



Complete Summary

GUIDELINE TITLE

Anaemia management in chronic kidney disease. A national clinical guideline for management in adults and children.

BIBLIOGRAPHIC SOURCE(S)

National Collaborating Centre for Chronic Conditions. Anaemia management in chronic kidney disease. National clinical guideline for management in adults and children. London (UK): Royal College of Physicians; 2006. 172 p. [295 references]

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [July 31, 2008, Erythropoiesis Stimulating Agents \(ESAs\)](#): Amgen and the U.S. Food and Drug Administration (FDA) informed healthcare professionals of modifications to certain sections of the Boxed Warnings, Indications and Usage, and Dosage and Administration sections of prescribing information for Erythropoiesis Stimulating Agents (ESAs). The changes clarify the FDA-approved conditions for use of ESAs in patients with cancer and revise directions for dosing to state the hemoglobin level at which treatment with an ESA should be initiated.
- [November 8, 2007 and January 3, 2008 Update, Erythropoiesis Stimulating Agents \(ESAs\)](#): The U.S. Food and Drug Administration (FDA) notified healthcare professionals of revised boxed warnings and other safety-related product labeling changes for erythropoiesis-stimulating agents (ESAs) stating serious adverse events, such as tumor growth and shortened survival in patients with advanced cancer and chronic kidney failure.

COMPLETE SUMMARY CONTENT

** REGULATORY ALERT **

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SCOPE

DISEASE/CONDITION(S)

Anaemia of chronic kidney disease

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Family Practice
Geriatrics
Internal Medicine
Neurology
Pharmacology
Psychiatry

INTENDED USERS

Advanced Practice Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To provide a user-friendly, clinical, evidence-based guideline for the National Health Service (NHS) that:

- Offers best clinical advice for anaemia management in chronic kidney disease (AMCKD)
- Is based on best published evidence and expert consensus
- Takes into account patient choice and informed decision-making
- Defines the major components of NHS care provision for anaemia of CKD
- Indicates areas suitable for clinical audit
- Details areas of uncertainty or controversy requiring further research
- Provides a choice of guideline versions for differing audiences

TARGET POPULATION

Adults and children with anaemia in chronic kidney disease

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation

1. Haemoglobin levels
2. Estimated glomerular filtration rate (eGFR)
3. Serum ferritin levels

Management

1. Erythropoiesis stimulating agents (ESAs), including consideration of:
 - Patient preference
 - Route of administration
 - Dose and frequency
 - Adjusting ESA therapy
2. Iron supplements (oral and intravenous)
3. Treatment of clinically relevant hyperparathyroidism
4. Blood transfusion
5. Maintenance of stable haemoglobin (Hb) levels
6. Monitoring
 - Iron status
 - Haemoglobin levels
7. Detecting ESA resistance
8. Managing ESA resistance
9. Use of patient-centered care, including
 - Provision of information to patient and General Practitioner (GP)
 - Establishment of protocols defining roles and responsibilities of healthcare professionals in primary and secondary care
 - Consideration of patient preferences about supervised- or self-administration, dose frequency, pain on injection, method of supplying ESA, and storage
 - Provision of culturally and age-appropriate patient education programmes

Interventions and practices considered but not recommended include measurement of erythropoietin levels, supplements of vitamin C, folic acid or carnitine, and androgens.

MAJOR OUTCOMES CONSIDERED

- Patient satisfaction
- Quality of life
- Sensitivity and specificity of diagnostic tests
- Morbidity and mortality
- Exercise capacity
- Blood pressure
- Haematocrit and haemoglobin levels
- Erythropoietin dose and plasma levels
- Parathyroid hormone levels
- Hospitalisation rate

- Cost effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Searching for the Evidence

The information scientist developed a search strategy for each question. Key words for the search were identified by the Guideline Development Group (GDG). In addition, the health economist searched for supplemental papers to inform detailed health economic work (for example modelling). Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence by the GDG. Conference paper abstracts and non-English language papers were excluded from the searches.

Each clinical question dictated the appropriate study design that was prioritised in the search strategy but the strategy was not limited solely to these study types. The research fellow or health economist identified titles and abstracts from the search results that appeared to be relevant to the question. Exclusion lists were generated for each question together with the rationale for the exclusion. The exclusion lists were presented to the GDG. Full papers were obtained where relevant. See Appendix A of the original full-length guideline document for literature search details.

Appraising the Evidence

The research fellow or health economist, as appropriate, critically appraised the full papers. In general, no formal contact was made with authors; however, there were ad hoc occasions when this was required in order to clarify specific details. Critical appraisal checklists were compiled for each full paper. One research fellow undertook the critical appraisal and data extraction. The evidence was considered carefully by the GDG for accuracy and completeness.

All procedures are fully compliant with:

- National Institute for Health and Clinical Excellence (NICE) methodology as detailed in the "Guideline development methods – information for National Collaborating Centres and guideline developers" manual.
- National Collaborating Centre for Chronic Conditions (NCC-CC) quality assurance document and systematic review chart, available at: www.rcplondon.ac.uk/college/ncc-cc

Updating the Guideline

Literature searches were repeated for all of the evidence-based questions at the end of the GDG development process, allowing any relevant papers published by 28 September 2005 to be considered.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence for Studies of Diagnostic Tests

Ia: Systematic review (with homogeneity)* of level-1 studies**

Ib: Level-1 studies**

II: Level-2 studies*** Systematic reviews of level-2 studies

III: Level-3 studies**** Systematic reviews of level-3 studies

IV: Evidence obtained from expert committee reports or opinions and/or clinical experience without explicit critical experience, based on physiology, bench research, or first principles.

*Homogeneity means there are no or minor variations in the directions and degrees of results between individual studies that are included in the systematic review.

**Level-1 studies are studies:

- That use a blind comparison of the test with a validated reference standard (gold standard)
- In a sample of patients that reflects the population to whom the test would apply.

***Level-2 studies are studies that have **only one** of the following:

- Narrow population (the sample does not reflect the population to whom the test would apply)
- Use a poor reference standard (defined as that where the "test" is included in the "reference", or where the "testing" affects the "reference")
- The comparison between the test and reference is not blind
- Case-control studies

****Level-3 studies are studies that have **at least two or three** of the features listed above.

Levels of Evidence for Studies of Interventions

1++ High quality meta-analyses, systematic review of randomised controlled trials (RCTs), or RCTs with a very low risk of bias

1+ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

1- Meta-analyses, systematic review of RCTs, or RCTs with a high risk of bias

2++ High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal

2+ Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal

2- Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal

3 Non-analytic studies (for example, case reports, case series)

4 Expert opinion, formal consensus

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Distilling and Synthesising the Evidence

The evidence from each full paper was distilled into an evidence table and synthesised into evidence statements before being presented to the Guideline Development Group (GDG). This evidence was then reviewed by the GDG and used as a basis on which to formulate recommendations.

Evidence tables are available online at www.rcplondon.ac.uk/college/NCC-CC.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Agreeing the Recommendations

The sign-off workshop employed formal consensus techniques to:

- Ensure that the recommendations reflected the evidence base
- Approve recommendations based on lesser evidence or extrapolations from other situations
- Reach consensus recommendations where the evidence was inadequate
- Debate areas of disagreement and finalise recommendations

The sign-off workshop also reached agreement on the following:

- Five to ten key priorities for implementation
- Five key research recommendations
- Algorithms

In prioritising key recommendations for implementation, the sign-off workshop also took into account the following criteria:

- High clinical impact
- High impact on reducing variation
- More efficient use of National Health Service (NHS) resources
- Allowing the patient to reach critical points in the care pathway more quickly

Writing the Guideline

The first draft version of the guideline was drawn up by the technical team in accord with the decision of the Guideline Development Group (GDG). The guideline was then submitted for two formal rounds of public and stakeholder consultation prior to publication. The registered stakeholders for this guideline are detailed on the National Institute for Health and Clinical Excellence (NICE) website, see www.nice.org.uk. Editorial responsibility for the full guideline rests with the GDG.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grading of Recommendations on Diagnostic Tests

Grade A (DS): Studies with level of evidence Ia or Ib

Grade B (DS): Studies with level of evidence II

Grade C (DS): Studies with level of evidence III

Grade D (DS): Studies with level of evidence IV

(DS = diagnostic studies)

Grading of Recommendations on Interventions

Grade A:

- Level 1++, and directly applicable to the target population, or
- Level 1+, directly applicable to the target population, and consistency of results
- Evidence drawn from a National Institute for Health and Clinical Excellence (NICE) technology appraisal

Grade B:

- Level 2++, directly applicable to the target population, and consistency of results, or
- Extrapolated evidence from studies rated as 1++ or 1+

Grade C:

- Level 2+, directly applicable to the target population and demonstrating overall consistency of results, or
- Extrapolated evidence from studies rated as 2++

Grade D:

- Evidence level 3 or 4, or
- Extrapolated from 2+, or
- Formal consensus

D (GPP):

- A good practice point (GPP) is a recommendation for best practice based on the experience of the Guideline Development Group

COST ANALYSIS**Health Economic Evidence**

Areas for health economic modelling were agreed by the Guideline Development Group (GDG) after the formation of the clinical questions. The health economist reviewed the clinical questions to consider the potential application of health economic modelling, and these priorities were agreed with the GDG.

The health economist performed supplemental literature searches to obtain additional data for modelling. Assumptions and designs of the models were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

Health Economic Model: Target Haemoglobin in Haemodialysis Patients

The aim of the model was to compare three alternative haemoglobin (Hb) targets in the anaemia management of haemodialysis patients over a 2-year period. The haemoglobin targets evaluated were: <11 g/dL, 11–12 g/dL and >12 g/dL. The cost per quality-adjusted life year gained was calculated.

Conclusion

The results suggest treating anaemia with a target Hb 11–12 g/dL is cost effective in haemodialysis patients based on a 30,000 pounds sterling threshold. However, there is uncertainty in the results of the model from lack of certainty in the input parameters. Nevertheless, the results are relatively robust based on one-way sensitivity analyses and threshold analyses. This analysis is a simplified model of the costs and benefits of treating anaemia in the haemodialysis population and a variety of assumptions have been used in the baseline analysis. Therefore, the results should be interpreted correspondingly.

Health Economic Calculation: Route of Administration of Erythropoiesis-Stimulating Agents (ESAs)

A cost-minimisation analysis based on equivalent effectiveness between intravenous (i.v.) and subcutaneous (s.c.) epoetin was performed. ESAs are made available to National Health Service (NHS) trusts through a system of tendering for local supply contracts. Costs therefore vary between locations and over time, and this should be borne in mind in applying the findings of this analysis.

Conclusion

The subcutaneous route of administration of epoetin vs intravenous route results in cost savings of approximately 1,100 pounds sterling + 727 pounds sterling per patient per year.

See Appendices C and D in the full length original guideline document for details on cost-effectiveness models and calculations.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guideline was validated through two consultations.

1. The first draft of the guideline (The full guideline, National Institute for Clinical Excellence (NICE) guideline and Quick Reference Guide) were consulted with Stakeholders and comments were considered by the Guideline Development Group (GDG)
2. The final consultation draft of the Full guideline, the NICE guideline and the Information for the Public were submitted to stakeholders for final comments.

The final draft was submitted to the Guideline Review Panel for review prior to publication.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Levels of evidence (I–IV) and grading of recommendations (A–D, GPP) are defined at the end of the Major Recommendations field.

Diagnostic Evaluation and Assessment of Anaemia

Diagnostic Role of Haemoglobin (Hb) Levels

D - Management of anaemia should be considered in people with anaemia of chronic kidney disease (CKD) when their haemoglobin level is less than or equal to 11 g/dL (**C**) (or 10 g/dL if younger than 2 years of age).

See section 3.2.1 in the original full-length guideline document for the associated algorithm.

Diagnostic Role of Glomerular Filtration Rate

D - An estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m² should trigger investigation into whether anaemia is due to CKD. When the eGFR is ≥ 60 mL/min/1.73m² the anaemia is more likely to be related to other causes.

See section 3.2.1 in the original full-length guideline document for the associated algorithm.

Diagnostic Tests to Determine Iron Status

A (DS) - Serum ferritin levels may be used to assess iron deficiency in people with CKD. Because serum ferritin is an acute phase reactant and frequently raised in CKD, the diagnostic cut-off value should be interpreted differently to non-CKD patients.

D (GPP) - Iron deficiency anaemia should be:

- Diagnosed in people with stage 5 CKD with a ferritin level of less than 100 micrograms/L
- Considered in people with stage 3 and 4 CKD if the ferritin level is less than 100 micrograms/L

B (DS) - In people with CKD who have serum ferritin levels greater than 100 micrograms/L, functional iron deficiency (and hence those patients who are most likely to benefit from intravenous iron therapy) should be defined by:

- Percentage of hypochromic red cells $>6\%$, where the test is available or
- Transferrin saturation $<20\%$, when the measurement of the percentage of hypochromic red cells is unavailable

Measurement of Erythropoietin

D (GPP) - Measurement of erythropoietin levels for the diagnosis or management of anaemia should not be routinely considered for people with anaemia of CKD.

Management of Anaemia

Initiation of Erythropoiesis Stimulating Agents (ESAs) Therapy in Iron-Deficient Patients

D (GPP) - ESA therapy should not be initiated in the presence of absolute iron deficiency without also managing the iron deficiency.

D (GPP) - In people with functional iron deficiency, iron supplements should be given concurrently when initiating ESA therapy.

Maximum Iron Levels in Patients With Anaemia of CKD

D (GPP) - In people treated with iron, serum ferritin levels should not rise above 800 micrograms/L. In order to prevent this, the dose of iron should be reviewed when serum ferritin levels reach 500 micrograms/L.

Clinical Utility of ESA Therapy in Iron-Replete Patients

D (GPP) - 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.

D (GPP) - ESAs need not be administered where the presence of comorbidities, or the prognosis, is likely to negate the benefits of correcting the anaemia.

D (GPP) - A trial of anaemia correction should be initiated when there is uncertainty over whether the presence of comorbidities, or the prognosis, would negate benefit from correcting the anaemia with ESAs.

D (GPP) - Where a trial of ESA therapy has been performed, the effectiveness of the trial should be assessed 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.

D (GPP) - All people started on ESA therapy should be reviewed after an agreed interval in order to decide whether or not to continue using ESAs.

Nutritional Supplements

A - Supplements of vitamin C, folic acid, or carnitine should not be prescribed as adjuvants specifically for the treatment of anaemia of CKD.

Androgens

C - In people with anaemia of CKD, androgens should not be used to treat the anaemia.

Hyperparathyroidism

C - In people with anaemia of CKD, clinically relevant hyperparathyroidism should be treated to improve the management of the anaemia.

Patient-Centred Care: ESAs

D - People offered ESA therapy, and their General Practitioners (GPs), should be given information about why ESA therapy is required, how it works, and what benefits and side effects may be experienced.

D (GPP) - 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.

D - People receiving ESA therapy should be informed about the importance of concordance with therapy and the consequences of poor concordance.

D (GPP) - When prescribing ESA therapy, healthcare professionals should take into account patient preferences about supervised- or self-administration, dose frequency, pain on injection, method of supplying ESA, and storage.

D - In order for people to self-administer their ESA in a way that is clinically effective and safe, arrangements should be made to provide ready, reasonable, and uninterrupted access to supplies.

Patient Education Programmes

D (GPP) - Culturally and age-appropriate patient education programmes should be offered 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 (e.g., about symptoms, iron management, causes of anaemia, associated medications, phases of treatment)
- Professional support (e.g., contact information, community services, continuity of care, monitoring, feedback on progress of results)
- Lifestyle (e.g., diet, physical exercise, maintaining normality, meeting other patients)
- Adaptation to chronic disease (e.g., previous information and expectations, resolution of symptoms)

Assessment and Optimisation of Erythropoiesis

Benefits of Treatment with ESAs

A - Treatment with ESAs should be offered to people with anaemia of CKD who are likely to benefit in terms of quality of life and physical function.

See section 3.2.2 in the original full-length guideline document for the associated algorithm.

Blood Transfusions

D - In people with anaemia of CKD, in whom kidney transplant is a treatment option, blood transfusions should be avoided where possible.

D (GPP) - In people with anaemia of CKD there may be situations where a transfusion is indicated clinically. In these cases, the relevant haematology guidelines should be followed.

Comparison of ESAs

A - The choice of ESA should be discussed 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.

Coordinating Care

D (GPP) - 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

Providing ESAs

D (GPP) - 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

ESAs: Optimal Route of Administration

C - The patient 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 (e.g., haemodialysis patients)
- Pain of injection
- Frequency of administration
- The lifestyle and preferences of the patient
- Efficacy (e.g., subcutaneous vs intravenous administration, or long-acting vs short-acting preparations)
- Cost of drug supply

A - 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.

ESAs: Dose and Frequency

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

- **B** - Determined by the duration of action and route of administration of the ESA
- **D (GPP)** - Adjusted to keep the rate of Hb increase between 1 and 2g/dL/month

Optimal Hb Levels

C - In people with anaemia of CKD, treatment should maintain stable Hb levels between 10.5 and 12.5 g/dL for adults and children older than 2 years of age, and between 10 and 12 g/dL in children younger than 2 years of age, reflecting the lower normal range in that age group. This should be achieved by:

- Adjusting treatment, typically when Hb rises above 12.0 or falls below 11.0 g/dL
- Taking patient preferences, symptoms, and comorbidities into account and revising the aspirational range and action thresholds accordingly

D (GPP) - In people who do not achieve a haemoglobin level above 10.5g/dL (or 10.0 g/dL in children younger than 2 years of age) despite correction of iron deficiency and exclusion of the known causes of resistance to ESA therapy (defined as treatment with ≥ 300 IU/kg/week of subcutaneous epoetin or ≥ 450 IU/kg/week of intravenous epoetin or 1.5 micrograms/kg/week of darbepoetin), lower levels of haemoglobin may have to be accepted.

D (GPP) - Age alone should not be a determinant for treatment of anaemia of CKD.

See section 3.2.3 in the original full-length guideline document for the associated algorithm.

Optimum Haemoglobin Levels In Children with Anaemia of CKD

Recommendations pertaining to children with anaemia of chronic kidney disease are presented in relevant sections throughout the guideline.

Adjusting ESA Therapy

C - Iron status should be optimised before or coincident with the initiation of ESA administration.

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

D (GPP) - Haemoglobin measurements should be taken into account when determining the dose and frequency of ESA administration:

- The cause of an unexpected change in Hb level should be investigated (i.e., intercurrent illness, bleeding) to enable intervention.
- ESA dose and/or frequency should be increased or decreased when Hb measurements fall outside action thresholds (usually below 11.0g/dL or above 12.0g/dL), or for example when the rate of change of haemoglobin suggests an established trend (e.g., >1g/dL/month).

See section 3.2.3 in the original full-length guideline document for the associated algorithm.

Treating Iron Deficiency: Correction

D (GPP) - People with anaemia of CKD who are receiving ESAs should be given iron therapy to maintain:

- Serum ferritin >200 micrograms/L
- Transferrin saturation >20% (unless ferritin >800 micrograms/L)
- Hypochromic red blood cells <6% (unless ferritin >800 micrograms/L)

Most patients will require 600–1,000 mg of iron for adults or equivalent doses for children, in a single or divided dose depending on the preparation. Patients with functional iron deficiency should be treated with intravenous iron. Peritoneal dialysis and non-dialysis patients who do not respond to oral iron will require intravenous iron. In appropriate circumstances, iron treatment can also be administered in the community.

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

See section 3.2.2 in the original full-length guideline document for the associated algorithm.

Treating Iron Deficiency: Maintenance

D (GPP) - Once ferritin >200 micrograms/L and hypochromic red cells (HRC) <6% or transferrin saturation (TSAT) >20%, people with anaemia of CKD who are receiving ESAs should be given maintenance iron. The dosing regimen will depend on modality, for example haemodialysis patients will require the equivalent of 50–60 mg intravenous iron per week (or an equivalent dose in children of 1 mg/kg/week). Peritoneal dialysis and non-dialysis patients who do not respond to oral iron will require intravenous iron.

See section 3.2.2 in the original full-length guideline document for the associated algorithm.

ESAs: Monitoring Iron Status During Treatment

Patients receiving ESA maintenance therapy should be given iron supplements to keep their:

- **D** - Serum ferritin between 200 and 500 micrograms/L in both haemodialysis patients and non-haemodialysis patients, and either
 - **B** - The transferrin saturation level above 20% (unless ferritin >800 micrograms/L) or
 - **D (GPP)** - Percentage hypochromic red cells (%HRC) less than 6% (unless ferritin >800 micrograms/L).

In practice it is likely this will require intravenous iron.

Monitoring Treatment of Anaemia of CKD

Monitoring Iron Status

C - 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 dependant on the product used and the amount of iron given.

D (GPP) - Routine monitoring of iron stores should be at intervals of 4 weeks to 3 months.

Monitoring Haemoglobin Levels

D (GPP) - In people with anaemia of CKD, haemoglobin should be monitored:

- 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

Detecting ESA Resistance

D (GPP) - 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 of subcutaneous epoetin or ≥ 450 IU/kg/week 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

D - 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. The GDG considered that PRCA should be confirmed when anti-erythropoietin antibodies are present and there is a lack of pro-erythroid progenitor cells in the bone marrow.

C - 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.

See section 3.2.4 in the original full-length guideline document for the associated algorithm.

Managing ESA Resistance

C - In haemodialysis patients with anaemia of CKD in whom aluminium toxicity is suspected, a desferrioxamine test should be performed and the patient's management reviewed accordingly.

ESA-induced PRCA should be managed in accordance with current best practice. Specialist referral should be considered.

Note: Current best practice for this rare condition is available from the PRCA Global Scientific Advisory Board (GSAB).

See section 3.2.4 of the original full-length guideline document for the associated algorithm.

Definitions:

Levels of Evidence for Studies of Diagnostic Tests

Ia: Systematic review (with homogeneity)* of level-1 studies**

Ib: Level-1 studies**

II: Level-2 studies*** Systematic reviews of level-2 studies

III: Level-3 studies**** Systematic reviews of level-3 studies

IV: Evidence obtained from expert committee reports or opinions and/or clinical experience without explicit critical experience, based on physiology, bench research, or first principles.

*Homogeneity means there are no or minor variations in the directions and degrees of results between individual studies that are included in the systematic review.

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- The comparison between the test and reference is not blind
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1+ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

1- Meta-analyses, systematic review of RCTs, or RCTs with a high risk of bias

2++ High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal

2+ Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal

2- Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal

3 Non-analytic studies (for example, case reports, case series)

4 Expert opinion, formal consensus

Grading of Recommendations

Grade A:

- Level 1++, and directly applicable to the target population, or
- Level 1+, directly applicable to the target population, and consistency of results
- Evidence drawn from a National Institute for Health and Clinical Excellence (NICE) technology appraisal

Grade B:

- Level 2++, directly applicable to the target population, and consistency of results, or
- Extrapolated evidence from studies rated as 1++ or 1+

Grade C:

- Level 2+, directly applicable to the target population and demonstrating overall consistency of results, or
- Extrapolated evidence from studies rated as 2++

Grade D:

- Evidence level 3 or 4, or
- Extrapolated from 2+, or
- Formal consensus

D (GPP):

- A good practice point (GPP) is a recommendation for best practice based on the experience of the Guideline Development Group

Grading of Recommendations on Diagnostic Tests

Grade A (DS): Studies with level of evidence Ia or Ib

Grade B (DS): Studies with level of evidence II

Grade C (DS): Studies with level of evidence III

Grade D (DS): Studies with level of evidence IV

(DS = diagnostic studies)

Grading of Recommendations on Interventions

Grade A:

- Level 1++, and directly applicable to the target population, or
- Level 1+, directly applicable to the target population, and consistency of results
- Evidence drawn from a National Institute for Health and Clinical Excellence (NICE) technology appraisal

Grade B:

- Level 2++, directly applicable to the target population, and consistency of results, or
- Extrapolated evidence from studies rated as 1++ or 1+

Grade C:

- Level 2+, directly applicable to the target population and demonstrating overall consistency of results, or
- Extrapolated evidence from studies rated as 2++

Grade D:

- Evidence level 3 or 4, or
- Extrapolated from 2+, or
- Formal consensus

D (GPP):

- A good practice point (GPP) is a recommendation for best practice based on the experience of the Guideline Development Group

CLINICAL ALGORITHM(S)

Clinical algorithms are provided in the original guideline document for:

- Diagnosis of anaemia of chronic kidney disease (CKD) in adults
- Initial management for adult patients (assumes haemoglobin [Hb] <11g/dL)
- Haemoglobin maintenance algorithm (assumes patient is receiving erythropoiesis stimulating agents [ESAs] and maintenance intravenous iron)
- Algorithm for adult patients with poor response to ESAs

EVIDENCE SUPPORTING THE RECOMMENDATIONS**TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS**

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS**POTENTIAL BENEFITS**

Appropriate treatment of anaemia in patients with chronic kidney disease to improve quality of life and prevent associated complications

POTENTIAL HARMS

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.
- The National Collaborating Centre for Chronic Conditions (NCC-CC) disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.
- The purpose of this guideline is to support clinical judgement, not to replace it. This means the treating clinician should:
 - Take into consideration any contraindications in deciding whether or not to administer any treatment recommended by this guideline.
 - Consider the appropriateness of any recommended treatment for a particular patient in terms of the patient's relevant clinical and non-clinical characteristics.
- Wherever possible, before administering any treatment the treating clinician should follow good practice in terms of:
 - Discussing with the patient why the treatment is being offered and what health outcomes are anticipated.
 - Highlighting any possible adverse events or side-effects that have been associated with the treatment.
 - Obtaining explicit consent to administer the treatment.
- For those recommendations involving pharmacological treatment, the most recent Summary of Product Characteristics should be followed for the determination of:
 - Indications
 - Drug dosage
 - Method and route of administration
 - Contraindications
 - Supervision and monitoring
 - Product characteristics
 - Except in those cases where guidance is provided within the recommendation itself

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation in the National Health Service (NHS)

The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in "Standards for better health" issued in July 2004. Implementation of clinical guidelines forms part of the developmental standard D2. Core standard C5 says that national agreed guidance should be taken into account when NHS organisations are planning and delivering care.

The National Institute for Health and Clinical Excellence (NICE) has developed tools to help organisations implement this guidance (listed below). These are available on their website (<http://guidance.nice.org.uk/cg39>) (see also the "Availability of Companion Documents" field).

- Slides highlighting key messages for local discussion
- Costing tools
 - Costing report to estimate the national savings and costs associated with implementation.
 - Costing template to estimate the local costs and savings involved.
- Implementation advice on how to put the guidance into practice and national initiatives which support this locally.

Suggested audit criteria based on the key priorities for implementation are listed in appendix C of the NICE version of the original guideline document (see "Availability of Companion Documents" field), and can be used to audit practice locally.

Key Priorities for Implementation

- Management of anaemia should be considered in people with anaemia of chronic kidney disease (CKD) when the haemoglobin (Hb) level is less than or equal to 11 g/dL (or 10 g/dL if under 2 years of age).
- 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.
- 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 which 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
- In people with anaemia of CKD, treatment should maintain stable Hb levels between 10.5 and 12.5 g/dL for adults and children aged over 2 years, and between 10 and 12 g/dL in children aged under 2 years, reflecting the lower normal range in that age group. This should be achieved by:
 - Considering adjustments to treatment, typically when Hb rises above 12.0 or falls below 11.0 g/dL
 - Taking patient preferences, symptoms and comorbidity into account and revising the aspirational range and action thresholds accordingly

- Age alone should not be a determinant for treatment of anaemia of CKD.
- People receiving ESA maintenance therapy should be given iron supplements to keep their:
 - Serum ferritin between 200 and 500 micrograms/L in both haemodialysis patients and nonhaemodialysis patients, and either
 - The transferrin saturation level above 20% (unless ferritin >800 micrograms/L) or
 - Percentage hypochromic red cells (%HRC) less than 6% (unless ferritin >800 micrograms/L)

In practice it is likely this will require intravenous iron.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
 Patient Resources
 Quick Reference Guides/Physician Guides
 Resources
 Slide Presentation

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Collaborating Centre for Chronic Conditions. Anaemia management in chronic kidney disease. National clinical guideline for management in adults and children. London (UK): Royal College of Physicians; 2006. 172 p. [295 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006

GUIDELINE DEVELOPER(S)

National Collaborating Centre for Chronic Conditions - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Guideline Development Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All group members made a formal "declaration of interests" at the start of the guideline development and provided updates throughout. The National Collaborating Centre for Chronic Conditions (NCC-CC) and the Guideline Development Group (GDG) Chair monitored these.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Anaemia management in people with chronic kidney disease. NICE guideline. London (UK): National Institute for Health and Clinical Excellence; 2006 Sep. 36 p. (Clinical guideline; no. 39). Electronic copies: Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).
- Anaemia management in people with chronic kidney disease. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence; 2006 Sep. 11 p. (Clinical guideline; no. 39). Electronic copies: Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).
- Anaemia management in people with chronic kidney disease. Costing report. Implementing NICE guidance in England. London (UK): National Institute for Health and Clinical Excellence; 2006 Sep. 34 p. (Clinical guideline; no. 39). Electronic copies: Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).
- Anaemia management in people with chronic kidney disease. Costing template. London (UK): National Institute for Health and Clinical Excellence; 2006 Sep. various p. (Clinical guideline; no. 39). Electronic copies: Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).
- Anaemia management in people with chronic kidney disease. Implementation advice. London (UK): National Institute for Health and Clinical Excellence; 2006 Sep. 17 p. (Clinical guideline; no. 39). Electronic copies: Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).
- Anaemia management in people with chronic kidney disease. Slide set. London (UK): National Institute for Health and Clinical Excellence; 2006 Sep. 24 p. (Clinical guideline; no. 39). Electronic copies: Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N1115. 11 Strand, London, WC2N 5HR.

Additionally, Audit Criteria can be found in section 3.3 of the [original guideline document](#).

PATIENT RESOURCES

The following is available:

- Treating anaemia in people with chronic kidney disease. Understanding NICE guidance. Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence; 2006 Sep. 12 p. (Clinical guideline; no. 39). Electronic copies: Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N1116. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This summary was completed by ECRI on February 15, 2007. The information was verified by the guideline developer on March 9, 2007. This summary was updated by ECRI Institute on March 21, 2008 following the FDA advisory on Erythropoiesis Stimulating Agents. This summary was updated by ECRI Institute on August 15, 2008 following the U.S. Food and Drug Administration advisory on Erythropoiesis Stimulating Agents (ESAs).

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