Anaemia and Renal Disease

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THE RENAL ASSOCIATION
founded 1950

Clinical Practice Guideline
Anaemia of Chronic Kidney Disease

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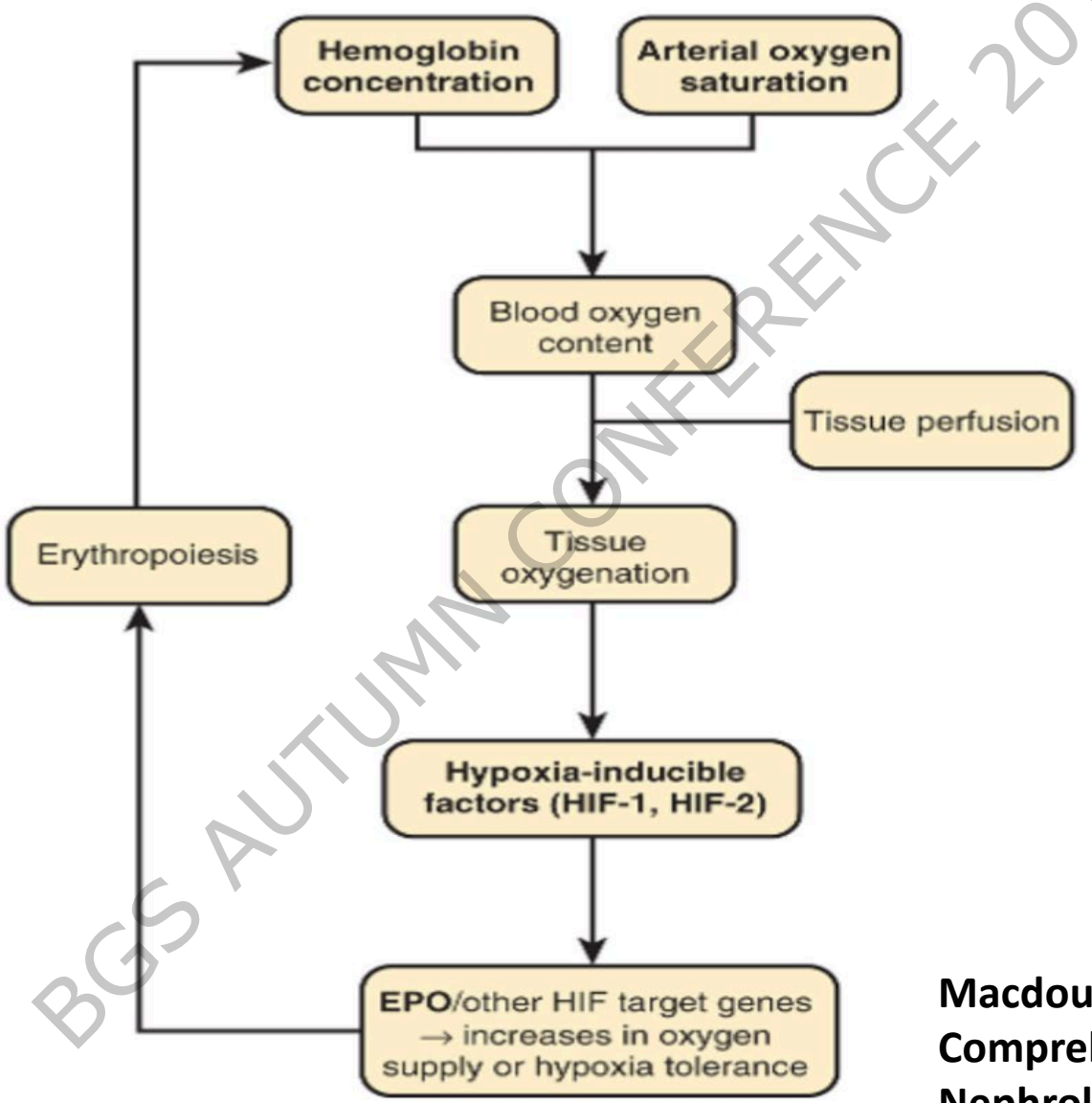
Anaemia in CKD: an overview

- Common complication of CKD
- Associated with left ventricular dysfunction and heart failure
- Reduces exercise capacity and quality of life
- Aetiology related to:
  - Iron deficiency and/or sequestration
  - Reduction in erythropoietin secretion
- Management is a combination of iron therapy and erythropoiesis stimulating agents (ESA)

Feedback Control of Erythropoiesis



Macdougall IC, Eckardt K-U in Comprehensive Clinical Nephrology 2018

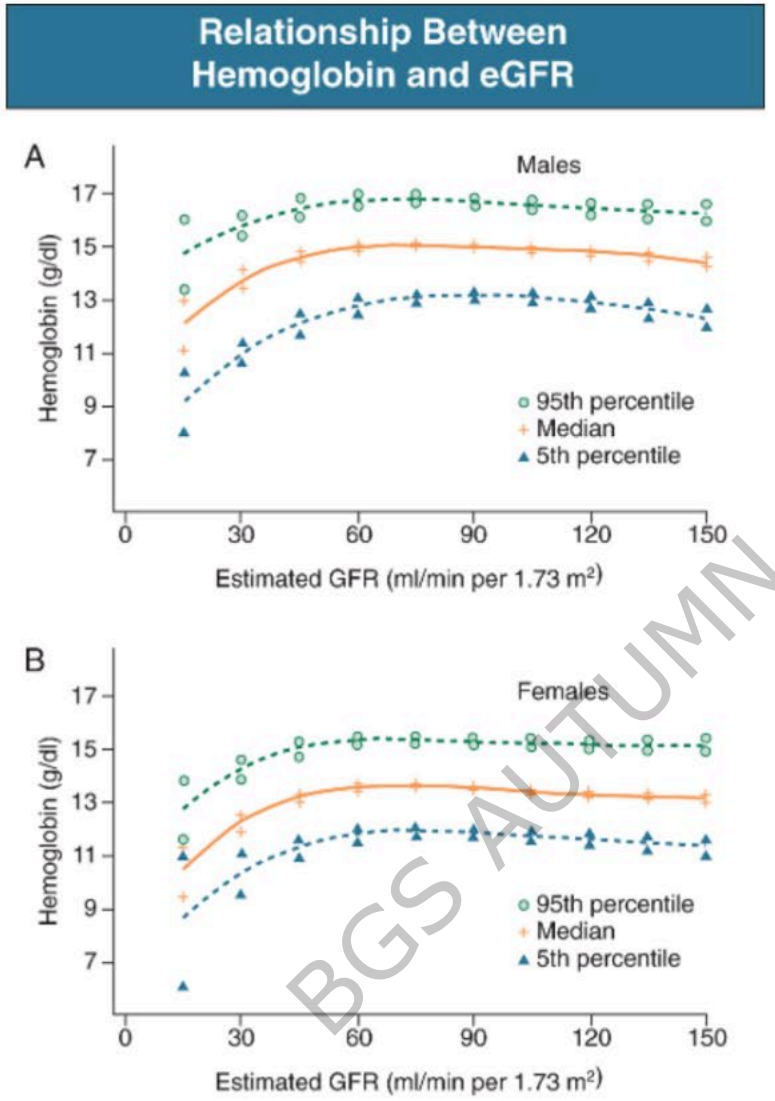


Figure 82.2: Relationship between hemoglobin (Hb) concentration and estimated glomerular filtration rate (GFR).

Data are from a cross-sectional survey of individuals randomly selected from the general U.S. population (Third National Health and Nutrition Examination Survey [NHANES III]). Results and 95% confidence interval are shown for males (A) and females (B) at each estimated GFR interval.

(From reference 11.)

Macdougall IC, Eckardt K-U in Comprehensive Clinical Nephrology 2018

Evaluation of anaemia in patients with CKD

- CKD patients should be investigated for cause and possible treatment if
  - Hb level <110glL or
  - they develop symptoms attributable to anaemia
- More likely for CKD to be cause of anaemia if GFR is <30ml/min/1.73m^2 (<45ml/min/1.73m^2 in patients with diabetes) and no other cause is identified
- Erythropoietin levels do not need to be measured to diagnose or manage anaemia related to CKD

Baseline investigations

- Standard anaemia investigations to exclude non-renal related anaemia - B12, folate
- Ferritin and transferrin saturation to determine iron status
- Further anaemia-related investigations if clinically indicated or above investigations normal

Definition of adequate iron status in CKD

- Patients should be iron replete to achieve and maintain target Hb whether receiving ESAs or not
- Definition of adequate iron status is:
  - serum ferritin of 100-500ug/L in non-HD patients
  - Either <6% hypochromic red cells, or reticulocyte Hb content >29 pg
  - TSAT > 20%

Treatment with iron therapy

- Oral iron may be sufficient to maintain iron status in CKD patients not on dialysis BUT
  - often poorly tolerated with GI side effects
  - adds to polypharmacy
  - interacts with other common drugs used in renal disease e.g. phosphate binders

Intravenous iron therapy

- Consider high dose, low frequency iv iron as treatment of choice when trying to achieve iron repletion
- Need to take into account:
  - availability of venous access
  - provision of resuscitation facilities
  - patient/caregiver burden
- Our local practice is for extra clinic visit to nurse-led clinic in main outpatients (so access to resuscitation)
  - Use Ferinject (ferric carboxymaltose) 500mg or 1g
  - Will delay to next clinic visit if extra clinic considered burden for patient/caregiver

Treatment with Erythropoiesis Stimulating Agents (ESA)

- Treatment with ESAs should be offered to patients with anaemia of CKD
  - if likely to benefit in terms of quality of life and physical function
  - to avoid blood transfusion, especially in patients eligible for transplantation
- Choice of ESA will depend on local availability.
- Target HB when using ESA is 100-120g/L
- ESA is administered subcutaneously for patients not on HD (CKD, peritoneal dialysis, transplant)
  - Mostly given weekly or fortnightly (can be longer interval with some formulations)
  - Longer intervals preferred for patients dependent on district or practice nurse administration

ESAs - practical points

- ESA administration should continue during acute illness, surgical procedures or other causes of hospitalization
- ESA and hypertension
  - accelerated hypertension is contraindication to ESA administration
  - otherwise, BP should be controlled with drug therapy or volume control and is not a reason not to give a dose
- Extreme caution should be used with ESAs if history of stroke or malignancy, particularly in those with active malignancy when cure is expected
- Intravenous iron to maintain high ferritin levels will lower ESA requirements - therefore important to monitor ferritin and TSAT

Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) (NEJM 2009)

- 4038 patients with diabetes, CKD and anaemia randomized to darbepoetin alfa to achieve Hb of 13, or to placebo with darbepoeitin rescue when Hb <9
- Primary end point death or cardiovascular event
- No difference in primary end points between the 2 groups
- Transfusion requirements halved in darbepoeitin group
- Fatal or nonfatal stroke in 101 patients in treatment group and 53 in control group
- Only modest improvement in fatigue in treatment group compared to control

Erythropoietin resistance

- Defined as failure to reach target Hb despite SC epoetin dose >300 IU/kg/week or darbepoeitin dose >1.5 ug/kg/week
- Check that the patient is iron replete - and if not, give iv iron
- Hyporesponsive patients who are iron replete should be screened clinically and by investigations for other common causes of anaemia
- Also consider whether patient is receiving their ESA (self-delivery or nurse-assisted)

ESAs and malignancy

- Post-hoc analysis of TREAT study showed that 7.4% with history of malignancy at baseline died from cancer in ESA arm compared to 0.6% in placebo arm (P=0.002)
- MHRA advises that ESAs should not be given to patients with cancer who do not fulfil criteria in authorized cancer indications, and that lowest dose of ESA is used to adequately control symptoms of anaemia
- NICE evaluation of RCTs of ESA in malignancies concluded that
  - ESAs can be used to treat anaemia in people on chemotherapy - reduces need for blood transfusions, increases Hb levels, and improves HRQOL
  - Could not assume that ESA either prolonged or shortened survival compared with treatment without an ESA

Patient or person?

George Grosz 1893–1959

Born Germany, worked Germany and USA

Grey Day
Grauer Tag
1921

Oil paint on canvas

Grosz first exhibited this work under the titled 'Council Official for Disabled Veterans' Welfare'. It was received as an explicit statement against the lack of support for veterans facing difficulties in post-war life. The suited official in the foreground is a caricatured bureaucrat with briefcase, coiffed moustache and pursed lips. He is walking away from a veteran, hunched in profile, whose welfare he is supposed to oversee. His position of power also contrasts with the faceless worker who crosses the modern city square behind.

Staatliche Museen zu Berlin, Nationalgalerie. 1954 erworben durch das Land Berlin
X68971

ESAs can be for years - Patricia

- 71 year old woman; diabetes 1998; CKD 3 2012; AKI following abdominoplasty 2014.
- Referred to haematology 2015 - anaemia. Hb 90s. Nil found apart from CKD. Started on ESA
- Stable renal function

Date	Creat	eGFR
6.9.18	175	25 ml/min
4.4.16	179	25 ml/min
3.3.15	193	23 ml/min

- On NeoRecormon 6000 Units weekly; Hb usually 110-115g/L; recent drop to 95 post knee surgery; NeoRecormon increased to x2/week

What happens when you travel? - Laura

- 84 year old Afro-Caribbean woman. Diabetes. CVA 2014 – good recovery. Blood transfusion 2015 in Grenada – PR bleeding diverticular disease
- Sep 17: seen in clinic with son. Some tiredness. No SOB – wants to go back to Grenada – would be happy to die there. Hb 97; ferritin 757; TSAT 21. Renal function:

Date	Creat	eGFRx1.2
7.9.17	369	12 ml/min
21.7.16	310	15 ml/min
4.6.15	222	22 ml/min

What happens when you travel? - Laura

- Re-appears in clinic July 18; has been in Grenada for 6 months. No problems while there. Feels well
- Blood tests:
  - Creatinine 483 umol/L; GFR 8 ml/min/1.73m^2
  - K 6.1; Bicarb 16
  - Hb 73
  - Ferritin 902; TSAT 18

GFR can decline very slowly: ESA contributing to well-being - Lyda

- Referred to renal clinic age 75 in July 13. Spanish-speaking from Columbia. Only complaint is pain in hands and back. Otherwise well
- Had been on ESA (NeoRecormon fortnightly) monitored by haematology clinic for 5 years
- Hb 101; Ferritin 85; Tsat 15 – given iv iron
- Renal function:

Date	Creat	eGFR
30.7.13	174	25 ml/min
3.7.12	153	29 ml/min
8.11.11	159	28 ml/min

GFR can decline very slowly: ESA contributing to well-being - Lyda

- Clinic – Nov 17. Well. Goes a walk every morning. Daughter planning trip to Jerusalem for her 80th birthday
- Hb 105 g/L
- Had had dose of iv iron in January 17
- Renal function:

Date	Creat	eGFR
23.11.17	416	9 ml/min
01.12.16	380	10ml/min
21.1.16	263	14 ml/min

GFR can decline very slowly: ESA contributing to well-being - Lyda

- Seen in clinic Oct 18. Now age 80. Had a fall and fractured humerus May 18. Getting stronger; doing own cooking
- Weight unchanged over 5 years – 47.4Kg 2013; 46.3 Kg now
- Eating well; denied tiredness
- Hb 107; ferritin 479; Tsat 15 - for iv iron

Date	Creat	eGFR
11.10.18	479	8 ml/min
23.11.17	416	9 ml/min
01.12.16	380	10 ml/min

Conservative care includes ESA - Jean

- 81 year old woman – diabetes with retinopathy; ex-smoker; in renal clinic since 2012
- Seen in clinic July 16. Had decided a year previously that she would have CAPD if needing dialysis. Conversation in clinic – changed her mind and wants conservative care. Aware of implications
- Hb 111; Ferritin 126. Not on ESA

Date	Creat	eGFR
14.7.16	344	11 ml/min
09.04.15	368	10 ml/min
31.7.14	316	12 ml/min

Conservative care includes ESA - Jean

- April 17 – lost 4Kg weight; diarrhoea; some cognitive deficit noticeable on conversation; still not wanting dialysis
- Hb 99; Ferritin 173; Tsat 18
- Oral iron stopped (? Contributing to diarrhoea); IV iron organised

Date	Creat	eGFR
26.01.17	377	10ml/min
29.09.16	322	12ml/min
09.07.15	300	12ml/min

Conservative care includes ESA - Jean

- **July 17**. Still losing weight. Remains independent. Conversation about prognosis – does not want dialysis; does not want resuscitation and advised to see GP for community DNAR register; palliative care referral offered but she is not keen
- Hb 95; Ferritin 272; Tsat 28
- Started on NeoRecormon 3000 units/week
- **Nov 17** – Seen in clinic. 'As good as it gets'. Husband giving weekly ESA. No concerns – gets help from husband

Conservative care includes ESA - Jean

- **22 Jan 18** – admitted with urosepsis and ischaemic R foot; Crea 545; eGFR 6 K 5.2; Hb 116
- **MfE review**- undiagnosed dementia; decompensated advanced frailty
- **26 Jan**- palliative care review
- **8 Feb**- discharged home with palliative support ; Crea 345; Hb 106
- Remained on weekly NeoRecormon during admission
- Died 2 weeks later at home

Conclusion

- Anaemia management key part of management of older patients with CKD
- There are questions
  - Long-term therapy – can we think of better ways of managing to avoid repeated hospital visits?
  - Are we treating Hb levels or the patient? Evidence of improved well-being weak
  - ESA may have been of benefit when started – but ? still of benefit as patient ages and becomes increasingly frail