What should my Haemoglobin be?

Clinical Practice Guidelines for Anaemia management in patients with chronic kidney disease.

Introduction.

Haemoglobin (Hb) is a protein molecule containing iron that gives red blood cells their colour and is responsible for carrying oxygen from the lungs to the tissues as the blood is pumped around the body by the heart. If the amount of Hb is less than normal (known as anaemia), the organs of the body are starved of oxygen reducing their ability to function properly and causing tiredness, weakness, and breathlessness. The red blood cells are manufactured in the bone marrow requiring iron and a hormone produced by the kidneys called Erythropoietin (EPO). If the kidneys fail, EPO production is impaired and the patient becomes anaemic. This can be counteracted by administering (by injection) ESAs (Erythropoietin Stimulating Agents). Oral or intravenous injections of iron may also be required to correct the anaemia. Hb is measured by estimating its concentration in the blood and the units of measurement are in grams per 100ml (i.e. grams per decilitre). Iron is normally absorbed from food via the gut (intestines). A protein called ferritin is produced in the liver to store any iron absorbed by the gut that is not immediately required by the bone marrow to make new Hb. Thus iron levels in the blood are estimated by measuring the serum ferritin. The concentration of ferritin is measured in nanograms per millilitre (ng/ml) or micrograms per litre (µg/L). It may be helpful to know that 1 gram = 1000 milligrams = 1,000,000 micrograms = 1,000,000,000 (1 billion) nanograms. In order for iron to be transported to the bone marrow it is incorporated into a protein called transferrin which is made by the liver and then carried to the bone marrow, where it is converted under the influence of EPO to haemoglobin.

Diagnosing the cause of iron deficiency in CKD patients may be difficult if other conditions such as infection are present, as inflammation prevents the iron from being mobilised from the body’s iron stores. However the inflammation also causes a rise in serum ferritin. As serum ferritin is used to as a proxy to estimate the patient’s iron levels, the raised levels will give the impression of iron overload. To avoid this error, further tests may be necessary. One such test is the TSAT (transferrin saturation test) which is the ratio of serum iron to the total iron-binding capacity of the blood expressed as a percentage and indicates how much serum iron is actually bound to transferrin. (A TSAT of 15% means that 15% of free iron is being carried by transferrin). The total iron-binding capacity (TIBC) measures the blood’s capacity to bind iron with transferrin. In inflammatory conditions, as explained above, the serum ferritin levels are raised, and the TIBC will appear reduced giving the conflicting impression of iron deficiency, so called functional iron deficiency. Other more sophisticated (and expensive) tests may clarify the diagnostic conundrum.
The TSAT is expressed as a percentage because this show how much carrying capacity is available

This appendix discusses three issues:

i) **what optimal levels of haemoglobin should be aimed for**

ii) **how they should be achieved**

iii) **what are the associated problems and risks in treatment.**

In normal individuals, depending upon age and gender, haemoglobin levels range between 13 and 15 grams per dl that is: per 100ml (decilitre). 1997, the DOQI guidelines on the treatment of anaemia in CKD patients, recommended a target range for Haemoglobin (Hb) of between 11 and 12 g/dl. Similar recommendations were made in 2006 by KDOQI and EBPG although no upper limit was defined for all stages of CKD by ERPG in 2004. For patients who also had diabetes or cardiovascular disease, it was generally not recommended to aim for these ‘higher’ target levels.

In patients whose anaemia was being treated with ESAs (Erythropoietin Stimulating Agents), the updated 2006 NKF-KDOQI guidelines recommended that the (lower limit) of the haemoglobin range should be \( \geq 11.0 \text{ g/dl} \) but there was insufficient evidence to routinely maintain an upper limit of \( \geq 13.0 \text{ g/dl} \). At this time the evidence showed that although quality of life may be improved by complete correction of the anaemia, there was none to support other measures of benefit, such as improved mortality.

In March 2007, the US Food and Drug Administration (FDA) changed the labelling for erythropoiesis stimulating agents (ESAs) and added a boxed warning stating that Hb targets of \( > 12 \text{ g/dl} \) should be avoided because of the increased risk of death and serious cardiac events. They also noted that ESAs should be used to increase haemoglobin but only to the lowest level necessary to avoid transfusion and thus to a level where patients become asymptomatic.

These recommendations created considerable confusion and concern. The new evidence from the CREATE and CHOIR studies was sufficient to justify updating the statements of the NKF-KDOQI guideline working group concerned with Hb targets. An Evidence Review Team analysed all data from 6 randomized controlled trials of anaemia management in CKD. On the basis of these results, the NKF-KDOQI working group recommended: the Hb target in patients receiving ESAs should generally be \( 11–12 \text{ g/dl} \) and not \( > 13 \text{ g/dl} \) because ‘the possibility of causing harm is greater than the potential of improving the quality of life and for decreasing the need for blood transfusions’.

In October 2007, KDIGO responded to the NKF-KDOQI updated recommendation by issuing a position statement with 3 conclusions:

i) Haemoglobin levels of \( > 13 \text{ g/dl} \) may be associated with harm in subjects treated with ESA

ii) Haemoglobin Levels of \( 9.5–11.5 \text{ g/dl} \) are associated with better outcomes than those of \( > 13 \text{ g/dl} \).

iii) There was no evidence either way for intermediate levels (\( 11.5–13 \text{ g/dl} \))
Limitations of the current knowledge of CKD-related anaemia were identified and deemed worthy of future research.

**The position of ERBP is as follows:**

i) **Haemoglobin target**

In 2004, EBPG suggested an Hb target ≥11 g/dl; values of >14 g/dl were considered undesirable in general, and the limit for patients with diseases of the heart and/or blood vessels was set at 12 g/dl. Caution of not exceeding Hb concentrations ≥12 g/dl was also recommended for patients with diabetes, especially if they had concurrent peripheral vascular disease. Since 2007, when the KDOQI Hb target update was published, no further data from new clinical trials have been published.

- In the opinion of the ERBP Work Group, it appears reasonable to maintain the lower limit of the target, although the actual evidence for choosing this value is also very limited. On the basis of new evidence, Hb values of 11–12 g/dl should be generally sought in the CKD population without aiming to exceed 13 g/dl.

Although harm is possible when aiming at higher Hb targets, it is likely that this applies mostly to selected populations such as patients with diabetes and/or clinically significant diseases of the heart and/or blood vessels. However, current evidence shows no benefit for higher targets in any subgroup and there is the additional consideration of the increased cost of higher ESA doses.

- The ERBP Work Group believes that there is a need for better understanding as to whether any harm may be associated with attempts to reach higher Hb values in patients with co-morbidities or those who are hypo-responsive to ESAs. Physicians need to accept that patients may be below or above the target for a given period of time.

- The ERBP Work Group agrees with the recent position of KDIGO that the quality-of-life data that are currently available vary in quality and are often inconclusive. As more reliable methods of assessing patient-related outcomes and functional status have now become available, there is room for new studies which will test the effect of correcting anaemia on the quality of life.

ii) **Anaemia evaluation**

In 2004, EBPG defined anaemia in CKD patients on the basis of their gender and age. In patients living below an altitude of 1500 m, Hb values were considered below normal if they were <11.5 g/dl in women and <13.5 g/dl in men (<12 g/dl in those aged >70 years), and it was recommended that ‘an anaemia work-up’ be started when Hb levels fall below these limits. (‘An anaemia work-up’ is a series of investigations into the cause of the anaemia)

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 a decrease in Hb among males aged >60 years is often attributable to other concurrent diseases and requires investigation in its own right.
• The ERBP Work Group agrees with this new definition.

   iii) Targets for iron therapy

The most widely used tests for iron levels are serum ferritin and transferrin saturation (TSAT) levels. In 2004 EBPG recommended lower limits of ferritin levels as 100 ng/ml and TSAT as 20%, with target ranges of 200–500 ng/ml (ferritin) and 30–50% (TSAT). Because of patient safety considerations, in 2006 KDOQI defined the lower ferritin limit on the basis of a patient’s CKD status: (100 ng/ml in non-HD-CKD and 200 ng/ml in HD-CKD); if serum ferritin levels are >500 ng/ml, iron administration should be discouraged.

• The ERBP Work Group agrees with the recommendations of the KDOQI guidelines.

   iv) New ESAs

In 2004 (EBPG) and 2006 (KDOQI) recommendations were made concerning the use of the three ESAs available at that time: epoetin alpha, epoetin beta and darbepoetin alpha. Since then, two more have been introduced: epoetin delta and CERA (continuous erythropoiesis receptor activator).

• In the opinion of the ERBP Work Group, epoetin delta should be administered similarly to epoetin alpha but (CERA), has a considerably longer half-life than the other licensed ESAs (~130 h) and should be administered once every 2 weeks for correcting the anaemia and once every 4 weeks to maintain the target level of haemoglobin. Its safety and tolerability is similar to that of other ESAs.

   v) Biosimilars

When a drug company’s patent on one of their products expires (generally after 20 years although less so in Europe) other manufacturers can make an equivalent but cheaper version. They are known as ‘Biosimilars’.

In Europe, the patent on epoetin alpha expired in December 2004 and that of epoetin beta, in 2005. HX575, a biosimilar of epoetin alpha, received marketing authorization throughout the European Union in August 2007 and is marketed by three companies under three different brand names. In December 2007, epoetin zeta, another biosimilar of epoetin alpha, also received EMEA (European Medicines Agency) marketing authorization.

Whilst biosimilars may be more affordable, their safety record is shorter than the original ESAs. In view of the delicate production process of these complex molecules, different brands cannot be considered equivalent, even if they have the same formula, as was demonstrated by the PRCA epidemic. The production process of biosimilars necessitates stringent pharmaco-vigilance monitoring as do all ESAs. It should be mandatory that biosimilars are not substituted for other r-HuEPOs (Recombinant human erythropoietins) without a physician’s prior approval. It is also noteworthy that ESA biosimilars are currently only approved for intravenous administration (direct injection into a vein) in CKD patients making them de facto, unsuitable for non-haemodialysis patients, although epoetin zeta has recently been approved for subcutaneous
vi) Pure red cell aplasia (PRCA)

Antibody-mediated (allergy-like) pure red cell aplasia (PRCA) is a rare but serious adverse event related to ESA therapy. There was an upsurge in the number of PRCA cases since 1998, mainly associated with the subcutaneous use of Eprex®. Eprex® is the epoetin alpha produced outside the United States. The breaking of the cold chain is potentially an important factor. Cold chain failure occurs when vaccines or other temperature sensitive products are exposed to temperatures outside the recommended range of storage. The subcutaneous use of Eprex® in CKD patients had been contraindicated in Europe by regulatory authorities since December 2002, and was strongly discouraged in Canada and Australia. The number of reported cases of PRCA has decreased sharply since 2003, with no more cases were reported in 2007. This may be due to: a change in the route of administration; the reinforcing the importance of not breaking the cold chain; and eliminating uncoated rubber syringe stoppers. The regulatory authorities consider the latter as the most significant factor and have recently re-authorised the subcutaneous use of Eprex® when vascular access is not available as long as there is an extensive pharmaco-vigilance plan in place.

- The ERBP Work Group considers it essential that suspected PRCA cases are carefully worked up and confirmed cases are closely monitored.

- With the data available, the ERBP Work Group considers that recommencement of treatment with ESA can be considered in patients with a history of PRCA, if anti-EPO antibodies are no longer detectable.

It has recently been reported that hematide, (a non-peptide erythropoietin receptor agonist which is currently under clinical development) corrects the anaemia induced by anti-erythropoietin antibodies as previously shown in a rat PRCA model. In 2010 this was also demonstrated in men (NEJM).

vii) Safety concerns in CKD patients with cancer

No direct relationship has yet been established between the presence of EPOr (Erythropoietin Receptor) on tumour cells and tumour proliferation in response to administering exogenous EPO. However the use of ESAs may increase the risk of venous thrombo-embolism in cancer patients.

ESA therapy is approved in patients with non-myeloid malignancies who have developed chemotherapy-associated anaemia in order to decrease transfusion requirements. But since 2004, there have been safety concerns in cancer patients, particularly in relation to off-label indications such as: anaemia not secondary to chemotherapy; or an Hb target of >12 g/dl.

In May 2007, the Oncologic Drugs Advisory Committee of the Food and Drug Administration (FDA) reassessed the ESA-related risks of: venous thrombo-embolism; poorer cancer outcomes; and cardiovascular disease in cancer patients receiving chemotherapy. They subsequently ordered that boxed warnings be added to the labels of the ESAs recommending that the lowest
ESA dose be used to increase Hb to a level high enough to avoid red blood cell transfusions. According to FDA indications, an Hb target of >12 g/dl should be avoided.

- In the opinion of the ERBP Work Group, ESA therapy should be cautiously used in patients with CKD and malignancies as no information is available concerning the risk of mortality and tumour growth in this subset of patients.