National Institute for Health and Care Excellence

2-year surveillance (2017) – Chronic kidney disease: managing anaemia (2015) NICE guideline NG8

Appendix A3: Summary of new evidence from surveillance

Diagnostic evaluation and assessment of anaemia

NG8-01 In patients with chronic kidney disease, what haemoglobin (Hb)/haematocrit (Hct) levels are associated with adverse outcomes and what are the effects of a) age b) gender c) ethnicity?

Recommendations derived from this question

1.1.1 Consider investigating and managing anaemia in people with chronic kidney disease (CKD) if:

- their haemoglobin (Hb) level falls to 110 g/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]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated

NG8-02 Diagnostic role of glomerular filtration rate

Recommendations derived from this question (no questions made in guideline)

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/1.73 m2 the anaemia is more likely to be related to other causes. [2006]

Surveillance decision

This review question should be updated.

2-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

In developing NG8, the guideline committee discussed the previous 2006 recommendation for the trigger threshold of the eGFR for investigation of anaemia being due to chronic kidney disease (CKD). Currently this is recommended to be below 60 ml/min, although the rationale for this was both consensus based and was considered contradictory in the old LETR tables.

Although no new evidence was assessed in the development of NG8 in 2014, the guideline committee felt that a threshold below 60ml/min was too high, did not reflect current practice and was out of date. The preferred threshold was agreed by the group to be less than 30ml/min in current clinical practice today. However, no new evidence was reviewed relating to the eGFR threshold.

At the time of development of NG8, the guideline committee also highlighted inconsistencies in the original guideline between the stated eGFR thresholds for investigating anaemia and that this should be addressed in a future update. The inconsistency lies the in the threshold stated as 60ml/min in section 4.2.4 of NG8 and stated as 40ml/min section 4.4.4.

During the 2 year surveillance review in 2016, topic experts were consulted and reiterated that the contradictory thresholds could be confusing and should be amended. No topic experts were aware of any new evidence relating to the eGFR threshold for investigating anaemia, but indicated that there is a pragmatic case for changing the threshold from 60 ml/min to 30 ml/min to reflect common clinical practice.

Impact statement

Based on topic expert feedback, there is a potential impact on recommendation 1.1.2 to review the trigger threshold of the eGFR for investigation of anaemia being due to CKD. There is also a potential need to correct inconsistencies in the full guideline relating to the threshold value as stated in sections 4.2.4 and 4.4.4. The wording of the trigger threshold of below 60 ml/min eGFR for investigation of anaemia being due to CKD was considered contradictory in the original anaemia management NICE guideline CG114 but was retained in NICE guideline NG8 (Recommendation 4.2.5 in the full guideline and recommendation 1.1.2 in the NICE version give the threshold at <60 ml/min while section 4.4.4 in the NG8 full guideline gives the threshold at <40 ml/min).

New evidence identified that may change current recommendations.

NG8-03 In people with suspected (or under investigation for) anaemia in chronic kidney disease, what is the comparative clinical and cost effectiveness of the following tests or combination of tests at predicting

response to iron, when each is followed by the appropriate treatment in order to improve patient outcomes?

What is the accuracy of the following tests, or combination of tests, at predicting response to iron therapy in patients with CKD?

• Iron (Fe), total iron binding capacity (TIBC), and transferrin saturation (TSAT = Fe/TIBC)

• Ferritin

• Soluble transferrin receptor (sTfR)

• % hypochromic red cells (HCRC)

• Reticulocyte haemoglobin content.

Recommendations derived from this question

1.1.3 Carry out testing to diagnose iron deficiency and determine potential responsiveness to iron therapy and long‑term iron requirements every 3 months (every 1–3 months for people receiving haemodialysis).

- Use percentage of hypochromic red blood cells (% HRC; more than 6%), but only if processing of blood sample is possible within 6 hours.
- If using percentage of hypochromic red blood cells is not possible, use reticulocyte Hb content (CHr; less than 29 pg) or equivalent tests – for example, reticulocyte Hb 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 request transferrin saturation or serum ferritin measurement alone to assess iron deficiency status in people with anaemia of CKD. [new 2015].

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated

NG8-04 Measurement of erythropoietin

Recommendations derived from this question (no questions made in guideline)

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

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated

Managing anaemia

NG8-05 Initiation of ESA therapy in iron-deficient patients

Recommendations derived from this question (no questions made in guideline)

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

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated

NG8-06 Maximum iron levels in patients with anaemia of CKD

Recommendations derived from this question (no questions made in guideline)

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.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

NG8-07 Clinical utility of ESA therapy in iron-replete patients

Recommendations derived from this question (no questions made in guideline)

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]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated

NG8-08 Nutritional supplements

Recommendations derived from this question (no questions made in guideline)

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]

Surveillance decision

This review question should not be updated.

2-year surveillance summary

An RCT[1] (n=60) found that paricalcitol, a synthetic vitamin D analogue, compared to calcitriol, increased haemoglobin (Hb) levels in patients with stage 3b-5 CKD and anaemia. The increase occurred with no modification of iron balance, inflammatory markers, and parathyroid plasma concentrations, and was associated with a decrease in 24hr-proteinuria.

Topic expert feedback

Topic expert feedback highlighted that paricalcitol is licensed for secondary hyperparathyroidism and would be a treatment alternative to cinacalcet. It is not licensed in the UK for the treatment of anaemia.

Impact statement

The new RCT evidence is insufficient to support the use of paricalcitol in patients with CKD-related anaemia, due to the small sample size of the single identified RCT. As paricalcitol is not licensed for the treatment of anaemia in CKD and was not considered in the evidence review for NG8, further research may be needed before it can be considered for inclusion in the guideline.

New evidence is unlikely to change guideline recommendations.

NG8-09 Androgens

Recommendations derived from this question (no questions made in guideline)

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

Surveillance decision

This review question should not be updated.

2-year surveillance summary

A systematic review[2] (8 studies, n=181) found insufficient evidence to confirm that the use of androgens is beneficial for adults with CKD-related anaemia.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

From the identified systematic review, there is insufficient evidence to support the use of androgens in adults with CKD-related anaemia. This is consistent with recommendation 1.2.9, which advises against the use of androgens for treating anaemia.

New evidence is unlikely to change guideline recommendations.

NG8-010 Hyperparathyroidism

Recommendations derived from this question (no questions made in guideline)

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

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

NG8-011 Patient-centred care: ESAs

Recommendations derived from this question (no questions made in guideline)

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]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

NG8-012 Patient education programmes

Recommendations derived from this question (no questions made in guideline)

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]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Assessment and optimisation of erythropoiesis

NG8-013 Benefits of treatment with ESAs

Recommendations derived from this question (no questions made in guideline)

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]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

NG8-014 Blood transfusions

Recommendations derived from this question (no questions made in guideline)

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 national guidance*. [2006, amended 2015]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

NG8-015 Comparison of ESAs

Recommendations derived from this question (no questions made in guideline)

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]

Surveillance decision

This review question should not be updated.

* NICE is developing the guideline 'Blood transfusion' (publication expected November 2015).

2-year surveillance summary

A systematic review[3] (56 studies, n=15,596) compared the efficacy and safety of ESAs (epoetin alfa, epoetin beta, darbepoetin alfa, or methoxy polyethylene glycol-epoetin beta and biosimilar ESAs, against each other, placebo, or no treatment) to treat anaemia in adults with CKD. In network analyses, there was moderate to low quality evidence that epoetin alfa, epoetin beta, darbepoetin alfa, and methoxy polyethylene glycol-epoetin beta prevented blood transfusions compared to placebo. However, the results showed insufficient evidence to suggest the superiority of any ESA formulation based on available safety and efficacy data.

Methoxy polyethylene glycol-epoetin beta

A systematic review[4] (4 studies, n=1155) found that methoxy polyethylene glycol-epoetin beta, a continuous EPO receptor activator, increased and maintained Hb concentrations to recommended target levels in CKD patients not on dialysis. However, it should be noted that the statistical significance of the results was not reported in the abstract, and the authors highlighted the limitation of the small number of studies and the need for further research.

Darbepoetin Alfa

A secondary analysis[5] (n=816) of an RCT found that heart failure patients with anaemia, diabetes mellitus, and CKD had an increased risk of stroke as a result of darbepoetin alfa treatment for anaemia. However, the applicability of the results to CKD patients without heart failure is limited.

A systematic review[6] (32 studies, n=9414) assessed the benefits and harms of darbepoetin alfa to treat anaemia in adults and children with CKD. The results indicated that darbepoetin alfa significantly reduced the need for blood transfusions in adults with CKD stage 3 to 5, but had little or no effect on mortality or quality of life. The effects of darbepoetin alfa in adults with CKD stage 5D and children with CKD were uncertain, along with the relative benefits and harms of darbepoetin alfa compared with other ESAs.

A systematic review[7] (9 studies, n=2024) found no significant difference in mortality between patients randomly assigned to epoetin alfa and darbepoetin alfa. Larger, longer term adequately powered trials were recommended by the authors.

Recombinant human erythropoietin

A systematic review[8] (19 studies, n=993) found that treatment with recombinant human EPO in predialysis patients improved Hb, reduced the requirement for blood transfusions and also improved quality of life and exercise capacity. However, the authors were unable to assess the effects of recombinant human EPO on progression of kidney disease, delay in the onset of dialysis or adverse events.

Roxadustat

An RCT[9] (n=145) found that in patients with non-dialysis CKD and anaemia, various starting dose regimens of roxadustat (FG-4592) were well tolerated and achieved anaemia correction with reduced serum hepcidin levels. After anaemia correction, Hb was maintained by roxadustat at various dose frequencies without intravenous iron supplementation.

An RCT[10] (n=54) found that in patients with end-stage renal disease on maintenance haemodialysis therapy, anaemia therapy with roxadustat was well tolerated and effectively maintained Hb levels over a 6 week dose-ranging study (n=54) and a 19 week treatment study (n=90) with various starting doses and adjustment rules.

An RCT[11] (n=60) found that roxadustat was well tolerated and corrected anaemia in incident haemodialysis and peritoneal dialysis patients with CKD, regardless of baseline iron repletion status or C-reactive protein level and with oral or intravenous (IV) iron supplementation; it also reduced serum hepcidin levels.

Topic expert feedback

Topic expert feedback highlighted the potential importance of oral hypoxia-inducible factor (HIF) inhibitors to act on the EPO pathway in the kidney to correct anaemia in CKD patients. A study[9] was cited that is covered in the evidence summary. Topic experts advised that this and other studies indicate that this group of oral drugs may offer a different and preferable route to EPO, which has to be given by the IV or subcutaneous route. They also reduce the levels of hepcidin, the main endogenous inhibitor of iron metabolism. This appears to mean that much less oral or IV iron will be

needed in CKD patients on an HIF inhibitor, as opposed to those on EPO.

However, larger trials are underway and the topic expert feedback indicated that no known HIF inhibitors are close to market in the EU or UK at this time.

Impact statement

The new systematic review and RCT evidence, in addition to topic expert feedback, indicates that there is insufficient evidence to confirm the superiority of any ESA formulation. This is consistent with recommendation 1.3.4, which states that there is no evidence to distinguish between ESAs in terms of efficacy. Larger trials are underway on HIF inhibitors in development, such as roxadustat, to provide more definitive evidence. In particular, the NICE Surveillance team will monitor publication of the Pyrenees study, which is investigating roxadustat in the treatment of anaemia in ESRD Patients on Stable Dialysis.

Further studies may also be needed to establish any impact on the guideline recommendations on the following ESAs:

- Methoxy polyethylene glycol-epoetin beta
- Darbepoetin Alfa
- Recombinant human EPO

New evidence is unlikely to change guideline recommendations.

NG8-016 Early or deferred ESA therapy

Recommendations derived from this question (no questions made in guideline)

- No recommendations were derived from this question

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

NG8-017 Coordinating care

Recommendations derived from this question (no questions made in guideline)

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]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

NG8-018 Providing ESAs

Recommendations derived from this question (no questions made in guideline)

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]

Surveillance decision

This review question should not be updated.

2-year surveillance summary

A systematic review[12] (17 studies) found that ESA treatment of anaemia to obtain higher Hb targets did not result in important differences in health-related quality of life (HRQOL) in patients with CKD.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The new systematic review evidence indicates that ESA treatment may not impact on HRQOL. This is unlikely to impact on the patient centred plan advised in recommendation 1.3.6, which relates to the practicalities of providing ESA treatment and not to outcomes such as quality of life.

New evidence is unlikely to change guideline recommendations.

NG8-019 ESAs: optimal route of administration

Recommendations derived from this question (no questions made in guideline)

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]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

NG8-020 ESAs: dose and frequency

Recommendations derived from this question (no questions made in guideline)

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]

Surveillance decision

This review question should not be updated.

2-year surveillance summary

A systematic review[13] found no evidence to assess the clinical benefits and harms of early versus delayed EPO for anaemia in patients with end stage kidney disease undergoing haemodialysis or peritoneal dialysis.

A systematic review[14] (33 studies, n=5526) found that longer-acting ESAs (darbepoetin and continuous erythropoietin receptor activator) administered at one to four week intervals were non-inferior to recombinant human EPO given one to three times/week in terms of achieving Hb targets in haemodialysis patients. There were no significant differences in adverse events. Further research was recommended to evaluate different frequencies of ESA in peritoneal and paediatric dialysis patients and to compare different longer-acting ESAs.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The guideline committee stated that the dose and frequency of administration of ESA is likely to depend on haemoglobin level and rate of change of haemoglobin, the class of ESA used and (in the case of short-acting ESAs) the route of administration, the CKD population under treatment, and various patient factors and patient preferences.

The new systematic review evidence on the optimum frequency and timing of ESA administration in patients undergoing dialysis is inconclusive and therefore unlikely to impact on recommendation 1.3.9, which states that dose and frequency should be determined by the duration of action and route of administration of the ESA. NG8 does not make recommendations for use of specific short acting or long acting ESAs.

New evidence is unlikely to change guideline recommendations.

NG8-021 Optimal Hb levels: What should be the aspirational Hb target range for patients undergoing treatment for anaemia in CKD?

Recommendations derived from this question

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, amended 2015]

1.3.12 Consider accepting Hb levels below the agreed aspirational range if:

- high doses[‡] of ESAs are required to achieve the aspirational range or
- the aspirational range is not achieved despite escalating ESA doses. [2011]

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

Surveillance decision

This review question should not be updated.

2-year surveillance summary

A secondary analysis[15] (n=321) of an RCT found that maintaining a high Hb target range in patients with stage 5 CKD not on dialysis through ESA therapy resulted in improved renal outcomes. The outcome was measured as a composite endpoint, consisting of death, initiation of renal replacement therapy, and doubling of the serum creatinine level. The observations made in patients with stage 5 CKD were maintained on further analysis of non-diabetic patients, but were not seen in those with diabetes or stage 4 CKD.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The new evidence based on RCT data relating to target Hb levels is consistent with recommendation 1.3.10, which advises that the aspirational Hb target ranges should take account of symptoms and comorbidities.

New evidence is unlikely to change guideline recommendations.

[†] The Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2007) notes that using ESAs to achieve Hb levels greater than 120 g/litre is associated with an increased risk of death and serious cardiovascular events in people with CKD. The MHRA advises that Hb levels greater than this should be avoided, and that patients should be monitored closely to ensure that the lowest approved dose of ESA is used to provide adequate control of the symptoms of anaemia. Use of ESAs to achieve Hb levels greater than 120 g/litre is not consistent with UK marketing authorisations for ESAs. If such use is considered, 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.

[‡] More than 175 international units per kg per week for haemodialysis population; more than 125 international units per kg per week for peritoneal dialysis population; more than 100 international units per kg per week for non-dialysis population. (Data provided by the UK Renal Registry and Guideline Development Group expert opinion.)

NG8-022 Adjusting ESA treatment

Recommendations derived from this question (no questions made in guideline)

1.3.14 Optimise iron status before or coincident with the initiation of ESA administration and during maintenance treatment with ESAs. [2006, amended 2011]

1.3.15 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]

1.3.16 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.
- 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]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

NG8-023 Concurrent illness

Recommendations derived from this question (no questions made in guideline)

No recommendations were derived from this question but instead the following research recommendation was made:

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?

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

NG8-024 What is the optimal management of anaemia of CKD in hospitalised patients who are on ESAs and have a concurrent acute infectious illness?

Recommendations derived from this question

No recommendations were derived from this question.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

NG8-025 Treating iron deficiency: correction

Recommendations derived from this question (no questions made in guideline)

1.3.17 Offer people with anaemia of CKD who are receiving ESAs iron therapy to achieve[§]:

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

If the above tests are not available or the person has thalassaemia or thalassaemia trait, 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 500–1000 mg of iron for adults or equivalent doses for children[**], in a single or divided dose depending on the preparation. Intravenous iron should be administered in a setting with facilities for resuscitation. [new 2015]

Surveillance decision

This review question should not be updated.

2-year surveillance summary

Pentoxifylline

A systematic review[16] (11 studies n=377) found no conclusive evidence to support the use of pentoxifylline for improving anaemia control in CKD patients. Further research was recommended with larger sample sizes and longer follow-up.

Ferric citrate

Two identically designed RCTs[17], CRUISE 1 and 2 (n=599) found that ferric pyrophosphate citrate delivered via dialysate during hemodialysis replaced iron losses, maintained Hb concentrations, did not increase iron stores and exhibited a safety profile similar to placebo.

An RCT[18] (n=441) studied ferric citrate as a phosphorus binder and iron source for patients with CKD and on dialysis. Ferric citrate controlled phosphorus compared with placebo was found to achieve significantly higher mean iron parameters. It also reduced IV iron and ESA use while maintaining Hb.

An RCT[19] (n=149) found that short-term use of ferric citrate over 12 weeks increased iron and Hb levels, and reduced levels of serum phosphate, urinary phosphate excretion, and FGF-23 in patients with stage 3 to 5 CKD.

[§] See recommendation 1.1.3 for tests of choice to determine iron deficiency.

[**] Refer to the Summary of Product Characteristics for the prescription of individual iron preparations. At the time of publication (June 2015), intravenous iron products available in the UK did not have a UK marketing authorisation for all ages of 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. Note that the marketing authorisation for ferumoxytol in the EU was withdrawn by the manufacturer in March 2015.

Ferric carboxymaltose

An RCT[20] (n=626) found that, compared with oral iron, IV ferric carboxymaltose in non-dialysis-dependent patients with CKD and iron deficiency anaemia targeting a ferritin of 400-600 micro g/L rapidly reached and maintained Hb level. It also delayed or reduced the need for other anaemia management including ESAs. No renal toxicity was observed, nor any difference in cardiovascular or infectious events.

Iron isomaltoside 1000

An RCT[21] (n=351) found that in non-dialysis-dependent CKD patients IV iron isomaltoside 1000 was both non-inferior to oral iron at Week 4 and sustained a superior increase in Hb from Week 3 until the end of the study at Week 8. There were no significant differences in adverse effects.

Ferumoxytol

An RCT[22] (n=162) found that in CKD patients with iron deficiency anaemia, ferumoxytol and iron sucrose showed comparable efficacy and adverse events rates. The primary end point was change in Hb from baseline to week 5.

Topic expert feedback

Topic expert feedback highlighted the Cruise 1 and 2 studies[17], as being relevant to the guideline, but did not state that these studies had a definite impact on the guideline. The studies are covered in the evidence summary. Topic expert feedback also confirmed that ferric pyrophosphate citrate is not licensed in the UK for anaemia in CKD.

Impact statement

The new systematic review and RCT evidence is unlikely to impact on recommendation 1.3.17, which does not specify any single type or route of administration of iron therapy. From an assessment of abstracts, it is unclear whether the populations of the included studies are directly relevant to NG8. The studies also considered different doses, frequency and treatment types, preventing any conclusive evidence to emerge. Further research may therefore be needed on the following interventions to establish an impact on the guideline:

- pentoxifylline
- ferric citrate, including ferric pyrophosphate citrate
- intravenous ferric carboxymaltose
- intravenous iron isomaltoside 1000
- ferumoxytol and iron sucrose

New evidence is unlikely to change guideline recommendations.

NG8-026 Treating iron deficiency: maintenance

Recommendations derived from this question (no questions made in guideline)

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

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]

[**] Refer to the Summary of Product Characteristics for the prescription of individual iron preparations. At the time of publication (June 2015), intravenous iron products available in the UK did not have a UK marketing authorisation for all ages of 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. Note that the marketing authorisation for ferumoxytol in the EU was withdrawn by the manufacturer in March 2015.

Surveillance decision

This review question should not be updated.

2-year surveillance summary

Iron isomaltoside 1000

An RCT[23] (n=351) found that iron isomaltoside 1000 and iron sucrose had comparative efficacy in maintaining Hb concentrations in haemodialysis patients with CKD and with iron deficiency anaemia. The frequency, type and severity of adverse events were similar between interventions over a short term 6-week duration. The authors acknowledged that the safety profiles may differ over a longer term period.

Ferric Citrate

A secondary analysis[24] (n=441) of an RCT found that treatment with ferric citrate as a phosphate binder resulted in increased iron parameters apparent after 12 weeks and reduced intravenous iron and ESA use while maintaining Hb over 52 weeks, with a safety profile similar to that of available binders.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The new RCT evidence is unlikely to impact on recommendation 1.3.18, which does not advise on any single dosing regimen of maintenance iron. In developing the recommendation, the guideline committee did not distinguish between the two IV iron preparations in use in the UK, as they both demonstrated low adverse event rates. Further research may be needed to establish the long term safety of iron isomaltoside 1000 and ferric citrate for Hb maintenance in patients with CKD and iron deficiency anaemia, and receiving haemodialysis.

New evidence is unlikely to change guideline recommendations.

NG8-027 ESAs: What is the most clinically and cost effective and safest dose, frequency, preparation and route of administration of iron for people with anaemia of CKD with iron deficiency prior to and during ESA treatment?

Recommendations derived from this question

ESAs: monitoring iron status during treatment

1.3.19 Offer iron therapy to people** receiving ESA maintenance therapy to keep their:

- percentage of hypochromic red blood cells less than 6% (unless serum ferritin is greater than 800 micrograms/litre)
- reticulocyte Hb 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).

The marker of iron status should be monitored every 1–3 months in people receiving haemodialysis.

In people who are pre-dialysis†† or receiving peritoneal dialysis, levels are typically monitored every 3 months. If these people have a normal full blood count there is little benefit in checking iron status. [new 2015]

Iron therapy for people who are iron deficient and not on ESA therapy

1.3.20 Offer iron therapy to people** with anaemia of CKD who are iron deficient and who are not receiving ESA therapy, before discussing ESA therapy.

- Discuss the risks and benefits of treatment options. Take into account the person's choice.
- For people who are not receiving haemodialysis, consider a trial of oral iron before offering intravenous iron therapy. If they are intolerant of oral iron or target Hb levels are not reached within 3 months (see recommendation 1.3.11), offer intravenous iron therapy.
- For people who are receiving haemodialysis, offer intravenous iron therapy. Offer oral iron therapy to people who are receiving haemodialysis only if:
  - intravenous iron therapy is contraindicated **or**
  - the person chooses not to have intravenous iron therapy after discussing the relative efficacy and side effects of oral and intravenous iron therapy. **[new 2015]**

1.3.21 Discuss the results of the iron therapy with the person or, where appropriate, with their family or carers and offer ESA therapy if needed (see recommendation 1.3.1). **[new 2015]**

Iron therapy for people who are iron deficient and receiving ESA therapy

1.3.22 Offer iron therapy to people** with anaemia of CKD who are iron deficient and who are receiving ESA therapy.

- Discuss the risks and benefits of treatment options. Take into account the person's choice.
- For adults and young people, offer intravenous iron therapy.
- For children who are receiving haemodialysis, offer intravenous iron therapy.
- For children who are not receiving haemodialysis, consider oral iron. If the child is intolerant of oral iron or target Hb levels are not reached within 3 months (see recommendation 1.3.11), offer intravenous iron therapy. **[new 2015]**

1.3.23 Offer oral iron therapy to adults and young people who are receiving ESA therapy only if:

- intravenous iron therapy is contraindicated **or**
- the person chooses not to have intravenous iron therapy after discussing the relative efficacy and side effects of oral and intravenous iron therapy. **[new 2015]**

1.3.24 When offering intravenous iron therapy to people not receiving haemodialysis, consider high-dose low-frequency‡‡ intravenous iron as the treatment of choice for adults and young people when trying to achieve iron repletion. Take into account all of the following:

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†† In people who are pre-dialysis[12] or receiving peritoneal dialysis, levels are typically monitored every 3 months. If these people have a normal full blood count there is little benefit in checking iron status. [new 2015]

**Refer to the Summary of Product Characteristics for the prescription of individual iron preparations. At the time of publication (June 2015), intravenous iron products available in the UK did not have a UK marketing authorisation for all ages of 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. Note that the marketing authorisation for ferumoxytol in the EU was withdrawn by the manufacturer in March 2015.

‡‡ The Guideline Development Group (GDG) considered this to be a maximum of 2 infusions. For adults, the GDG considered there would be a minimum of 500 mg of iron in each infusion. Refer to the Summary of Product Characteristics for the prescription of individual iron preparations.

- preferences of the person with anaemia of CKD or, where appropriate, 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[§§] may be more appropriate for all children[**] and for adults who are receiving in-centre haemodialysis. **[new 2015]**

Surveillance decision

This review question should not be updated.

2-year surveillance summary

People who are iron deficient and receiving ESA therapy

An RCT[26] (n=626) assessed IV ferric carboxymaltose targeting higher (400-600mug/L) or lower (100-200mug/L) ferritin versus oral iron in anaemic patients with non-dialysis dependent CKD and iron deficiency not receiving an ESA. Hepcidin, the key regulator of iron homeostasis, levels rose in response to either IV or oral iron therapy, but the speed and extent of the rise was greatest with IV iron targeting a higher ferritin level. However neither the baseline level nor the change in hepcidin was able to predict response to therapy.

Unspecified ESA treatment status

An RCT[25] (n=136) found that among patients with CKD and iron deficiency anaemia, but not on dialysis, IV iron therapy with iron sucrose, compared with oral ferrous sulfate, was associated with an increased risk of serious adverse events, including those from cardiovascular causes and infectious diseases. The trial was terminated early on the recommendation of an independent data and safety monitoring board, based on little chance of finding differences in measured GFR slopes, but a higher risk of serious adverse events in the intravenous iron treatment group. The trial did not report in the abstract whether the participants were receiving ESA therapy.

An RCT[27] (n=60) found that IV iron treatment was associated with improved myocardial functional parameters and cardiac dimensions in patients with anaemia and CKD. Also, ferritin and transferrin saturation levels were increased, as were Hb levels, whereas inflammatory markers were reduced. It should be noted that the cardiac outcomes were not directly relevant to the outcomes of the NG8 review protocols, and the abstract did not report whether the participants were receiving ESA therapy.

A post-hoc analysis[28] of 2 RCTs (n=767) compared the safety and efficacy of different IV iron products, ferumoxytol and iron sucrose, across CKD patients with all stages of renal function. The efficacy and safety of ferumoxytol was found to be comparable to iron sucrose in patients with varying degrees of renal function. However, it should be noted that the authors did not fully report the statistical significance of results in the abstract, nor whether the participants were receiving ESA therapy.

A systematic review[29] (24 studies, n= 2,369 patients with CKD stages 3 to 5 and n=818 patients with CKD stage 5D) found that patients treated with IV iron were more likely to reach an Hb response of more than 1g/dL than oral iron supplementation for CKD stages 3-5 and stage 5D. Safety analysis showed similar rates of mortality and serious adverse effects. IV iron replacement was associated with higher risk for hypotension but fewer gastrointestinal adverse events. The authors did not report in the abstract whether the participants were receiving ESA therapy.

[§§] The Guideline Development Group (GDG) considered this to be more than 2 infusions. For adults, the GDG considered there would typically be 100–200 mg of iron in each infusion. Refer to the Summary of Product Characteristics for the prescription of individual iron preparations.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

People who are iron deficient and receiving ESA therapy

The new RCT evidence supporting the use of intravenous iron therapy targeting a higher ferritin level is consistent with recommendation 1.3.24 for non-dialysis CKD patients, which advises consideration of high-dose low-frequency intravenous iron as the treatment of choice for adults and young people when trying to achieve iron repletion.

People who are iron deficient and not on ESA therapy

The new systematic review evidence indicating similar rates of mortality and serious adverse effects is likely to be consistent with recommendations 1.2.22 and 1.2.23, in supporting the use of IV iron replacement unless contraindicated. However, it was not clear from the abstract of this review or the abstracts of the other identified RCTs whether they covered people receiving ESA therapy or not and the collective evidence on intravenous iron treatment was inconclusive. As such it is unlikely to impact on the guideline recommendations, which are structured by ESA treatment status.

New evidence is unlikely to change guideline recommendations.

Monitoring treatment of anaemia of CKD

NG8-028 Monitoring iron status

Recommendations derived from this question (no questions made in guideline)

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. [2006]

1.4.2 Routine monitoring of iron stores to prevent iron overload using serum ferritin should be at intervals of 1–3 months. [2006, amended 2015]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

NG8-029 Monitoring Hb levels

Recommendations derived from this question (no questions made in guideline)

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]**

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

NG8-030 Detecting ESA resistance

Recommendations derived from this question (no questions made in guideline)

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]

Surveillance decision

This review question should not be updated.

2-year surveillance summary

A secondary analysis[30] (n=53) of an RCT evaluated the determinants of severity of ESA resistance in patients with CKD and primary ESA-resistance. All patients, except one, were receiving dialysis. Serum alkaline phosphatase was associated with severity of ESA resistance. However the authors recommended large prospective studies to confirm this association.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The new evidence based on RCT data indicated that serum alkaline phosphatase may be associated with severity of ESA resistance, but was based on a very small sample size and may require confirmation by larger prospective studies to establish any impact on the guideline recommendations.

New evidence is unlikely to change guideline recommendations.

NG8-031 Managing ESA resistance

Recommendations derived from this question (no questions made in guideline)

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]

Surveillance decision

This review question should not be updated.

2-year surveillance summary

Vitamin E-coated dialyzer therapy

A systematic review[31] found that vitamin E-coated dialyzer therapy decreased erythropoietin resistance index in haemodialysis patients. However, it did not decrease weekly EPO dose and intima-media thickness of the carotid artery, and did not improve the serum Hb or albumin levels. In addition, there was no significant difference in serum cholesterol, triglycerides, high density lipoprotein and low density lipoprotein. It should be noted that the number of included studies, sample sizes and proportions of patients with CKD were not reported in the abstract.

Pentoxifylline

An RCT[32] (n=53) found that pentoxifylline did not significantly modify ESA hyporesponsiveness, but increased Hb concentration in patients with CKD with ESA-hyporesponsive anaemia. All patients, except one, were receiving dialysis.

A secondary analysis[33] of the RCT (n=32) found that pentoxifylline did not alter oxidative stress biomarkers in ESA-hyporesponsive CKD patients. Replicating results from the main study, pentoxifylline significantly increased Hb concentration compared with controls.

A secondary analysis[34] (n=26) of an RCT evaluated the effects of pentoxifylline on the iron-regulatory hormone hepcidin in ESA-hyporesponsive CKD patients. Hepcidin-25 concentration at 4 months adjusted for baseline did not differ significantly in pentoxifylline vs. placebo treated patients, although the difference between the groups mean hepcidin-25 concentration translated into a >25% reduction of circulating hepcidin-25 due to pentoxifylline compared to the placebo baseline.

Topic expert feedback

Topic expert feedback highlighted a study[32] which is included in the evidence summary.

Impact statement

Vitamin E-coated dialyzer therapy

The new systematic review evidence on vitamin E-coated dialyzer therapy was inconclusive and limited by partial reporting in the abstract. As such it is unlikely to impact on the guideline recommendations.

Pentoxifylline

The new evidence suggests that pentoxifylline may increase Hb concentration and modulate hepcidin-25. However, the studies did not report on toxicity and adverse events in the abstracts, and further studies may therefore be needed to determine whether pentoxifylline therapy represents a safe strategy for increasing Hb levels in patients with CKD and with ESA-hyporesponsive anaemia.

New evidence is unlikely to change guideline recommendations.

NG8-032 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?

Recommendations derived from this question

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 kidney transplant, in addition to Hb 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]**

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Research recommendations

RR – 01 What is the optimal management (in terms of clinical and cost effectiveness) of anaemia of chronic kidney disease (CKD) in patients who are receiving erythropoietic stimulating agents (ESAs) and have a significant concurrent acute infectious illness?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 02 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?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 03 What is the most effective type of intervention to treat haemodialysis patients with ESA‑resistant anaemia?

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the evidence is insufficient to impact on the recommendations.

The new evidence suggests that pentoxifylline may increase Hb concentration and modulate hepcidin-25. However, the studies did not report on toxicity and adverse events in the abstracts and further studies may be needed to determine whether pentoxifylline therapy represents a safe strategy for increasing Hb levels in patients with CKD and with ESA-hyporesponsive anaemia.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 04 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 haemodialysis)?

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the evidence is insufficient to impact on the recommendations.

New RCT evidence suggests that, in CKD patients not receiving dialysis, IV iron isomaltoside 1000 may be both non-inferior to oral iron at Week 4 and could sustain a superior increase in haemoglobin for 3 to 8 weeks, without significant differences in adverse effects. However, further research may be needed to establish its longer term safety profile, to fully address the research recommendation.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 05 In people with anaemia of CKD opting for conservative management, what is the clinical and cost effectiveness of treating to differing target haemoglobin (Hb) levels?

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the evidence is insufficient to impact on the recommendations.

New evidence based on RCT data suggested that, in non-diabetic patients with stage 5 CKD not on dialysis, maintaining a high Hb target range through ESA therapy may result in improved renal outcomes. However, the study did not consider a lower than usual ‘permissive’ target Hb level, as specified in the research recommendation. Further research on permissive versus normal target Hb levels in people specifically opting for conservative management may be needed to fully address the research recommendation.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

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