Guidelines on Anaemia Management in Patients with Chronic Kidney Disease (CKD)

This guideline is for use in adult patients with an estimated Glomerular Filtration Rate (eGFR) of less than 60ml/min/1.73m^2 and not on dialysis. It is intended for use by the Renal Department Multidisciplinary Team (MDT).

Responsibilities for the management of anaemia in CKD

- The recognition and diagnosis of anaemia in patients with CKD is the responsibility of the patient's named consultant and other members of the renal medical team.
- Once the patient has been referred to the renal anaemia team, the team will be responsible for the on-going monitoring and treatment of anaemia, in consultation with the patients named consultant where necessary. The renal anaemia team will not be responsible for co-ordinating management if an appropriate referral is not received
- Anaemia medications in patients with CKD should only be prescribed by the renal consultants, trained renal middle grade doctors, trained renal specialist nurses or renal pharmacists.

When to begin investigating and managing anaemia in CKD?

a) Haemoglobin (Hb) falls to 110 g/L or less.

or

b) Symptoms attributable to anaemia such as tiredness, shortness of breath, lethargy and /or palpitation.

Reviewed by Dr A McClean, CKD Nursing Team, Kate Webb & Imran Anwar
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Consider causes for anaemia if Hb less than 110 g/L in CKD

Low Mean Cell Volume (MCV) less than 80 femtolitres (fL)
1) Iron deficiency (e.g. Chronic gastrointestinal (GI) bleed)
2) Thalassemia

Normal MCV 80 to 100 fL
1) Anaemia due to Chronic Disease (ACD)

High MCV more than100 fL
1) B12/folate deficiency
2) Reticulocyosis e.g. secondary to haemolysis or acute GI bleed
3) Aplastic anaemia
4) Alcoholism with liver disease
5) Bone marrow pathology e.g. myelodysplastic syndromes, myeloid leukemia, myeloma
7) Azathioprine

Note:

1) In cases of thalassemia, the MCV may be low even though the patient is not iron deficient.

2) High MCV may be seen in patients receiving Erythropoiesis Stimulating Agent (ESA).

Baseline investigations

All anaemic patients with CKD should have Hb, Percentage of Hypochromic Red blood cells (%HCR), Ferritin, B12, Folate, and Parathyroid Hormone (PTH) checked within 3 months at the time of presentation. As %HCR is not available in Leighton, Transferrin Saturation (TSAT) should be checked as an alternative marker.

Treatment targets

- Target Hb: 100 to 120 g/L
- Target Ferritin: 200-500microgam/L
- Target %HRC less than 6% (unless ferritin is greater than 800 microgram/l) for Royal Stoke and County Patients
- Target TSAT more than 20% (unless ferritin is greater than 800 microgram/l) for Leighton patients

Interpretation of iron studies

	Ferritin (microgram/l)	%HRC (RSUH + County)	MCV (fL)	TSAT (Leighton)
Functional Iron Deficiency	More than 100	More than 6%	80-100	Less than 20%
Absolute Iron Deficiency	Less than 100	More than 6%	Usually less than 80	Less than 20%
Iron Replete	More than 100	6% or below	80-100	20% or above

- Do not use Serum Ferritin or TSAT measurement alone to assess iron deficiency status.
- Absolute iron deficiency should prompt investigation and treatment.
- Functional iron deficiency with anaemia should be treated to ensure iron stores are replete.

Treatment guidance

	Iron Replete	Iron Deficiency
Hb 100-120 g/L	Monitor	Oral or IV iron as clinically indicated (please see below)
Hb 90-100 g/L	ESA	IV iron then ESA if Hb still less than 100 g/L
Hb less than 90 g/L	ESA	IV iron and ESA

Choosing between oral and IV iron in CKD patients

For patients with CKD (not on dialysis) who require iron replacement, consider a trial of oral iron as first line therapy.

Offer IV iron therapy only if:

- Patient is intolerant of oral iron
- Patient is unresponsive to oral iron, i.e. target ferritin levels are not reached within 3 months
- Patient is on ESA therapy

Ferric carboxymaltose (Ferinject®) dosage schedule

Ferinject® is indicated for treatment of iron deficiency when oral iron preparations are ineffective or cannot be used. The diagnosis of iron deficiency must be based on laboratory tests.

The use of Ferinject® is contraindicated in cases of:

• Hypersensitivity to the active substance, to Ferinject® or any of its excipients (consult SPC)

• Known serious hypersensitivity (anaphylaxis) to other parenteral iron products

• Anaemia not attributed to iron deficiency, e.g. other microcytic anaemia

• Evidence of iron overload or disturbances in the utilisation of iron

If there is evidence of absolute or functional iron deficiency and ferritin is less than 500microgram/l please use table below:

Hb	Patient body weight				
g/L	Less than 35 kg	35.1kg to 37.4kg	37.5kg to 49.9kg	50kg to 69.9kg	Greater than 70 kg
Less than 100	500 mg	**Week 1:** 700mg **Week 2:** 700mg	**Week 1:** 750mg **Week 2:** 750mg	**Week 1:** 1000mg **Week 2:** 500mg	**Week 1:** 1000mg **Week 2:** 1000mg
100 to 140	500 mg	**Week 1:** 500mg **Week 2:** 500mg	**Week 1:** 500mg **Week 2:** 500mg	1,000 mg	**Week 1:** 1000mg **Week 2:** 500mg
Greater than 140	500 mg	500mg	500mg	500 mg	500 mg

- Ferinject® should be diluted in 100mls sodium chloride 0.9% and given IV over 15 minutes via butterfly or venflon.
- Monitor patients carefully for signs and symptoms of hypersensitivity reactions during and following each administration of Ferinject®.
- **Hypersensitivity reactions can occur even when a previous administration has been tolerated. Caution is therefore needed with EVERY dose of IV iron, even if previous administrations have been well tolerated.**
- **Ferinject® should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured. The patient should be observed for adverse effects for at least 30 minutes following each Ferinject® injection.**
- If any signs of a reaction- stop Ferinject®, monitor vitals, ask for an urgent doctor's review. record details in CyberRen and Medisec, complete Medicines Health Regulatory Agency (MHRA) Yellow card & complete Trust Datix®.

Hypersensitivity reactions associated with Intravenous Iron products

- Cardiac Arrest
- The Medicines and Healthcare products Regulatory Agency (MHRA) have advised that intravenously administered iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic / anaphylactoid reactions. Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes.
- The risk is enhanced for patients with known allergies including drug allergies, including patients with a history of severe asthma, eczema or other atopic allergy.
- There is also an increased risk of hypersensitivity reactions to intravenous iron complexes in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis).

- Ferinject® should only be administered when staff trained to evaluate and manage anaphylactic reactions are immediately available, in an environment where full resuscitation facilities can be assured.

- If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardio respiratory resuscitation and equipment for handling acute anaphylactic / anaphylactoid reactions should be available, including an injectable 1:1000 adrenaline solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate (see below). **All patients need to be reviewed by a doctor in the event of anaphylactic reaction even if it was a mild reaction.**

For further information on acute anaphylaxis please consult UHNM Medical Guidelines

Emergency medications used in case of anaphylactic reactions

The following medicines must be prescribed for all patients receiving IV iron and only administered if an anaphylactic reaction is suspected:

Adrenaline (1:1000) 500micrograms IM STAT (repeat after 5 minutes if required)

Chlorphenamine 10 mg IV STAT (max 40mg in 24 hours)

Hydrocortisone 200mg IM or slow IV STAT

Contact cardiac arrest team (extension 2222)

Test dose for intravenous Iron

There are no clear data that an initial test dose minimizes risk of anaphylaxis: conversely, it may give false reassurance because hypersensitivity reactions have been reported in patients that had a negative initial test dose. Hence an initial test dose is not recommended.

Infection

The manufacturer cautions the use of IV Iron during an infective illness. The patient's consultant should be informed and IV iron should only be given if the patient's consultant judges that the benefits outweigh the risks.

Other

IV Iron should be used with caution in patients suffering from asthma, eczema or atopic allergies.

Pregnancy

- There are no adequate and well-controlled trials of Ferinject® in pregnant women. A careful benefit/risk evaluation is required before use during pregnancy and Ferinject® should not be used during pregnancy unless clearly necessary.
- Iron deficiency occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with Ferinject® should be confined to the second and third trimester if the benefit is judged to outweigh the potential risk for both the mother and the foetus.

- Animal data suggest that iron released from Ferinject® can cross the placental barrier and that its use during pregnancy may influence skeletal development in the fetus.

Breast-feeding

- Clinical studies showed that transfer of iron from Ferinject® to human milk was negligible (≤1%). Based on limited data on breast-feeding women it is unlikely that Ferinject® represents a risk to the breast-fed child.

Fertility

- There are no data on the effect of Ferinject® on human fertility. Fertility was unaffected following Ferinject® treatment in animal studies.

Reassessment of anaemia parameters following IV iron infusion

The Hb level should be re-assessed by the renal anaemia team no earlier than 4 weeks following final Ferinject® administration to allow adequate time for erythropoiesis and iron utilisation. In the event the patient requires further iron, the iron need should be recalculated using the dosing table (see page 5).

- Repeat Hb, ferritin, and %HRC in 4 -6 weeks after IV Ferinject® load. Note TSAT will be measured for Leighton patients only (in lieu of %HRC).
- Repeat further course if there is evidence of absolute or functional iron deficiency and ferritin is less than 500microgram/l (see interpretation of iron study table on page 3)
- Repeat iron indices 3 monthly.

Erythropoiesis Stimulating Agent (ESA)

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

Measurement of erythropoietin levels should not be routinely considered for diagnosis in CKD with anaemia.

ESA should only be initiated after correcting Iron, B12 and folate deficiency.

ESA treatment responsibilities:

- ESA must be prescribed by the renal team (e.g. renal consultants, trained renal middle grade doctors, trained renal specialist nurses or renal pharmacists).
- Home delivery is arranged by the CKD team, who will also be responsible for training patients/carers to administer ESA.
- It is the responsibility of the renal anaemia specialist nurse, in consultation with the patient's named consultant, to monitor response to treatment and adjust dosing.
- The patient's General Practitioner (GP) must be informed on initiation of therapy and it must be communicated that they will not be responsible for prescribing / supplying ESA therapy.
- It is departmental policy that the patient / carer will administer ESA treatment. If this is not possible, and in exceptional circumstances, the patient's GP practice or local District Nurse services may be asked to administer ESA therapy. However the department acknowledges that the patient's GP practice or local District Nurse services do not have an obligation to help with administration and if they decline to do so the patient will need to have treatment on the Kidney Unit.

Treatment with ESA should be patient centred. After referral to the CKD anaemia team each patient will be contacted by a renal anaemia specialist nurse and given:

- Information about how ESA works, its benefits and side effects
- A plan for drug supply and administration
- Instructions for monitoring blood pressure and acceptable parameters
- Regular blood tests and reviews
- Awareness of the importance of concordance with therapy

ESA preparation

The Renal Department at UHNM is currently using **Darbepoetin alfa (Aranesp®)**.

This reflects ESA choice on the North Staffordshire Joint Formulary.

Darbepoetin alfa is available in two forms: pre-filled syringes and sure-click injection. However the Renal Department at UHNM recommends using the pre-filled syringe device and the dosing recommendations in this guideline reflects this.

Dose of darbepoetin alfa

Weight Range (kg)	Dose	Frequency
35 – 46.9	30 micrograms	Fortnightly
47 -59.9	40 micrograms	Fortnightly
60 – 74.9	50 micrograms	Fortnightly
75 – 89.9	60 micrograms	Fortnightly
90 - 100	70 micrograms	Fortnightly
For dosing patients less than 35kg or more than 100kg discuss with their named consultant		

This dosing strategy is for darbepoetin alfa prefilled syringes which are available in 10, 20, 30, 40, 50, 60, 80, 100, 130, 150, 300 and 500micrograms.

Blood Pressure

ESA treatment may result in a rapid rise in, and very high absolute levels of, blood pressure. This could result in hypertensive encephalopathy. Therefore careful monitoring of blood pressure is essential during treatment.

Check blood pressure before every darbepoetin alfa (ESA) administration. If blood pressure is greater than 160/90mmHg suspend ESA and restart only when blood pressure controlled. If blood pressure rises on ESA this should be controlled with antihypertensive medication.

Pregnancy

- There are no adequate and well-controlled studies with darbepoetin alfa in pregnant women.
- Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/ foetal development, parturition or postnatal development.
- No alteration of fertility was detected.
- Caution should be exercised when prescribing darbepoetin to pregnant women.
- Amgen no longer have a pregnancy surveillance programme. Pregnancy is monitored as part of the normal surveillance programme. Women who become pregnant can contact Amgen Medical Information via 01223 436 441. Amgen safety will conduct a normal follow-up (a data collection form during pregnancy, one post-delivery and short update forms at 6 & 12 months these forms will be sent to the patient).

Breast-feeding

- It is unknown whether darbepoetin is excreted in human milk. A risk to the breast-feeding child cannot be excluded.
- A decision must be made whether to discontinue breast-feeding or to discontinue / abstain from darbepoetin therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

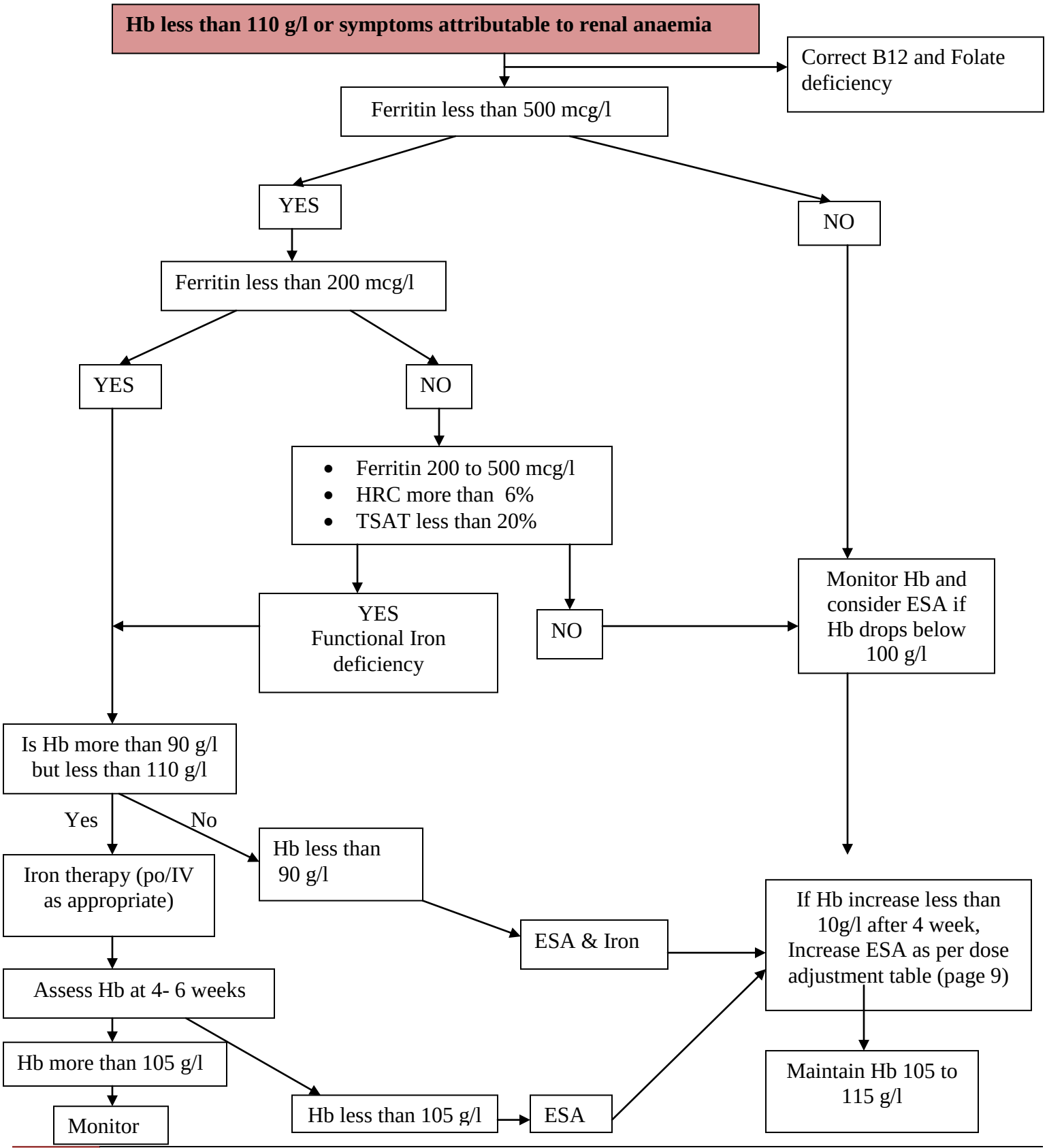
Monitoring bloods on ESA - darbepoetin alfa

- Induction Phase of ESA. Monitor the following every 4 weeks: -
  - FBC
  - Ferritin
  - U&E
  - % HRC (RSUH + County)
  - TSAT (for Leighton patients)

- Maintenance Phase of ESA. Continue to monitor the above every 8 weeks.

- This monitoring will be coordinated by the renal anaemia team, with input from the patient's named consultant when necessary.

Summary of initial management of anaemia in CKD patients



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Dose adjustment of ESA - darbepoetin alfa

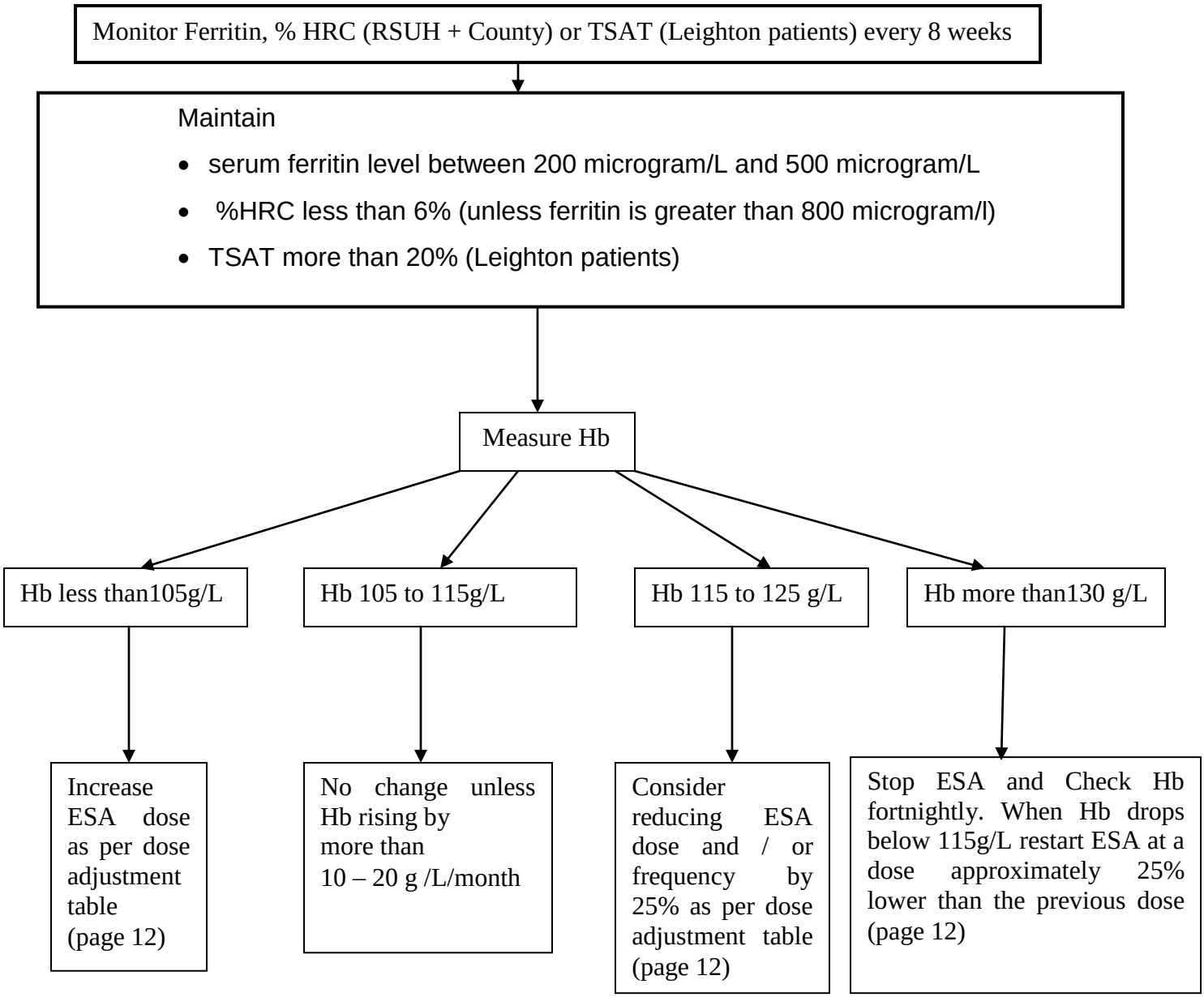
- The renal anaemia team will maintain the aspirational Hb range between 100 and 120 g/l for adults (unless a different aspirational range has been agreed with the patient's named consultant).
- Do not wait until Hb levels are outside the aspirational range before adjusting treatment (consider adjusting ESA dose if Hb level falls less than 105 and more than 115 g/l).

ESA adjustment schedule for adult patients – make adjustments based on absolute Hb level and / or rate of change of Hb more than 10 g/L/month

To utilise patients darbepoetin stock, initially consider either increasing dose frequency for doses that need to be increased or decreasing dose frequency (minimum monthly) for doses that need to be decreased, before changing dose.

Current Dose (microgram/fortnight)	**Increased Dose** (microgram/fortnight)	**Decreased Dose** (microgram/fortnight)
30	40	20
40	50	30
50	60	40
60	80	50
70	90	50
80	100	60
90	110	70
100	130	80

Maintenance algorithm for CKD patients on ESA ± IV iron



Individualising the aspirational range

There are times when it is appropriate to individualise the aspirational range for Hb. Consider individualising the aspirational range for example for physically inactive patients and patients with physically demanding job / lifestyle. This should be a consultant decision. If deciding to maintain Hb outside the aspirational range, the risks and benefits should be discussed with the patient and documented in clinical notes

When to suspect ESA resistance

- NICE states this should be suspected when anaemia is not corrected despite a dose equivalent to greater than 1.5micrograms/kg/week of darbepoetin alfa.
- There is continued need for administration of high doses of ESAs to maintain the aspirational range.

Main conditions associated with ESA resistance

1) Iron deficiency

2) Chronic blood loss

3) Intercurrent illness such as Infections and inflammations

4) Vitamin deficiencies (eg: Folate & vitamin B12 deficiency)

5) Hyperparathyroidism

6) Bone Marrow pathology e.g. multiple myeloma, myelodysplasia

7) Other malignancy

8) Hemoglobinopathies (eg: Thalassemia, Sickle cell)

9) Malnutrition

10) Aluminium Toxicity

Criteria for escalation to patient's named consultant

- ESA resistance is suspected
- There is any suspicion of infection / sepsis
- Newly diagnosed cancer – The decision to use ESA should be based on an assessment of the benefits and risks for individual patients.
- Blood Pressure is greater than 160/90 mmHg while on ESA.
- If patient is pregnant or breast feeding.
- Suspected pure red cell aplasia (PRCA)

This should be suspected if Hb decreases by 1g/L/day, corresponding to the life span of red cells, in absence of GI blood loss in patients with or without ESA resistance. As iron use is largely abolished in PRCA as a result of absence of marrow erythropoietic activity. Therefore, ferritin levels are very high with a very low reticulocyte count.

Guideline disclaimer

Please note this clinical guideline is expected to cover the anaemia management of the majority of patients with CKD. It is estimated that it will provide clinically appropriate options for 80% of patients. All patient are individuals, however, and it is recognised that there will be some situations where prescribing outside of theses clinical guidelines may be necessary.

Please note these guidelines have been created using information within NICE Clinical Guideline NG8, "CKD: managing anaemia" (June 2015) with adaptations in line with local policy, as agreed by the UHNM Renal Department.