic red cells (%HRC) less than 6% (unless serum ferritin is greater than 800 micrograms/l). - reticulocyte haemoglobin count or equivalent tests above 29 pg (unless serum ferritin is greater than 800 micrograms/l) or - transferrin saturation level above 20% and serum ferritin level above 100 micrograms/litre (unless serum ferritin is greater than 800 micrograms/litre)</td>
</tr>
<tr>
<td>In practice it is likely this will require intravenous iron. [2006] (1.3.12.1)</td>
<td>Levels should be monitored every month in people receiving haemodialysis and every 3 months in people receiving pre-dialysis or peritoneal dialysis. [new 2015] (1.3.20)</td>
</tr>
</tbody>
</table>

status:
Once percentage hypochromic red blood cells are less than 6%, reticulocyte haemoglobin count or equivalent tests above 29 pg, or transferrin saturation is greater than 20% and serum ferritin level is greater than 100 micrograms/litre, offer people with anaemia of CKD who are receiving ESAs maintenance iron. The dosing regimen will depend on modality, for example haemodialysis patients will need the equivalent of 50–60 mg intravenous iron per week (or an equivalent dose in children of 1 mg/kg/week). [new 2015] (1.3.19)

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21 At the time of publication (May, 2015), intravenous iron did not have a UK marketing authorisation for use in children and young people for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council’s Prescribing guidance: prescribing unlicensed medicines for further information.

22 See 1.1.3 for tests of choice to determine iron deficiency.
**Amended recommendation wording (change to meaning)**

Recommendations are labelled [2006, amended 2015] if the evidence has not been reviewed but changes have been made to the recommendation wording (indicated by highlighted text) that change the meaning.

<table>
<thead>
<tr>
<th>Recommendation in 2011 guideline</th>
<th>Recommendation in current guideline</th>
<th>Reason for change</th>
</tr>
</thead>
<tbody>
<tr>
<td>In people with anaemia of CKD, there may be situations where a transfusion is indicated clinically. In these cases, the relevant haematology guidelines should be followed. [2006] (1.3.2.2)</td>
<td>In people with anaemia of CKD, there may be situations where a transfusion is indicated clinically. In these cases, follow the relevant haematology guidelines. [2006, amended 2015] (1.3.3)</td>
<td>The reference has been removed as this evidence has not been reviewed by NICE. The NICE clinical guideline on Transfusion is currently in development and will form the basis of relevant haematology guidance in this area. This guideline is expected to publish in October 2015. Changed to the active voice.</td>
</tr>
<tr>
<td>Routine monitoring of iron stores should be at intervals of 4 weeks to 3 months. [2006] (1.4.1.2)</td>
<td>Routine monitoring of iron stores to prevent iron overload using serum ferritin should be at intervals of 3 months. [2006, amended 2015] (1.4.2)</td>
<td>Based on new evidence, serum ferritin is now recommended for assessment of iron overload only and not for diagnosis of iron deficiency. This recommendation has been amended to reflect this new evidence base. The frequency of monitoring is also covered elsewhere (see recommendation 1.3.20).</td>
</tr>
</tbody>
</table>

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Changes to recommendation wording for clarification only (no change to meaning)

<table>
<thead>
<tr>
<th>Recommendation numbers in current guideline</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1, 1.2.2, 1.3.9, 1.3.11, 1.3.17</td>
<td>‘Litre’ spelt out in full in line with house style.</td>
</tr>
<tr>
<td>1.1.5, 1.2.2, 1.2.5-1.2.7, 1.2.10, 1.2.11, 1.2.13--1.2.16, 1.3.1, 1.3.2, 1.3.4, 1.3.15, 1.3.17, 1.4.3, 1.4.5, 1.4.7</td>
<td>Changed to the active voice.</td>
</tr>
<tr>
<td>1.3.9, 1.3.11, 1.3.17</td>
<td>All Hb levels measured in g/decilitre changed to g/litre with a 0 added to reflect changes to practice.</td>
</tr>
<tr>
<td>1.4.5</td>
<td>The phrase, ‘the Guideline Development Group considered that…’ was removed.</td>
</tr>
</tbody>
</table>