CLINICAL PRACTICE GUIDELINES

Anaemia of CKD

UK Renal Association

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Acknowledgements

Introduction

This clinical practice guideline provides recommendations on the management of anaemia of chronic kidney disease (CKD) and serves as an update of the 4th edition module published online in 2007. The recommendations in this update have been graded using the modified GRADE system to indicate both the strength of each recommendation (strong or weak) and level of evidence for the recommendation (A-D).[1,2] As in the previous module The Renal Association (RA) endorses the NICE Guidelines for Anaemia Management in Chronic Kidney Disease (CKD) 2006[3].

These guidelines are an updated version of the previous "Complications of CKD Guidelines-Anaemia Section". For this updated version, a systematic literature review was performed using MEDLINE & PUBMED, focusing on the topics of:

- Renal anaemia;
- Anaemia & CKD;
- Iron deficiency;
- Iron therapy;
- Iron Toxicity;
- EPO, ESA;
- Anaemia & dialysis;
- Blood Transfusion and dialysis;
- Renal transplant and anaemia;
- Renal transplant & EPO;
- Renal transplant & blood transfusion;
- Immunosuppression & anaemia;
- Immunosuppression & EPO;
- Imunosuppression & blood transfusion.

The search covered the period from January 2007 to November 2009. Articles not written in English were not assessed. Articles available in abstract forms; letters; case reports; editorials or review articles were also excluded. Articles were assessed for relevance to the guideline topic, eligibility for inclusion in the evidence base for that guideline and methodological quality. Articles were considered of particular relevance if they were describing:

- Prospective randomized or quasi-randomized trials;
- Controlled trials;
- Meta-analysis of several trials;
- Cochrane systematic reviews

Where evidence was available from RCTs and systematic reviews, recommendations were based on these publications. Where there was a lack of evidence from high-quality studies, recommendations were based on the best available evidence, taking in account the European Renal Best Practice (ERBP) for Anaemia in CKD[4] and the KDOQI Guidelines for management of anaemia in CKD[5] as well as the NICE guidelines[3]. The guideline has been harmonised with the 2010 update of the NICE guidance on anaemia management in CKD[6].

The KDIGO website (www.kdigo.org)[7] is a useful site of reference for comparison of evidence based guidelines internationally.

References

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4. Locatelli F, Aljama P, Barany P et al. Revised European best practice Guidelines for the management of anaemia in patients with chronic renal failure. Nephrol.Dial.Transplant. 2004; 19 Suppl 2: ii1-47
5. KDOQI; National Kidney Foundation Clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease in adults. Am J Kidney Dis. 2006 May; 47(5 Suppl 3):S16-85.
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7. www.kdigo.org

Summary of clinical practice guidelines on anaemia of CKD

1. Anaemia of CKD (Guidelines 1.1 – 1.6)

Guideline 1.1 – Evaluation of anaemia - Screening for anaemia

We recommend that haemoglobin (Hb) levels should be tested at least annually in CKD patients. (1B)

Guideline 1.2 - Evaluation of anaemia - Haemoglobin level

We recommend that all patients with chronic anaemia associated with chronic kidney disease (CKD) should be investigated for possible treatment, irrespective of the stage of kidney disease or requirement for renal replacement therapy. (1A)

Anaemia should be evaluated in CKD patients with Hb < 11g/dL or symptoms attributable to anaemia.

Guideline 1.3 - Evaluation of anaemia - Renal function

We suggest that CKD should be considered as a possible cause of anaemia when the glomerular filtration rate (GFR) is <60 ml/min/1.73m^2. It is more likely to be the cause if the GFR is < 30mls/min/ 1.73m^2 (<45 in diabetics) and no other cause, i.e. blood loss, folic acid or vitamin B12 deficiency, is identified. (2B)

Guideline 1.4 - Evaluation of anaemia - Erythropoietin measurement

We recommend that measurement of erythropoietin levels should not routinely be considered for the diagnosis or management of anaemia for patients with CKD. (1A)

Guideline 1.5 - Evaluation of anaemia –Baseline investigations

We recommend that initial clinical and laboratory evaluation of anaemia should be performed prior to initiation of treatment for anaemia in CKD patients. (1A)

Guideline 1.6 – Evaluation of anaemia – Baseline investigations

We recommend that laboratory evaluation should include the following tests (1B):

- Full blood count (FBC) including—in addition to the Hb concentration—red blood cell indices (mean corpuscular haemoglobin [MCH], mean corpuscular volume [MCV], mean corpuscular haemoglobin concentration [MCHC]), white blood cell count, differential count and platelet count.
- Absolute reticulocyte count to assess bone marrow responsiveness (if indicated).
- Serum ferritin to assess iron stores.
- Serum transferrin saturation (TSAT) or reticulocyte Hb content (CHr) to assess adequacy of iron for erythropoiesis.
- Percentage of hypochromic red blood cells (HRC).
- Plasma/serum C-reactive protein (CRP) - to assess inflammation.

Based on the initial assessment and in selected cases, the following tests may be useful to diagnose the cause of anaemia in some patients with CKD (1B):

- Serum B12 and red cell folate concentrations.
- Tests for haemolysis (plasma/serum levels of haptoglobin, lactate dehydrogenase, bilirubin, Coombs' test).
- Plasma/serum and/or urine protein electrophoresis.
- Hb electrophoresis and bone marrow examination.

2. Anaemia of CKD (Guidelines 2.1 – 2.10)

Guideline 2.1 - Treatment of Anaemia - Erythropoiesis Stimulating Agents

We recommend that treatment with Erythropoiesis Stimulating Agents (ESAs) should be offered to patients with anaemia of CKD who are likely to benefit in terms of quality of life and physical function and to avoid transfusion in patients considered suitable for transplantation. (1A)

Guideline 2.2 - Treatment of Anaemia - Choice of ESA

We recommend that the decision on the choice of ESA is based on local availability of ESAs. (1B)

Guideline 2.3 - Treatment of Anaemia with ESA therapy - Target Hb

We recommend that patients with CKD on ESA therapy should achieve Hb between 10-12 g/dl. (1B)

Guideline 2.4 - Treatment of Anaemia without ESA therapy - Target Hb

We recommend that these Hb targets apply exclusively to patients receiving ESA and are not intended to apply to the treatment of iron deficiency in patients receiving iron therapy without the use of ESAs. (1B)

Guideline 2.5 - Treatment of Anaemia - Initial ESA dose

We recommend that the initial ESA dose should be determined by the patient's Hb level, the target Hb level, the observed rate of increase in Hb level and clinical circumstances. (1B)

Guideline 2.6 - Treatment of Anaemia with ESA therapy - Route of administration

We suggest that the route of ESA administration should be determined by the CKD stage, treatment setting, efficacy, safety, and class of ESA used; subcutaneous (SC) route is the access of choice in non-HD patients, while convenience may favour intravenous (IV) administration in HD patients. (2B)

Guideline 2.7 - Treatment of Anaemia with ESA therapy - Frequency of administration

We suggest that the frequency of administration should be determined by the CKD stage, treatment setting and class of ESA. Less frequent administration using long acting ESAs may be the treatment of choice in non–HD patients. (2B)

Guideline 2.8 - Treatment of Anaemia with ESA Therapy - **ESA dose adjustments**

We recommend that adjustments to ESA doses should be considered when Hb is <10.5 or >11.5 g /dL in order to balance the benefit and safety to patients given the current evidence base. These thresholds for intervention should achieve a population distribution centred on a mean of 11g/dl with a range of 10-12. (1B)

Guideline 2.9 - Treatment of Anaemia with ESA Therapy - ESA dose adjustments

We suggest that ESA doses should ideally be decreased rather than withheld when a downward adjustment of Hb level is needed. (2B)

Guideline 2.10 - Treatment of Anaemia with ESA Therapy – ESA dose adjustments

We recommend that ESA administration in ESA-dependent patients should continue during acute illness, surgical procedures or any other cause of hospitalisation. (1B)

3.   Anaemia of CKD (Guidelines 3.1 – 3.4)

Guideline 3.1 - Treatment of Anaemia with Iron therapy – Iron repletion

We recommend that patients should be iron replete to achieve and maintain target Hb whether receiving ESAs or not. (1A)

Guideline 3.2 - Treatment of Anaemia with Iron therapy - Initiation of ESA and iron status

We recommend that ESA therapy should not be initiated in the presence of absolute iron deficiency (ferritin <100ng/ml). In patients with functional iron deficiency, iron supplements should be given prior to or when initiating ESA therapy. (1A)

Guideline 3.3 - Treatment of Anaemia with Iron therapy - Route of Administration

We suggest that oral iron will, in general, be sufficient to attain and maintain the Hb above targets in ESA treated CKD patients not yet requiring dialysis and in those on peritoneal dialysis (PD). (2B)
In contrast most HD patients will require intravenous iron. (2A)

Guideline 3.4 - Treatment of Anaemia with Iron therapy - Upper limit for iron therapy

We recommend that serum ferritin should not exceed 800ng/ml in patients treated with iron, and to achieve this iron management should be reviewed when the ferritin is > 500ng/ml. (1B)

4. Anaemia of CKD (Guidelines 4.1 – 4.5)

Guideline 4.1 - Monitoring of treatment - Hb during ESA therapy

We recommend that Hb concentration should be monitored every month in the correction phase and every 1-3 months for stable patients in the maintenance phase. More frequent monitoring will depend on clinical circumstances. (1B)

Guideline 4.2 - Monitoring of treatment - Iron therapy

We recommend regular monitoring of iron status (1-3 monthly) during treatment to avoid toxicity (1B): a serum ferritin consistently greater than 800 ng/ml is suggestive of iron overload. (1B)

Guideline 4.3 - Monitoring during Intravenous Iron Administration

We recommend that resuscitative medication and personnel trained to evaluate and resuscitate anaphylaxis should be present at each administration of iron dextran. (1A)

Guideline 4.4 - Monitoring of treatment - Resistance to ESA therapy

We recommend that inadequate response ('resistance') to ESA therapy is defined as failure to reach the target Hb level despite SC epoetin dose >300 IU/kg/week (450 IU/kg/week IV epoetin), or darbepoetin dose >1.5mcg/kg/week. Hyporesponsive patients who are iron replete should be screened clinically and by investigations for other common causes of anaemia. (1A)

Guideline 4.5 - Monitoring of treatment - Hypertension during ESA therapy

We recommend that blood pressure should be monitored in all patients receiving ESAs and, if present, hypertension be treated by volume removal and/or hypotensive drugs. (1A)

5. Anaemia of CKD (Guidelines 5.1 – 5.2)

Guideline 5.1 - Blood Transfusion

We recommend that in patients with anaemia of CKD, especially those in whom renal transplantation is an option, red blood cell transfusion should be avoided if possible. (1A)

Guideline 5.2 - Blood Transfusion

We recommend if red blood cell transfusion becomes essential (usually in the setting of acute blood loss, acute haemolysis or severe sepsis) transfusion should be based on policies set by local transfusion guidelines rather than Hb targets for ESA therapy in chronic anaemia of CKD. (1B)

6. Anaemia of CKD (Guideline 6.1)

Guideline 6.1 - Post-transplantation Anaemia

We recommend that the treatment guidelines for anaemia in renal transplant patients should be similar to those for CKD patients not on dialysis. (1B)

Summary of Audit Measures

1. Proportion of CKD patients with eGFR < 30ml/min by 4 variable MDRD method with an annual Hb level
2. Proportion of patients starting an ESA without prior measurement of serum ferritin and/or TSAT
3. Proportion of patients on renal replacement therapy with Hb level < 10 who are not prescribed an ESA
4. Each renal unit should audit the type, route and frequency of administration and weekly dose of ESA prescribed
5. The proportion of CKD stage 4-5 patients with Hb 10 -12 g/dl
6. The proportion of patients treated with an ESA with Hb > 12 g/dl
7. Each renal unit should monitor ESA dose adjustments
8. Proportion of patients with serum ferritin levels < 100ng/ml at start of treatment with ESA
9. Proportion of predialysis and PD patients receiving iron therapy; type: oral vs. parenteral
10. Proportion of HD patients receiving IV iron
11. Prevalence of resistance to ESA among renal replacement therapy patients
12. Proportion of HD patients who received a blood transfusion within the past year

Rationale for clinical practice guidelines for anaemia of CKD

1.   Anaemia of CKD (Guidelines 1.1 – 1.6)

Guideline 1.1 – Evaluation of anaemia - Screening for anaemia

We recommend that haemoglobin (Hb) levels should be tested at least annually in CKD patients. (1B)

Audit Measure

Proportion of CKD patients with eGFR < 30ml/min by 4 variable MDRD method with an annual Hb level

Rationale

There is not enough literature to suggest the ideal frequency of Hb testing in CKD patients who are not on ESA therapy. Alternatively data from clinical trials have shown that the rate of Hb decline in these patients is a gradual one.[1,2] In a Canadian study to assess the effect of ESA therapy on left ventricular mass in CKD patients[2] 172 patients were assigned to either receive therapy with erythropoietin α subcutaneously to maintain or achieve Hb level targets of 12.0 to 14.0 g/dL, or to the control/ delayed treatment group with mean Hb levels of 9.0 ± 0.5 g/dL. During 2 years follow up a significant proportion of patients eventually required ESA therapy. However, among those who did not require ESA therapy, mean Hb values remained relatively stable throughout the study period.

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1. Roger SD, McMahon LP, Clarkson A, et al. Effects of early and late intervention with epoetin α on left ventricular mass among patients with chronic kidney disease (stage 3 or 4): Results of a randomized clinical trial. J Am Soc Nephrol 2004; 15:148-156.
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Guideline 1.2 - Evaluation of anaemia - Haemoglobin level

We recommend that all patients with chronic anaemia associated with chronic kidney disease (CKD) should be investigated for possible treatment, irrespective of the stage of kidney disease or requirement for renal replacement therapy. (1A)

Anaemia should be evaluated in CKD patients with Hb < 11g/dL or symptoms attributable to anaemia.

Rationale

The Renal Association (RA) and Royal College of Physicians endorse the NICE Guidelines for Anaemia Management in Chronic Kidney Disease (CKD) 2006[1] .The reader is referred to these guidelines as well as the European Renal Best Practice (ERBP) for Anaemia in CKD[2] and the KDOQI[3] Guidelines for management of anaemia in CKD. The KDIGO website (www.kdigo.org)[4] is a useful site of reference for comparison of evidence based guidelines internationally.

Anaemia is defined as having a Hb value below the established cut off defined by the World Health Organisation[5]. Different defined groups have different cut offs. For adults:

- Men and postmenopausal women Hb<13.0g/dl
- Premenopausal women Hb<12.0g/dl

In 2006, KDOQI modified this definition by giving a single criterion for diagnosing anaemia in adult males (Hb <13.5 g/dl, regardless of age) because the decrease in Hb among males aged >60 years is often attributable to associated co-morbidities.[3]

In addition to gender, age and pregnancy other factors influence Hb level including smoking, altitude, race and genetic disorders (thalassaemia and sickle cell disease). In CKD a patient's anaemia should be defined using these same criteria. The degree of renal impairment affects the likelihood of any patient developing anaemia. Although current treatment with ESAs is not recommended unless Hb falls consistently below 11.0g/dl, other causes of anaemia should be excluded in patients with Hb below normal range. The current definition for anaemia applies to adult patients older than 18 years, of all races and ethnic groups, and living at relatively low altitude (<1,000 m or 3,000 ft).[5] With increasing altitude, endogenous erythropoietin production is increased; as a result, Hb concentration can be expected to increase by about 0.6 g/dL in women and 0.9 g/dL in men for each 1,000m of altitude above sea level.[6]

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Guideline 1.3 - Evaluation of anaemia - Renal function

We suggest that CKD should be considered as a possible cause of anaemia when the glomerular filtration rate (GFR) is <60 ml/min/1.73m^2. It is more likely to be the cause if the GFR is < 30mls/min/ 1.73m^2 (<45 in diabetics) and no other cause, i.e. blood loss, folic acid or vitamin B12 deficiency, is identified. (2B)

Audit measure

Proportion of CKD patients with eGFR < 30ml/min by 4 variable MDRD method[1] with an annual Hb level

Rationale

The prevalence of anaemia in patients with CKD increases as the GFR progressively falls[1]. NHANES III data demonstrate a prevalence of anaemia of 1%, 9% and 33% in CKD patients with an eGFR of 60, 30 and 15ml/min respectively.[2] UK data of > 112,000 unselected patients in the general population showed a population prevalence of CKD 3-5 of 4.9%.[3] In these patients the prevalence of gender specific anaemia (<12 men: < 11 women) was 12%.

Anaemia is more prevalent among patients with diabetes. In addition, anaemia of CKD develops earlier in patients with diabetes compared with non-diabetics.[4-8] In a cross-sectional study involving over 800 patients with diabetes, anaemia has been found to be two to three times more prevalent in patients with diabetes compared with the general population at all levels of GFR.[9]

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Guideline 1.4 - Evaluation of anaemia - Erythropoietin measurement

We recommend that measurement of erythropoietin levels should not routinely be considered for the diagnosis or management of anaemia for patients with CKD. (1A)

Rationale

In renal anaemia, serum erythropoietin (EPO) levels are lower than appropriate for the degree of anaemia. In CKD patients with anaemia, erythropoietin titres are not lower but may be equal to or even higher than in normal non-anaemic individuals.[1-3] Measurement of erythropoietin level is very rarely helpful.

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Guideline 1.5 - Evaluation of anaemia – Baseline investigations

We recommend that initial clinical and laboratory evaluation of anaemia should be performed prior to initiation of treatment for anaemia in CKD patients. (1A)

Audit measure

Proportion of patients starting an ESA without prior measurement of serum ferritin and/or TSAT

Rationale

Although relative erythropoietin deficiency is common among patients with anaemia and CKD, other potential causes should be identified or excluded. A clinical and laboratory evaluation of the cause of anaemia should precede initiation of ESA therapy. The recommended laboratory evaluation aims at assessing:

- The degree and cause of anaemia,
- Bone marrow responsiveness, and
- Iron stores and iron availability for erythropoiesis.

Anaemia due to causes other than erythropoietin deficiency should be suspected when:

- The severity of the anaemia is disproportionate to the deficit in renal function,
- There is evidence of iron deficiency,
- There is evidence of haemolysis, or
- There is evidence of bone marrow disorder as manifest by leucopaenia or thrombocytopaenia.

Guideline 1.6 – Evaluation of anaemia – Baseline investigations

We recommend that laboratory evaluation should include the following tests (1B):

- **Full blood count (FBC) including—in addition to the Hb concentration— red blood cell indices (mean corpuscular haemoglobin [MCH], mean corpuscular volume [MCV], mean corpuscular haemoglobin concentration [MCHC]), white blood cell count, differential count and platelet count.**
- **Absolute reticulocyte count to assess bone marrow responsiveness (if indicated).**
- **Serum ferritin to assess iron stores.**
- **Serum transferrin saturation (TSAT) or reticulocyte Hb content (CHr) to assess adequacy of iron for erythropoiesis.**
- **Percentage of hypochromic red blood cells (HRC).**
- **Plasma/serum C-reactive protein (CRP) to assess inflammation.**

Based on the initial assessment and in selected cases, the following tests may be useful to diagnose the cause of anaemia in some patients with CKD (1B):

- **Serum B12 and red cell folate concentrations.**
- **Tests for haemolysis (plasma/serum levels of haptoglobin, lactate dehydrogenase, bilirubin, Coombs' test).**
- **Plasma/serum and/or urine protein electrophoresis.**
- **Hb electrophoresis and bone marrow examination.**

Rationale

Although relative erythropoietin deficiency is common among patients with anaemia and CKD, other potential causes should be identified or excluded. A clinical and laboratory evaluation of the cause of anaemia should precede initiation of ESA therapy. The recommended laboratory evaluation aims at assessing:

- The degree and cause of anaemia,
- Bone marrow responsiveness, and
- Iron stores and iron availability for erythropoiesis.

Anaemia due to causes other than erythropoietin deficiency should be suspected when:

- The severity of the anaemia is disproportionate to the deficit in renal function,
- There is evidence of iron deficiency,
- There is evidence of haemolysis, or
- There is evidence of bone marrow disorder as manifest by leucopaenia or thrombocytopaenia.

a) Assessment of anaemia severity

In CKD patients not yet requiring dialysis and in those on peritoneal dialysis (PD), the timing of the blood sample draw is not critical because plasma volume in these patients remains relatively constant. In haemodialysis (HD) patients, interdialytic weight gain contributes to a decrease in Hb level, whereas intradialytic ultrafiltration leads to an increase in Hb level. Thus, a predialysis sample underestimates the euvolaemic Hb level, whereas a postdialysis sample over-estimates the euvolaemic Hb. In a study of 68 stable HD patients receiving recombinant human erythropoietin (rHuEPO) subcutaneously, average mean pre-dialysis Hb was 1 gm/dL lower than average postdialysis Hb.[1] There was a strong linear inverse correlation between percentage of change in Hb and haematocrit (Hct) values and percentage of change in body weight. In another study of 49 stable HD patients, among all pre-HD and post-HD Hb values, levels measured at the end of short dialysis intervals were closest to the mean Hb value of the week, derived from calculation of the area under the curve for the readings of the week.[2] Given the relationship between Hb level and the dialysis related weight change, midweek pre-dialysis sampling should be optimal for regular Hb monitoring.

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2. Bellizzi V, Minutolo R, Terracciano V et al. Influence of the cyclic variation of hydration status on haemoglobin levels in hemodialysis patients. Am J Kidney Dis 2002; 40:549-555.

b) Assessment of Bone Marrow Responsiveness

In general, anaemia of CKD is normochromic and normocytic and is morphologically indistinguishable from the anaemia of chronic illness. Initial assessment of anaemia in CKD patients should aim at identifying other factors that may influence the response to treatment. In addition to Hb, other indices of the FBC report may provide important clinical information:

- Macrocytosis could be due to folate or vitamin B_{12} deficiency.
- In addition to anaemia of CKD, microcytosis could be due to iron deficiency or haemoglobinopathies.
- Macrocytosis with leucopaenia or thrombocytopaenia could be due to several factors such as alcohol intake, nutritional deficit (vitamin B_{12} or folate deficiency), or myelodysplasia.
- Haemolysis is suggested by the presence of macrocytosis, high lactate dehydrogenase and positive Coombs' test.

The normal absolute reticulocyte count ranges from 40,000 to 50,000 cells/µL. Although it has a significant inter-patient variability, this test may be useful as a semi-quantitative marker of erythropoietic activity.

c) Evaluating Iron Status in Anaemic Patients with CKD

The aim of evaluating iron status is to assess:

1. Iron level in tissue stores and

2. The adequacy of iron utilisation for erythropoiesis.

Serum ferritin level is the only available blood marker of storage iron. There are several tests to assess adequacy of iron for erythropoiesis: TSAT, MCV, MCH, percentage of hypochromic red blood cells (HRC) and reticulocyte Hb content (CHr).

Tests limitations:

- HRC estimation is a useful test for assessment of iron availability but is limited by the effect of sample storage time and need for special analysers. Long sample storage time (> 4 hours) may spuriously increase HRC.
- MCV and MCH are decreased only after long-standing iron deficiency.
- TSAT is the most widely used test to assess the adequacy of iron supply for erythropoiesis but is limited by high day to day variations. TSAT is also influenced by nutritional status and inflammation.
- It is preferable to test Hb, ferritin, and TSAT or CHr together because the combination provides an important insight into erythropoiesis, iron storage and iron availability to bone marrow.

In patients with CKD not on dialysis, serum ferritin levels less than 25 ng/mL in males and less than 12 ng/mL in females suggest depletion of iron stores as a cause of anaemia; but serum ferritin level is less reliable in the evaluation of iron stores in HD patients, because ferritin level is affected by other factors in addition to iron storage status. In relatively healthy HD patients, before widespread use of IV iron therapy, the finding of a ferritin level less than 50 ng/mL was not uncommon[1] and was associated with absent bone marrow iron in approximately 80% of patients.[2] However, in HD patients with several co-morbidities, absent iron stores may still be found at ferritin levels approaching or even exceeding 200 ng/mL.[3]

Iron-deficiency erythropoiesis is most likely to contribute to anaemia when TSAT results are less than 16%. However, the clinical utility of TSAT is impaired by the absence of a diagnostic threshold, above which deficient iron utilisation can be excluded as a cause of anaemia.[4]

There is little information in literature to guide the approach to CKD patients who show laboratory evidence of iron deficiency. Nevertheless, given the high prevalence of GI blood loss due to variety of causes in this patient population, deciding on a subsequent management plan, including endoscopy, depends on the clinical presentation. This supports the recommendation that CKD patients who present with anaemia and iron deficiency should undergo careful clinical assessment prior to the initiation of anaemia therapy.[5,6,7]

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2. Anaemia of CKD (Guidelines 2.1 – 2.10)

Guideline 2.1 - Treatment of Anaemia - Erythropoiesis Stimulating Agents

We recommend that treatment with Erythropoiesis Stimulating Agents (ESAs) should be offered to patients with anaemia of CKD who are likely to benefit in terms of quality of life and physical function and to avoid transfusion in patients considered suitable for transplantation. (1A)

Audit measure

Proportion of patients on renal replacement therapy with Hb level < 10 g/dL who are not prescribed an ESA

Rationale

Treatment of anaemia in CKD with ESA can be expensive[1], takes time to work and carries a small but significant risk to the patient. It is therefore reasonable, as with any therapy, to treat only those who are expected to benefit in the time frame that therapy is being considered. For example, patients with severe sepsis/inflammation/acute bleeding are unlikely to respond. Patients with a very short life expectancy (days or weeks) are not likely to survive long enough for therapy to provide benefit in terms of an increase in Hb. The clinician and patient should agree on a therapeutic plan and, at an appropriate time, review whether therapy is providing enough benefit to continue treatment.

Reference

1. National Collaborating Centre for Chronic Conditions, Royal College of Physicians. Guideline on anaemia management in chronic kidney disease. 2006. National Institute for Clinical Excellence.

Guideline 2.2 - Treatment of Anaemia - Choice of ESA

We recommend that the decision on the choice of ESA is based on local availability of ESAs. (1B)

Audit measure

Each renal unit should audit the type, route and frequency of administration and weekly dose of ESA prescribed

Rationale

Many studies have been published comparing different ESA products against each other when used at different dosing intervals, by different routes of administration and in different patient groups. All the available products are efficacious when administered according to the manufacturers' recommendations. The choice of ESA will be dependent upon the clinician and patient agreeing a management plan and local supply arrangements.[1]

Reference

1. National Collaborating Centre for Chronic Conditions, Royal College of Physicians. Guideline on anaemia management in chronic kidney disease. 2006. National Institute for Clinical Excellence.

Guideline 2.3 - Treatment of Anaemia with ESA therapy - Target Hb

We recommend that patients with CKD on ESA therapy should achieve Hb between 10-12 g/dl. (1B)

Guideline 2.4 - Treatment of Anaemia without ESA therapy - Target Hb

We recommend that these Hb targets apply exclusively to patients receiving ESA and are not intended to apply to the treatment of iron deficiency in patients receiving iron therapy without the use of ESAs. (1B)

Audit measures

The proportion of CKD stage 4-5 patients with Hb 10-12 g/dl.
The proportion of patients treated with an ESA with Hb > 12 g/dl.

Rationale for Guidelines 2.3 and 2.4

- In determining target Hb guidelines it is important to assess potential benefits (in terms of possible improved survival, improvement in health related quality of life - HRQoL - and avoidance of transfusion) vs. potential harms (increased mortality, increased risk of vascular events).
- Although several studies have shown that higher Hb targets lead to improvements in both physical and mental health domains[1-4] the HRQoL benefits of higher Hb targets diminish over time.[1,5] In addition, there is no apparent Hb threshold above which there is definitively a quality-of-life improvement in the higher Hb treatment arms.
- Recently the Anaemia Working Group of ERBP expressed its view that Hb values of 11-12 g/dL should be generally sought in the CKD population without intentionally exceeding 13 g/dL.[6]
- The rationale behind choosing a wide target Hb range (10-12 g/dl) is that when the target Hb level is narrow (i.e.1 g/dL), variability in achieved Hb levels around the target is high,

the fraction of prevalent patients with achieved Hb levels within the target range is low and ESA dose titration is required frequently during maintenance therapy.

- The health economics of anaemia therapy using ESAs has been subject to a NICE systematic review[7] which concludes that treating to a target Hb 11-12g/dl is cost effective in HD patients. In a US study the incremental cost per quality-adjusted life year (QALY) of target Hb 12.0-12.5 g/dl vs.11.0-12.0 g/dl was $613,015. An additional $828,215 per additional QALY gained was required to achieve a target Hb of 14g/dl versus 12.0-12.5g/dl. To put this guideline into current context, Table 1 summarises the mean Hb data for prevalent UK dialysis patients from the Eighth (2005) and Eleventh (2008) UK Renal Registry Reports.[8,9]

Table 1: Hb data for UK prevalent HD patients[8,9]

	Hb (Mean±sd)	Hb > 10 g/dl	90% Hb range	Interquartile Hb range	Hb > 11 g/dl
2005	11.7±1.6	85%	9.2-14.6	10.6-12.8	68%
2008	11.6±1.5	86%	8.9-14	10.6-12.6	68%

- Besarab et al[4] reported a study of normalisation of haemoglobin in patients with high cardiovascular risk on haemodialysis. Normalisation of haemoglobin showed no benefit in risk reduction but did show an improvement in quality of life. The treatment arm showed a trend towards increased risk of death and vascular access failure and the trial was stopped on the grounds that the study was unlikely to show benefit from normalisation.

- There have been two important studies of patients not yet on dialysis – CHOIR[10] and CREATE[1]. The outcome of the CHOIR study showed no benefit of higher haemoglobin outcome in CKD patients randomised to Hb of 11.3g/dl vs. 13.5g/dl. Higher outcome target Hb had an increased risk (using composite end-points of death, myocardial infarction, or hospitalisation for congestive cardiac failure) and no incremental improvement in quality of life. The limitation of this study is that, compared with the group assigned to the lower Hb treatment target, the higher Hb target group showed at baseline a statistically greater proportion of patients with a history of hypertension and coronary artery bypass graft. A report posted by the study sponsor (PROCRIT ®: Clinical Study Report PR00-06-014 (CHOIR) Synopsis, 12 September 2006; available at: www.clinicaltrials.gov, last accessed January 12, 2007) indicates that patients assigned to the higher Hb treatment arm also had a significantly greater severity of congestive heart failure (CHF) at baseline. The results of a multivariate analysis, included in this report, indicate that after adjustment for baseline conditions (CHF by National Health and Nutrition Examination Survey CHF score, atrial fibrillation/flutter, serum albumin level, reticulocyte count, and age), the relationship between treatment assignment and primary composite outcome events is no longer statistically significant (hazard ratio [HR], 1.24; 95% confidence interval [CI], 0.95 to 1.62; p = 0.11 compared with the unadjusted HR of 1.34; 95% CI, 1.03 to 1.74; p = 0.03 reported in the publication[11]). A secondary analysis of the CHOIR trial suggested that higher doses of epoetin α were associated with an increased risk of death, myocardial infarction, congestive heart failure or stroke compared with lower epoetin doses, and with poorer outcomes.[11] Another secondary analysis of the CHOIR study found that, among patients with diabetes mellitus, the percentage of patients reaching the primary end point of death, myocardial infarction, congestive heart failure or stroke within 3 years was similar in the high and low haemoglobin arms of the

trial (24.8% versus 24.7%, respectively; p = 0.249). By contrast, among patients without diabetes mellitus at baseline, 36.4% of patients randomized to the higher haemoglobin target had reached the primary end point after 3 years compared with 24% of those randomized to the lower haemoglobin target (HR 1.70; 95% CI 1.03–2.81; p= 0.04). In other words, individuals without diabetes mellitus randomized to the higher haemoglobin target had a significantly greater risk of reaching the primary end point after 3 years than individuals with diabetes mellitus randomized to the lower haemoglobin target.[12]

- The CREATE[1] study reported that early correction of anaemia to normal Hb (13-15g/dl vs. 10.5-11.5g/dl) did not reduce risk of cardiovascular events. Indeed the hazards ratio for primary endpoints of death from any cause or death from cardiovascular disease consistently (but not significantly) favoured the lower haemoglobin target group. The trend to increase in events appeared to occur after initiation of dialysis but there was no difference in endpoints after censoring of data from patients who started dialysis. Quality of life was significantly better in the higher Hb outcome group. Although GFR was not significantly different between the two groups, more patients started renal replacement therapy earlier in the higher Hb outcome group (p =0.03) with the difference apparent from 18 months. An important limitation of this trial is that the event rate was much lower than predicted; thus, the power to detect a difference in event rates was decreased.

- Other important limitation (s) of these trials is the lack of assessment of Hb cycling around each target Hb. In addition, important subgroups of patients enrolled in large trials, such as young adults, patients returning to dialysis after failed renal transplant, or patients with chronic lung disease were not identified or assessed in any of these trials.

- Further analysis of outcome of high target Hb was performed by the KDOQI team. An Evidence Review Team analysed all data from randomized controlled trials of anaemia management in CKD, including, CHOIR[10], CREATE[1] and other studies. Combining mortality outcomes from eight studies involving 3038 subjects with CKD who were not on dialysis (the CHOIR and CREATE studies contributed most of the weight to the analysis) revealed no difference between the higher and lower Hb target[13], but combining adverse cardiovascular events from six studies involving 2850 subjects showed an increased risk among the patients assigned to the higher Hb targets (a RR of 1.24, 95% CI 1.02–1.51)[13], although it is worth noting that the CHOIR and CREATE studies contributed most of the weight to the analysis. Among dialysis patients, combining mortality (four studies, 2391 subjects) or cardiovascular outcomes (three studies, 1975 subjects) showed no statistically significant difference between the higher and lower Hb level with The Hb Normalisation Study[4] contributing most of the weight to the analysis.

- In the TREAT study[14], 4038 patients with diabetes, chronic kidney disease not on dialysis, and anaemia, were randomly assigned in a 1:1 ratio to darbepoetin α, to achieve a haemoglobin level of approximately 13 g/dL or to placebo, with rescue darbepoetin α when the haemoglobin level was less than 9.0 g/dL. The primary end points were the composite outcomes of death or a cardiovascular event (nonfatal myocardial infarction, congestive heart failure, stroke, or hospitalization for myocardial ischemia) and of death or end-stage renal disease. After a median follow up of 29 months, there was no difference between the two arms in the primary outcome of death, cardiovascular event or end stage renal disease. Fatal or nonfatal stroke occurred in 101 patients assigned to darbepoetin α and 53 patients assigned to placebo (HR, 1.92; 95% CI, 1.38 to 2.68; p < 0.001). The investigators concluded that for many involved in clinical decision making this risk of prescribing an ESA in this patient population will outweigh the potential benefits.[14]

- Data from observational studies have, however, not shown increased hazard risk among patients who achieved higher haemoglobin. In one study, data from haemodialysis

patients in the UK Renal Registry from 1999 to 2005 were analysed for the relative risk of death at different haemoglobin concentrations. Haemoglobin concentrations above the reference range (10–11 g/dl) consistently showed a 35% lower relative risk of death, while patients with haemoglobin below 10 g/dl had a 28% higher mortality. The greatest mortality was seen in patients with haemoglobin <9 g/dl (73% increased risk of death, although due to the small numbers, this was not statistically significant). On the other hand, the lowest death rate was seen in patients with haemoglobin levels between 12 and 13 g/dl (64% reduced mortality).[15]

- The effect of cumulative ESA dose was also reported in another retrospective study. In this study, which looked at data from Medicare's end-stage renal disease program between 1999 and 2007, different US dialysis centres' annual anaemia management practice were characterised by estimating their typical use of ESAs and intravenous iron in haemodialysis patients within 4 hematocrit categories. Monthly mortality rates were assessed using Cox proportional hazards regression to correlate centre-level patterns of ESA and iron use with 1-year mortality risk in 2,69,717 incident haemodialysis patients. Monthly mortality rates were highest in patients with haematocrit less than 30% (mortality, 2.1%) and lowest for those with haematocrit of 36% or higher (mortality, 0.7%). After adjustment for baseline case-mix differences, dialysis centres that used larger ESA doses in patients with haematocrit less than 30% had lower mortality rates than centres that used smaller doses (highest vs. lowest dose group: HR, 0.94; 95% CI, 0.90-0.97). Centres that administered iron more frequently to patients with haematocrit less than 33% also had lower mortality rates (highest vs. lowest quintile, HR, 0.95; 95% CI, 0.91-0.98). However, centres that used larger ESA doses in patients with haematocrit between 33% and 35.9% had higher mortality rates (highest vs. lowest quintile, HR, 1.07; 95% CI, 1.03-1.12). More intensive use of both ESAs and iron was associated with increased mortality risk in patients with haematocrit of 36% or higher.[16]

Despite the limitation(s) of each trial, these studies support the current haemoglobin outcome recommendations in this document and the NICE update recommendations on management of anaemia in patients with chronic kidney disease[17].

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Guideline 2.5 - Treatment of Anaemia - Initial ESA dose

We recommend that the initial ESA dose should be determined by the patient's Hb level, the target Hb level, the observed rate of increase in Hb level and clinical circumstances. (1B)

Rationale

For initiation of ESA therapy, several points are to be considered:

- Type(s) of licensed ESAs available
- Initial ESA dose
- ESA dose adjustment: dose required for Hb correction vs. maintenance
- Route of ESA administration

- Frequency of ESA administration that best fit patient requirements and achieve maximal convenience
- Patient monitoring for the anticipated response in terms of Hb rise, rate of Hb rise, possible adverse effect (e.g. hypertension).

In general, the aim of initial ESA therapy is to achieve a rate of increase in Hb levels of 1 to 2 g/dL per month. This rate of rise is considered safe as evidenced from interventional trials on ESA naïve patients.[1-3] In CKD patients with initial Hb levels less than target range, these trials have shown the mean initial rate of Hb level increase to be in the range of 0.7 to 2.5 g/dL in the first 4 weeks. This rate of Hb increase is affected by the patient population, initial ESA dose, and the frequency and route of ESA administration.

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Guideline 2.6 - Treatment of Anaemia with ESA therapy - Route of administration

We suggest that the route of ESA administration should be determined by the CKD stage, treatment setting, efficacy, safety, and class of ESA used; subcutaneous (SC) route is the access of choice in non-HD patients, while convenience may favour intravenous (IV) administration in HD patients. (2B)

Audit measure

Each renal unit should audit the type, route and frequency of administration and weekly dose of ESA prescribed

Rationale

In the outpatient setting, SC administration is the only routinely feasible route of administration for non HD CKD patients. For HD patients, either SC or IV administration is feasible.

Among short-acting ESAs, subcutaneous administration is associated with approximately 30% reduction in dose requirements compared to that of IV administration for the same target Hb outcome. This has been proven in a large multicenter RCT on long term HD patients who had their haematocrit maintained within target range while on epoetin α either via SC or IV route. Patients were then randomised to IV or SC route. Upon randomization, ESA doses were first decreased to allow haematocrit levels to decrease to less than target range. Doses were titrated upward to again achieve target haematocrit levels, and then were adjusted to maintain haematocrit in the target range during a 26-week maintenance phase. Among 107

patients who completed the trial, those assigned to SC route showed 27% lower ESA doses than those assigned to IV administration.[1] However, not all patients showed a dose decrease after conversion from IV to SC, and some patients showed a dose increase.

Among long-acting agents, efficacy of SC administration appears to be equivalent to that of IV route at the examined dosing frequencies.[2-5]

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Guideline 2.7 - Treatment of Anaemia with ESA therapy - Frequency of administration

We suggest that the frequency of administration should be determined by the CKD stage, treatment setting and class of ESA. Less frequent administration using long acting ESAs may be the treatment of choice in non–HD patients. (2B)

Rationale

The frequency of ESA administration should be determined by the CKD treatment setting and the class of ESA. Maximum efficacy is achieved by using the dosing intervals that are ESA class specific. In HD patients receiving SC short-acting ESA therapy, ESA efficacy is maximal when the drug is given thrice weekly. ESA efficacy decreases and dose requirement increases when the dosing frequency is extended from thrice-weekly to once-weekly administration.[1] Increasing the time interval between dosages of long acting ESAs could also result in an increase in dose requirements.[2]

References

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Guideline 2.8 - Treatment of Anaemia with ESA Therapy - ESA dose adjustments

We recommend that adjustments to ESA doses should be considered when Hb is <10.5 or >11.5 g/dL in order to balance the benefit and safety to patients given the current evidence base. These thresholds for intervention should achieve a population distribution centred on a mean of 11 g/dl with a range of 10-12. (1B)

Guideline 2.9 - Treatment of Anaemia with ESA Therapy - ESA dose adjustments

We suggest that ESA doses should ideally be decreased rather than withheld when a downward adjustment of Hb level is needed. (2B)

Guideline 2.10 - Treatment of Anaemia with ESA Therapy

We recommend that ESA administration in ESA-dependent patients should continue during acute illness, surgical procedures or any other cause of hospitalisation. (1B)

Audit measure

Each renal unit should monitor ESA dose adjustments

Rationale for Guidelines 2.8 – 2.10

- It is acknowledged that in a dialysis population the Hb distribution results in the majority of Hb values not lying within the range 11-12g/dL.[1-3] The updated NICE Guidelines for anaemia management in chronic kidney disease[3] recommend an outcome Hb of 10-12. It is anticipated that if a population Hb distribution is centred on this outcome with a mean of 11g/dl, then 85% of the population will have Hb > 10.0g/dl.

- In HD patients, withholding ESA doses for Hb levels greater than the target range is associated with subsequent downward Hb excursions often to levels less than target range[4]. The time between withholding ESA doses and return of Hb to target range is variable and unpredictable. In HD patients with Hb values greater than 14.0 g/dL, the median time for Hb to return to 12.0 g/dL or less after withholding of a SC-administered ESA is 7-9 weeks. The difference between withholding long and short acting ESAs on the rate of Hb reduction is not significant.[5]

- Either 10-16% ESA dose changes[6] or up to 25% dose changes[7] can be equally effective maintenance dose-titration strategies. This was shown in two separate studies. The first was a computer-assisted support decision system algorithm that had been tested in a 24 month prospective study on chronic HD patients on SC epoetin α. In this study, the monthly dose of epoetin was adjusted according to monthly Hb level using lower and upper Hb thresholds beyond which the ESA dose was increased or decreased

respectively. The average dose change was 10-16% of baseline ESA dose. Hb outcome was maintained with medians between 11.3 and 11.8 g/dL, and a median epoetin α dose reduction from 136 to 72 IU/kg/ week. The second study examined the effect of initiating a fixed monthly downward ESA dose adjustment in response to monthly Hb levels > 13.0 g/dL. The study examined a large database containing 95,000 HD patients on epoetin therapy.[4] At baseline approximately 35% patients showed average 3-month Hb results within the target range of 11 to 12 g/dL, and 15% showed average 3-month Hb results greater than 13.0 g/dL. When a computer-mandated 25% monthly dose decrease was initiated for end-of month Hb results greater than 13.0 g/dL, the mean Hb level did not change, but the percentage of patients with Hb values greater than 13.0 g/dL increased and the percentage of patients with Hb values <11 g/dL increased.

- ESA dose adjustment may be higher during initiation (or titration after switch between different ESAs) than maintenance phases of ESA therapy. In a randomized double blind trial comparing a short-acting ESA with a long-acting ESA in haemodialysis patients previously receiving epoetin α, dose adjustments were made in 25% increments or decrements of the baseline dose, aiming to maintain individual Hb concentrations within a range of 9.0 to 13.0 g/dL.[6] Approximately 70% of patients required dose adjustment in the 20-week titration period, and 50% required dose adjustment during the 8 week maintenance period.

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3.   Anaemia of CKD (Guidelines 3.1 – 3.4)

Guideline 3.1 - Treatment of Anaemia with Iron therapy – Iron repletion

We recommend that patients should be iron replete to achieve and maintain target Hb whether receiving ESAs or not. (1A)

Rationale

A definition of adequate iron status[1] is a serum ferritin

- 200-500 ng/L in HD patients,
- 100-500 ng/ml in non-HD patients and
- Either <6% hypochromic red cells (HRC), or TSAT>20%

The aim of iron treatment targets is to optimise anaemia therapy while minimising potential toxicity. Therapy targets aim at:

1. Minimising the ESA doses required to maintain target Hb levels in patients on ESA therapy and
2. Maximising the Hb level and minimising the need to initiate ESA therapy to achieve target-range Hb levels in patients not on ESA therapy.

Increasing the Hb in anaemic patients places the greatest demand for iron in the erythropoietic tissues. During ESA induction therapy iron requirements will depend on the rate of erythropoiesis, the Hb deficit, and ongoing iron loses. Once the target Hb has been reached and Hb stabilised, the iron requirements will be dependent on ongoing iron losses. When adequate iron status is achieved, CKD patients on ESA therapy should be given maintenance iron.

Several studies have reported that the dose of ESA required to achieve and maintain a given Hb outcome is inversely related to iron stores.[2-7] Iron deficiency (absolute or functional) was the main cause of ESA resistance in the UK but this has now been solved by iron replacement strategies.[8] In HD patient populations, the inverse relationship between ESA dose and iron stores continues to maintain a linear relationship up to a mean ferritin of 500ng/ml. Compliance with ferritin >200 predicts compliance of the RA minimum standard for Hb of >85% Hb values >10.0g.dL.[9] The evidence behind the statement that TSAT generally should be maintained at greater than 20% stems from a single RCT comparing higher to lower TSAT targets; patients randomized to a target TSAT of 30% to 50% demonstrated a 40% reduction in ESA dose compared with those assigned to a target of 20% to 30%.[10]

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Guideline 3.2 - Treatment of Anaemia with Iron therapy - Initiation of ESA and iron status

We recommend that ESA therapy should not be initiated in the presence of absolute iron deficiency (ferritin <100ng/ml). In patients with functional iron deficiency iron supplements should be given prior to or when initiating ESA therapy. (1A)

Audit measure

Proportion of patients with serum ferritin levels < 100ng/ml at start of treatment with ESA

Rationale

Iron is a required for production of new red cells. Iron must be supplied to the erythropoietic tissue at an adequate rate, particularly if stimulated by ESA therapy. If iron stores are low ESAs can still be used if renal anaemia is a likely contributor to the anaemia as long as iron is made directly available to the erythropoietic tissues coincident with the initiation of ESA therapy.[1]

Reference

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Guideline 3.3 - Treatment of Anaemia with Iron therapy - Route of Administration

We suggest that oral iron will, in general, be sufficient to attain and maintain the Hb above targets in ESA treated CKD patients not yet requiring dialysis and in those on peritoneal dialysis (PD). (2B)
In contrast most HD patients will require intravenous iron. (2A)

Audit measure

Proportion of predialysis and PD patients receiving iron therapy; type: oral vs. parenteral
Proportion of HD patients receiving IV iron

Rationale

The evidence base for intravenous iron over oral iron in predialysis patients and PD patients is limited. Oral iron, if tolerated, appears to be adequate in most patients particularly in

combination with ESA therapy. In patients who appear resistant to ESA therapy on oral iron, or are intolerant of oral iron, a therapeutic trial of IV iron trial seems reasonable. A study in predialysis patients and PD patients with functional iron deficiency despite oral iron therapy is needed. One randomised study of IV iron versus oral iron in predialysis patients demonstrated a greater improvement in Hb outcome in those on IV iron but no difference in the proportion of patients who had to commence ESA after the start of the study.[1] Two studies in predialysis patients not on ESA (one without oral iron and the other after oral iron therapy) demonstrated improvements in Hb outcome after IV iron.[2,3] Oral iron is easy and cheap to prescribe. It seems reasonable to treat patients who have not responded to or been intolerant of oral iron with IV iron.

Two randomised controlled studies of oral versus IV iron supplementation in predialysis patients receiving concomitant ESAs are in agreement. In the first study over a mean 5.2 months follow-up there was no difference in Hb or ESA dose between the oral and IV group receiving ESA.[4] Iron stores were greater in the IV than oral group. Similar findings appeared in a later study comparing 5 weeks of IV iron or 29 days of thrice daily oral iron. There was no difference in Hb or ESA dose but greater increase in ferritin in the IV group.[5] In PD patients a cross-over study of oral and IV iron demonstrated higher Hb and lower ESA doses after 4 months oral iron followed by a washout period and a single total dose of IV iron.[6]

At present oral iron should remain first line treatment and IV iron used if patients are intolerant of oral iron or remain absolutely or functionally iron deficient despite oral iron. From the evidence to date IV iron is at least equivalent to oral iron therapy in efficacy and so can be administered to patients unable to take oral iron.[1,4]

HD patients have additional iron losses from GI bleeding, blood tests and losses in the dialysis lines that result in iron supplementation requirements that outstrip the capacity of the gut to absorb iron. Maintenance IV iron in HD patients greatly reduces ESA requirements and costs.[1,4,7-12] Maintaining iron stores/maintaining a population ferritin outcome at steady state in a HD population requires 50-60mg/week of intravenous iron[8-10]. In PD patients and patients not on dialysis the evidence is not as strong. Hence for this patient population a lower ferritin of 100ng/ml is quoted by NICE.[13]

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Guideline 3.4 - Treatment of Anaemia with Iron therapy - Upper limit for iron therapy

We recommend that serum ferritin should not exceed 800ng/ml in patients treated with iron, and to achieve this iron management should be reviewed when the ferritin is > 500ng/ml. (1B)

Rationale

The UK Renal Registry Report 2005[1] demonstrates that the proportion of individuals in a HD population with ferritin values >100ng/ml or >200ng/ml or indeed >800ng/ml is dependent on the median ferritin. As the distribution increases the compliance with values above minimum standards improves but the risk of breaching 800ng/ml (and therefore risk of toxicity) also increases. At a median ferritin of 500ng/ml 5-25% of individual patients may have a ferritin>800ng/ml. The lower the standard deviation for ferritin, the lower will be the risk of a significant proportion of patients breaching 800ng/ml. Discontinuation of adequate maintenance IV iron when an individual's ferritin is > 500ng/ml produces a population mean that straddles the 500ng/ml ceiling.[2] Ongoing iron therapy in patients with ferritin >500ng/ml results in a higher median ferritin outcome.[3]

Interpretation of iron status results and deciding on the need for further iron therapy should include a concomitant assessment of changes in Hb level and ESA dose over time. Examples:

- A dropping ferritin as well as decreasing Hb levels signifies blood loss e.g. on HD or bowel related: iron therapy is indicated; further investigation may be required depending on the clinical scenario.
- A decreasing ferritin level after initiation of ESA therapy, with a concomitant rise in Hb level indicates a response to ESA with a shift of iron from stores to bone marrow: further iron therapy is guided by target ferritin level.

- An increasing ferritin level after reduction of ESA dose to bring Hb level down to target range indicates ferritin level is rising as Hb synthesis is dropping: further iron therapy may be postponed.
- A rising ferritin level and a drop in TSAT suggest an inflammatory condition: a source of inflammation may be sought: sepsis, vascular access, surgery, recent hospitalisation: further iron therapy depends on target ferritin level and clinical scenario.
- Ongoing high requirements for IV iron to maintain a given ferritin level also point to ongoing blood loss.

The finding of a TSAT less than 20% coupled with a ferritin level greater than 500 ng/mL poses a particularly difficult problem for clinicians. This situation may be caused by iron test variability,[4] inflammation, or reticuloendothelial iron blockade. Evidence on the risks and benefits of IV iron therapy in these patients is almost entirely lacking. The effect of iron therapy in this group of patients was assessed in The Dialysis patients' Response to IV iron with Elevated ferritin (DRIVE) trial[5], which evaluated the efficacy of intravenous ferric gluconate in 134 patients with high ferritin (500–1200 ng/ml) and low TSAT levels (≤ 25%) who were anaemic despite a high rHuEPO dose (≥225 IU/kg/week or≥22 500 IU/week). After 6 weeks the patients receiving ferric gluconate (125 mg IV at eight consecutive HD sessions) showed a significant increase in Hb in comparison with controls. However, the study has a number of limitations because, given the short follow-up, it provides no information about safety and iron overload.

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4. Anaemia of CKD (Guidelines 4.1 – 4.5)

Guideline 4.1 - Monitoring of treatment - Hb during ESA therapy

We recommend that Hb concentration should be monitored every 2-4 weeks in the correction phase and every 1-3 months for stable patients in the maintenance phase. More frequent monitoring will depend on clinical circumstances. (1B)

Rationale

It is important to closely monitor Hb response to treatment to monitor for possible adverse events and plan ESA dose modification. More frequent Hb monitoring may be needed for

patients with unstable Hb, out of target Hb level, anticipated Hb drop due to blood loss/ haemolysis, infection or suboptimal dialysis.

The response to ESA therapy varies widely between different patient groups and individuals within those groups. In addition, an individual's response can vary greatly dependent on other clinical variables. During ESA initiation therapy, after drug dose adjustments or changes in an individual's clinical condition, more frequent monitoring is advised in order that under-treatment (ongoing anaemia) and overtreatment (rapidly rising Hb/hypertension or polycythaemia) may be avoided.[1-3]

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Guideline 4.2 - Monitoring of treatment - Iron therapy

We recommend regular monitoring of iron status (1-3 monthly) during treatment to avoid toxicity (1B): a serum ferritin consistently greater than 800 ng/ml is suggestive of iron overload. (1B)

Rationale

Intravenous iron therapy in particular has potential risks as well as benefits. Toxicity associated with high ferritin outcomes was originally reported in the context of multiple transfusions in the pre-ESA era. The risk persists that intravenous iron may reproduce similar toxicity and thus regular monitoring during therapy is required. Similarly with ongoing iron losses on HD regular monitoring to avoid worsening iron deficiency is required.[1-3]

Clinical settings in which more frequent iron testing may be necessary include the following:

1. Initiation of ESA therapy
2. Achieving less-than-target Hb level during ongoing ESA therapy
3. Recent bleeding
4. After surgery
5. After hospitalization
6. Monitoring response after a course of IV iron
7. Evaluation for ESA hypo-responsiveness

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3. NKF-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: update 2000. Am J Kidney Dis 2001; 37: S182-S238.

Guideline 4.3 - Monitoring during Intravenous Iron Administration

We recommend that resuscitative medication and personnel trained to evaluate and resuscitate anaphylaxis should be present at each administration of iron dextran. (1A)

Rationale

- All forms of IV iron may be associated with acute adverse events (AEs).
- Immune mechanisms (including mast cell–mediated processes leading to a clinical syndrome resembling anaphylaxis) may have a role in some cases.
- Anaphylactoid reactions appear to occur more frequently with iron dextran.[1]
- Labile or free iron reactions occur more frequently with nondextran forms of iron.[2] The rate of life-threatening reactions to iron dextran administration is 0.6% to 0.7%.[3,4]
- In patients receiving iron dextran, there remains a risk for significant AE in patients who had successfully received previous test or treatment doses suggesting that the risk for first-dose AE may recur in prevalent patients after an interval free from iron dextran exposure.[5]

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Guideline 4.4 - Monitoring of treatment - Resistance to ESA therapy

We recommend that inadequate response ('resistance') to ESA therapy is defined as failure to reach the target Hb level despite SC epoetin dose >300 IU/kg/week (450 IU/kg/week IV epoetin), or darbepoetin dose >1.5mcg/kg/week. Hyporesponsive patients who are iron replete should be screened clinically and by investigations for other common causes of anaemia. (1A)

Audit measure

Prevalence of resistance to ESA among renal replacement therapy patients

Rationale

Extensive publications are available on the topic of resistance to ESA therapy including the Revised European Best Practice Guidelines[1] which defines ESA resistance as above. Failure to respond at an earlier stage in therapy should however raise suspicion of ESA resistance. Comparison of the individual Hb outcome achieved and the dose of ESA used can provide a useful way of highlighting individuals that are ESA resistant during local unit audit.[2,3] ESA therapy is efficacious in most patients. However many conditions and treatment variables can cause or explain apparent resistance to ESA therapy. Adequate investigation and management of these underlying conditions is crucial in achieving satisfactory outcome haemoglobin values as well as requiring therapy in their own right.

Anti-erythropoietin antibody associated pure red cell aplasia (PRCA) is a very rare cause of resistance characterised by transfusion dependency, low reticulocyte count, lack of pro-erythroid progenitor cells in the bone marrow and neutralising anti-erythropoietin antibodies.[4] In 2005, a report concerning 170 CKD patients who developed epoetin-associated PRCA was made available by the Research on Adverse Drug Events and Reports (RADAR) Project.[5] Of the 34 patients who received epoetin after the onset of PRCA, 56% recovered epoetin responsiveness; the highest rate of epoetin responsiveness was observed among those who had no detectable anti-erythropoietin antibodies at the time of epoetin administration (89%). Given these data, it is advisable that retreatment with ESA can be considered in patients with a history of PRCA if anti-EPO antibodies are no longer detectable.

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Guideline 4.5 - Monitoring of treatment - Hypertension during ESA therapy

We recommend that blood pressure should be monitored in all patients receiving ESAs and, if present, hypertension be treated by volume removal and/or hypotensive drugs. (1A)

Rationale

Hypertension is the most common complication in CKD and can be aggravated by ESA treatment.[1] Early studies demonstrated higher incidence rates of hypertension though ESA

doses used were higher and Hb responses faster in these trials. It is now more common to start at low doses and increase gradually according to response. The commonest cause of hypertension in CKD is not ESA therapy. Exacerbation of hypertension in ESA therapy patients may be associated with polycythaemia or rapidly rising haemoglobin levels. These complications should be looked for in hypertensive patients but in the absence of these complicating factors and in the absence of severe hypertension, ESA therapy can usually continue. Hypertension should be adequately controlled prior to initiating ESA therapy. ESA therapy should be discontinued in malignant hypertension.

Reference

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5. Anaemia of CKD (Guidelines 5.1 – 5.2)

Guideline 5.1 - **Blood Transfusion**

We recommend that in patients with anaemia of CKD, especially those in whom renal transplantation is an option, red blood cell transfusion should be avoided if possible. (1A)

Guideline 5.2 - **Blood Transfusion**

We recommend if red blood cell transfusion becomes essential (usually in the setting of acute blood loss, acute haemolysis or severe sepsis) transfusion should be based on policies set by local transfusion guidelines rather than Hb targets for ESA therapy in chronic anaemia of CKD. (1B)

Audit Measure

Proportion of HD patients who received a blood transfusion within the past year

Rationale for guidelines 5.1 and 5.2

CKD results in chronic anaemia, the degree of which usually reflects the severity of CKD. As with any chronic anaemia, patients tend to deal with this by various compensatory mechanisms. Blood transfusion is rarely an acute requirement except in emergencies such as acute blood loss, acute haemolysis or severe sepsis/inflammation. Hence the risk benefit ratio of the intervention needs to be analysed before prescribing a red blood cell transfusion to treat anaemia in patients with chronic kidney disease.

The potential risks associated with blood transfusion include transfusion reactions, iron overload and transfusion acquired infections. In the presence of severe chronic anaemia, transfusion may lead to congestive cardiac failure, particularly in the elderly. A review of transfusion outcome in patients with acute coronary artery syndromes revealed a greater mortality rate in transfusion recipients.[1] Another review suggested that treatment of mild to moderate anaemia resulted in increased mortality.[2] Also transplant recipient sensitisation may occur following transfusion resulting in longer transplant register waiting times and difficulty

in finding a cross match negative donor. A study from Ireland looking at causes of sensitisation of potential allograft recipients showed that the level of sensitisation increased with the number of units of blood transfused and also demonstrated a direct relationship between degree of sensitisation and waiting time for transplantation.[3] Blood transfusions can induce antibodies to histocompatibility leukocyte antigens that can reduce the success of kidney transplantation; thus transfusions generally should be avoided in patients awaiting a renal transplant.[4]

The use of ESAs can greatly reduce the need for red blood cell transfusions in patients with anaemia of CKD when target Hb concentrations are achieved and maintained.[5-6] Since the introduction of ESAs and reduction in routine blood transfusion in anaemic patients with CKD sensitisation has markedly reduced.[7] With the advent of new immunosuppressant regimens after 1995, the use of pretransplantation transfusion have been rendered largely obsolete.[8] The K-DOQI anaemia guideline recommends that no single Hb concentration justifies or requires transfusion and the target Hb recommended for chronic anaemia management should not serve as a transfusion trigger.[8] NICE agrees that there are clinical reasons to minimise blood transfusion in anaemia of CKD and if blood transfusion is essential the relevant haematology guidelines should be followed (e.g. the British Committee for Standards in Haematology (BCSH) guidelines **www.bcshguidelines.com**).[9]

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9. Guideline on anaemia management in chronic kidney disease. 2006. National Institute for Health and Clinical Excellence.

6.   Anaemia of CKD (Guideline 6.1)

Guideline 6.1 - **Post-transplantation Anaemia**

We recommend that the treatment guidelines for anaemia in renal transplant patients should be similar to those for CKD patients not on dialysis. (1B)

Rationale

Post transplantation Anaemia (PTA) is common.[1-3] Apart from the usual causes of anaemia due to CKD, renal transplant recipients have various unique factors predisposing to anaemia.

Factors causing PTA:

1. GFR: anaemia in transplant patients reflects the degree of GFR similar to other patients with CKD.[3]
2. Immunosuppressive medications: Mycophenolate and azathioprine are myelosuppressive agents. Calcineurin inhibitors may cause anaemia by microangiopathic haemolysis.[4-8] OKT3 may also cause haemolytic uraemic syndrome (HUS).[9,10] Sirolimus has also been associated with anaemia.[11-13] It may interfere with post erythropoietin receptor binding intracellular signalling and may occasionally cause HUS.[13,14]
3. Angiotensin converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB) use: ACE inhibition has been linked with anaemia.[3,15] Its pathogenesis is multifactorial and may include inhibition of endogenous EPO production, production of an erythropoiesis-inhibiting protein[16] and inhibition of angiotensin II mediated stimulation of erythrocyte precursors.[17]
4. Antibiotic use: various common antibiotics may cause anaemia including trimethoprim-sulfamethoxazole.
5. Infections: viral infections such as cytomegalovirus and parvovirus B19 and antiviral agents such as ganciclovir may cause anaemia in transplant patients.[18,19]
6. Malignancy: malignancies including post transplant lymphoproliferative disorder may result in anaemia.
7. Haemolytic anaemia: haemolytic anaemia may result from HUS or minor blood group incompatibility in transplant patients.[20-22]
8. Rejection episodes: Acute rejection may cause reduced endogenous EPO production.[23] Severe vascular rejection may cause microangiopathy.
9. Chronic inflammation: Failing renal transplant causes a chronic inflammatory state resulting in EPO hyporesponsiveness.

Safety of ESA in transplant patients:

A few early retrospective studies suggested increased incidence of delayed graft function in patients on ESA prior to transplantation.[24,25] However Registry data has since shown reduced incidence of delayed graft function despite increasing use of ESA. It has also been shown that ESA use prior to renal transplantation does not reduce production of or response to endogenous EPO.[26,27] Studies in the early post transplant period did not show significant adverse events including delayed graft function or hypertension.[28,29] Studies in the late transplant period have shown increased incidence of hypertension.[30,31] ESAs, most probably, do not accelerate rate of graft function decline and one study suggested that correction of anaemia slowed the decline in allograft function.[32]

Efficacy of ESA in transplant patients:

Studies in the early post transplant period have shown that ESA is effective in these patients, although the dose required may be higher than in pretransplant period.[28,29]

Similarly studies in late post transplant period have shown efficacy of ESA in these patients.[30-31,33-34]

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