Anaemia of Chronic Kidney Disease (ACKD)

Management on the move……

Kate Taylor
Anaemia Nurse Specialist
Nottingham Renal & Transplant Unit
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Aim

- To develop your knowledge and understanding of the diagnosis and treatment of ACKD

- To provide a forum within which to critically appraise it's contemporary management

Learning Outcomes

- Define ACKD
- Discuss the pathophysiology and factors contributing to ACKD
- Identify the investigations required to facilitate the diagnosis and management of ACKD
- Appraise the current therapeutic targets and treatment options
- Discuss the risks/benefits of the contemporary management of ACKD

Defining Anaemia

WHO (2011) definition of anaemia:

≤11g/dl children 6-59 months

≤11.5g/dl children 5-11yrs

≤12g/dl children 12-14yrs

≤11g/dl pregnant women

≤12g/dl non-pregnant women (15yrs and above)

≤13g/dl men (15yrs and above)

- **Is anaemia due to CKD (ACKD)?**

eGFR≥60mls/min- consider other causes

- **Consider investigating & treating if:**

Hb≤11g/dl (Hb≤10.5g/dl if < 2yrs old)

or symptoms of anaemia develop

KDIGO (2012) ACKD children

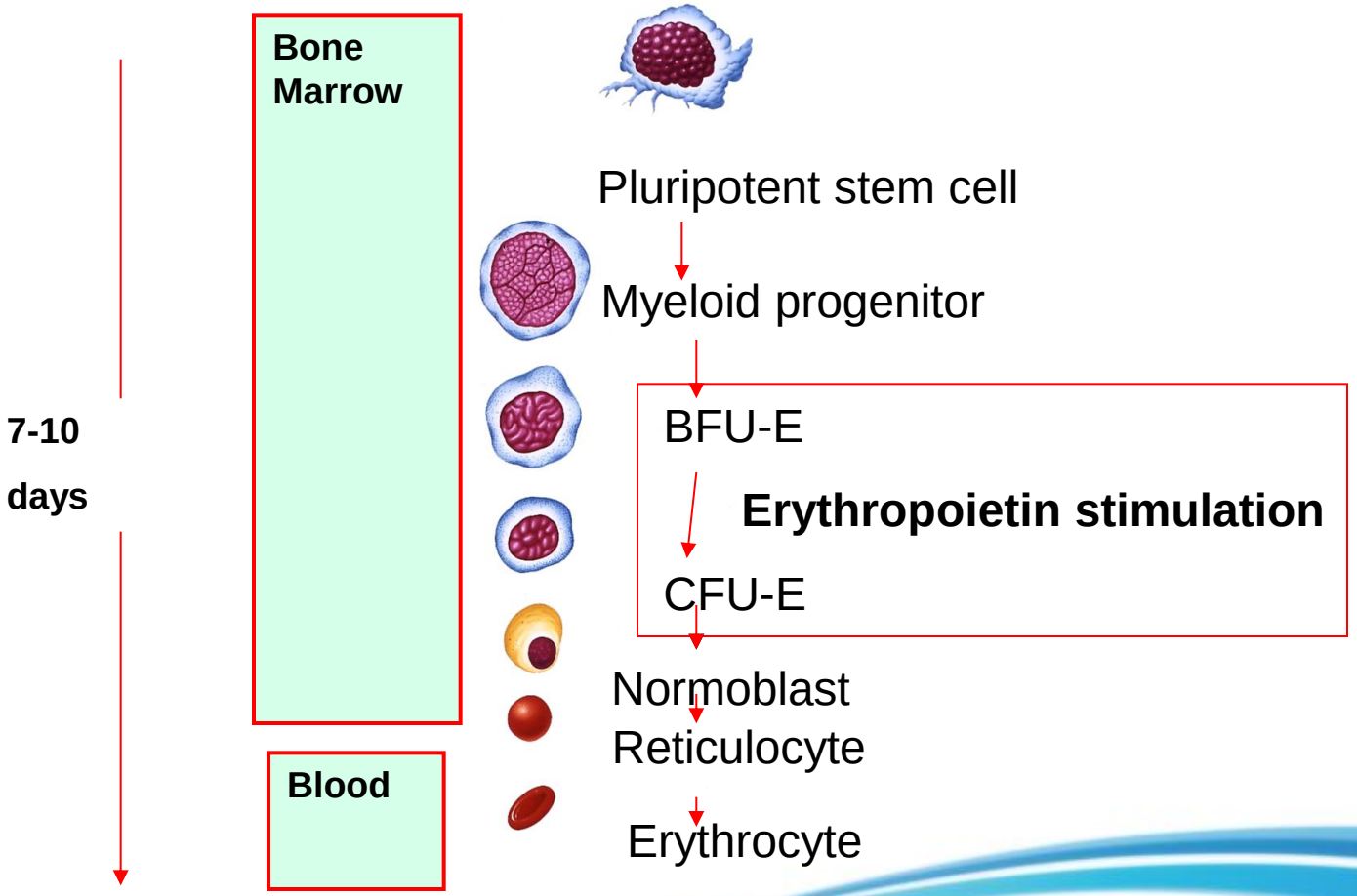
- Annual testing of Hb, regardless of stage
- Diagnosis when Hb < 5th percentile age/sex

- 0.5 to 5yrs - <11g/dl
- 5-12yrs - <11.5g/dl
- 12-15yrs - <12g/dl
- >15yrs - <13g/dl (males) and <12g/dl (females)

Common signs & symptoms

- Fatigue, weakness, reduced exercise tolerance
- Loss of appetite
- Breathlessness (exertion)
- Pallor
- Headache
- Increased sensitivity to cold
- Dizziness, fainting, tachycardia
- Irritability
- Depression
- Reduced cognition & concentration
- Nausea, abdominal discomfort
- Altered sleep pattern
- Reduced libido +/- sexual dysfunction
- Inability to work & socialise

Erythropoiesis



Factors required for erythropoiesis

- Iron

65% stored iron used to form haemoglobin

Deficiency results in hypochromic microcytic anaemia

- Vitamin B_{12} (190-800ng/l)

Needed to maintain RBCs, normal cell division (megaloblastic anaemia)

Dietary lack of Vit B_{12} (pernicious anaemia)

- Folic acid (3.9-14mcg/l)

Deficiency limits cell division & erythropoiesis (megaloblastic anaemia)

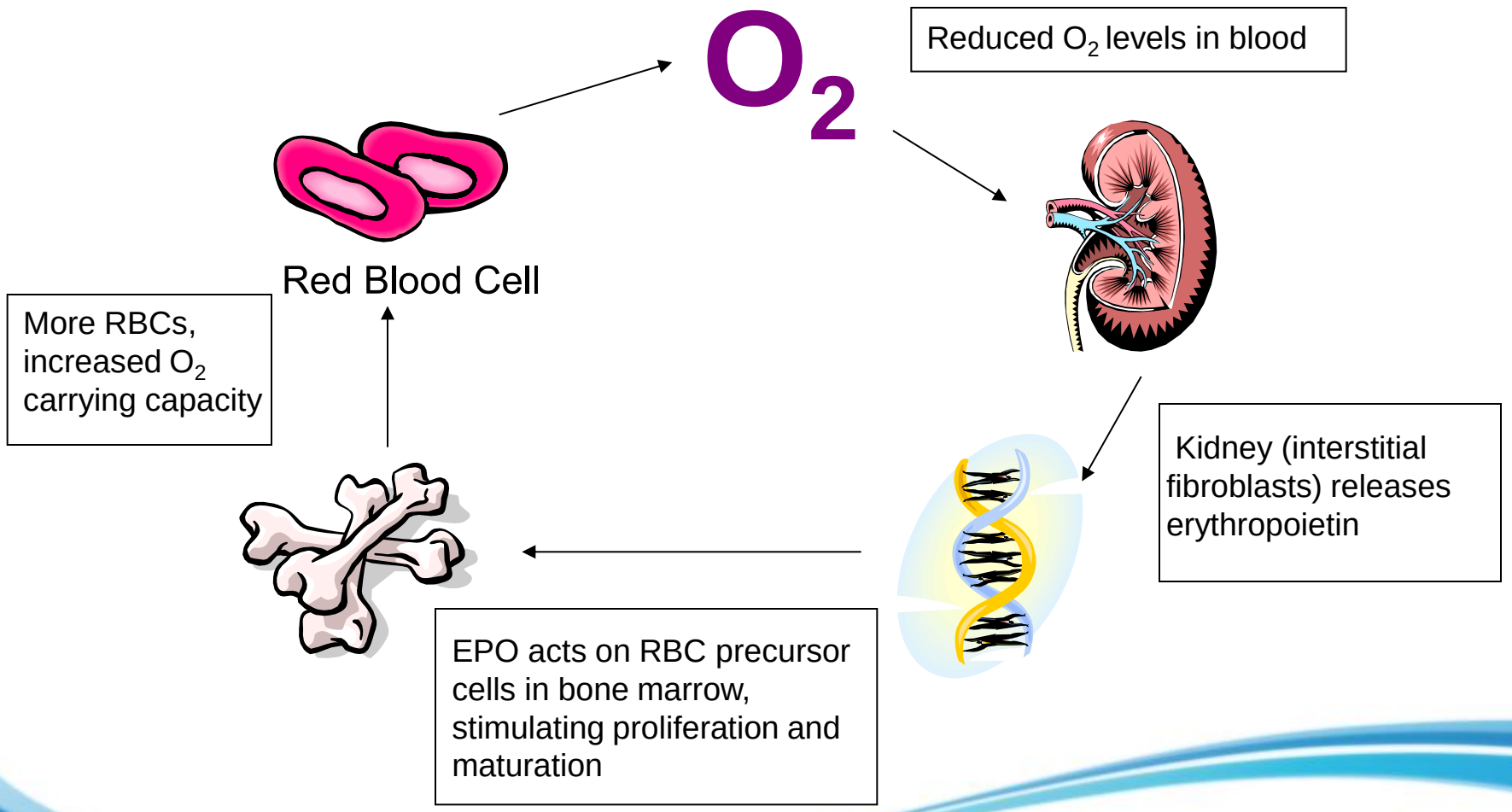
- Other factors affecting normal Hb levels:

Age, gender, ethnicity, smoking

Control of Erythropoiesis

- Mainly controlled by erythropoietin, secreted by the kidney (90%) and liver(10%, *primary source in foetus*)
- Secreted in response to a fall in oxygen levels detected by the by interstitial fibroblast cells in the kidney
- Renal disease leads to a reduction in the production of erythropoietin
- Hepcidin controls iron absorption (GI) and release from reticuloendothelial system
- CKD-chronic inflammation/cytokines
- Increased hepcidin, reduced absorption/release of iron

Erythropoiesis (EPO) Stimulation

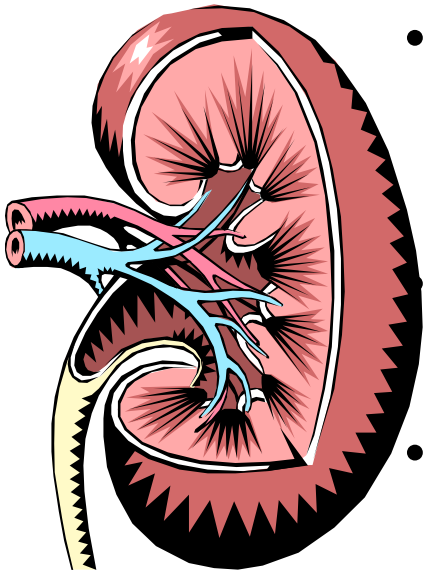


Reference: Adapted from Erythropoietins and erythropoiesis, ed Molineux G, Foote MA, Elliott SG. Pub Birkhauser-Verlag 2003 p17

Causes of Anaemia

1) Dietary deficiencies of iron, vitamin B_{12}, or folic acid
2) **Haemolytic anaemia – HUS**
3) Haemoglobinopathies- thalassaemia, sickle cell
4) Congenital PRCA- Diamond Blackfan, Fanconi
5) Acquired PRCA- infection, drugs, autoimmune
6) **Transient erythroblastopenia (TEC)- viral illness**
7) Drugs- cytotoxic, immunosuppressive, ACE1
8) Anaemia of chronic disease - associated with chronic inflammation or infection e.g. rheumatoid arthritis
9) **ACKD** – principally a result of the diseased kidney (CKD stages 3b-5; GFR < 45mls/min) not producing sufficient erythropoietin

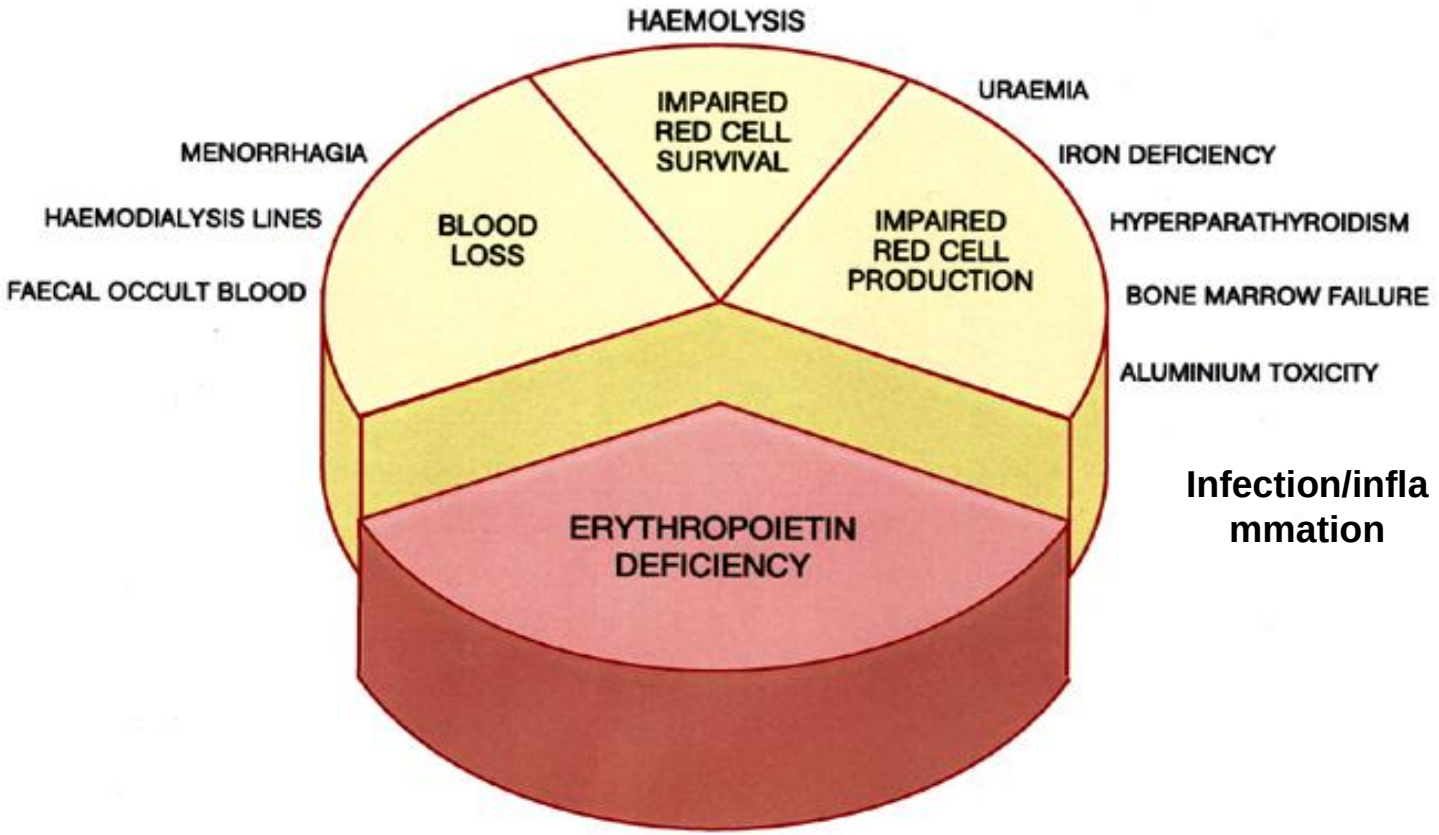
ACKD



- Normochromic, normocytic
- Lower levels of kidney function associated with lower Hb levels (44% pts CKD 4/5)
- Increased prevalence in stage 3B CKD onwards (eGFR ≤ 44mls/min); generally when GFR < 30mls/min

  1:5 patients with diabetes and stage 3 CKD has anaemia
- Severity worsens with more advanced stages of CKD & those patients with proteinuria
- NHANES (2002) 1% - GFR 60mls/min; 9% GFR 30mls/min; 33-67% GFR 15mls/min
- ACKD very common in children at onset of dialysis

Factors Contributing to ACKD



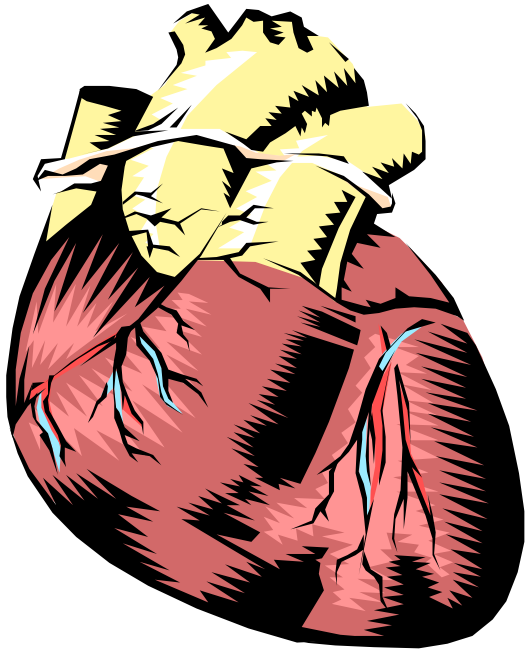
Consequences of Anaemia

- Reduced O_2 utilisation
- Cardiovascular
  - ↑ stroke volume
  - ↑ heart rate
  - ↑ cardiac output
  - ↓ peripheral vascular resistance
  - left ventricular hypertrophy/dilatation
- Increased progression of CKD
- Reduced immune responsiveness

Consequences of ACKD

- cardiovascular complications are the primary cause of mortality in patients with CKD

- anaemia is an important independent risk factor for the development & progression of LVH & HF and of adverse cardiovascular outcomes including mortality



Benefits of Anaemia Management

Reduction in:

- cardiac output
- angina
- LVH
- Depression
- hospitalisations/LOS
- transfusions

Benefits of Anaemia Management

Nottingham University Hospitals NHS
NHS Trust

Improvement in:

- quality of life
- exercise capacity
- cognitive function
- social activity participation
- sleep pattern
- sexual function
- appetite
- school attendance/capacity for work
- depression & fatigue

We are here for you

Benefits (QoL) of Treating ACKD

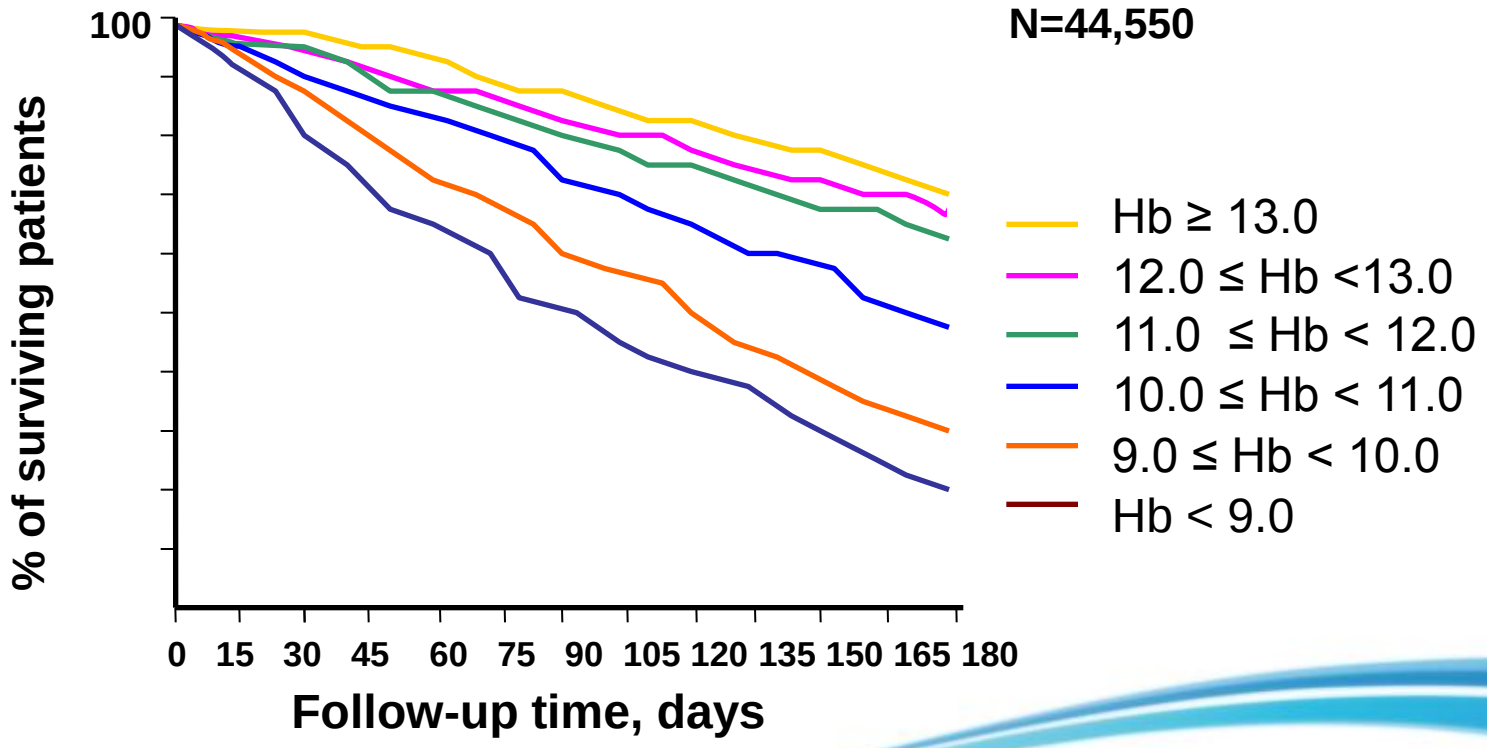
Well established QoL benefits of Hb >11g/dL

Outcome	RCTs	n	Evidence	Quality of evidence
Benefits in dialysis patients				
QoL generic	4	466	Benefit	Moderately high
QoL kidney-specific instrument	4	1,113	Likely some benefit	Moderately high
Benefits in non-dialysis patients				
QoL	2	238	Likely some benefit	Relatively low

NKF-K/DOQI *AJKD* 2006;47(5 Suppl3):S11-145

Benefits (Survival) of Treating ACKD.....

Survival in Stage 5 CKD increases with > Hb Levels



Ofsthun et al. *Kidney Int* 2003; 63:1908-14

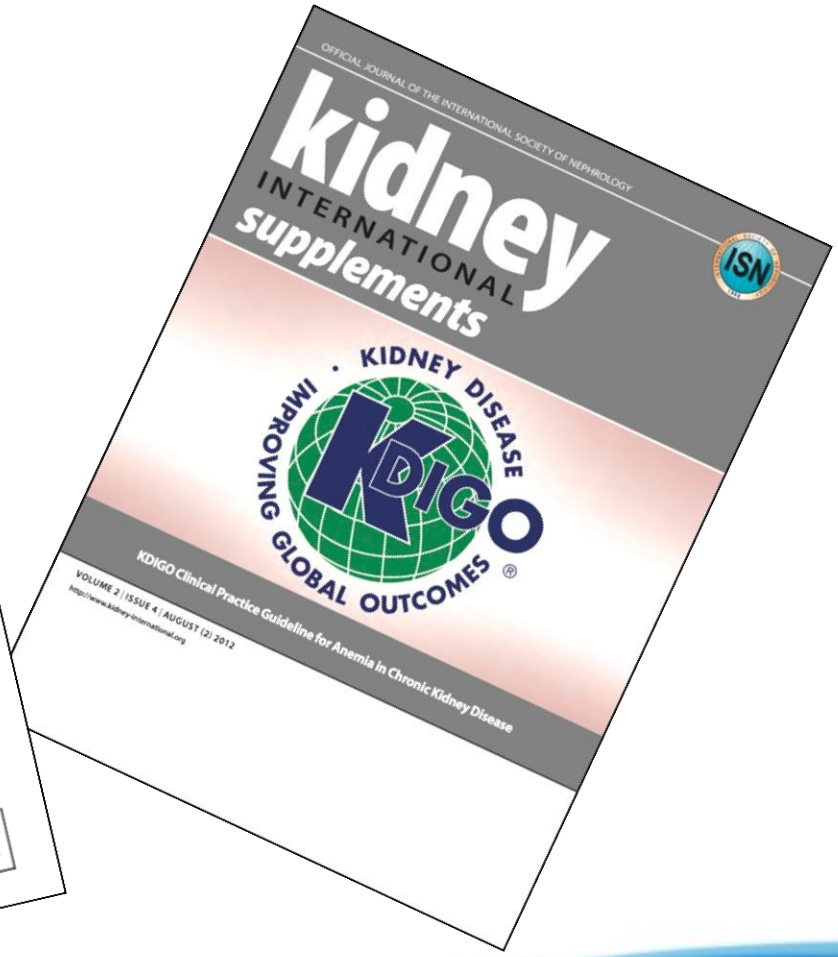
Treating ACKD: What Hb Target to Aim For?

Treatment targets ACKD

Renal Association Standards (2002)	European Best Practice Guidelines (2004)	Kidney/Dialysis Outcomes Quality Initiative (2006)	NICE Guidelines (2006)	Renal Association Guidelines (2007)	NICE Guidelines (2011) KDIGO Guidelines (2012)
Hb ≥10g/dl	**Hb** >11g/dl	**Hb** ≥11g/dl	**Hb** 10.5 – 12.5 g/dl		**Hb** 10.0 – 12.0g/dl 9.5 -11.5 (< 2yrs)

Study	N (pts)	Hb target (g/dl)Death, CV event	ESA	GFR range (ml/min)	Primary endpoint	P value
CHOIR (2006)	603	13.5 v 11.3	Epoetin Alfa	15-50	Death, MI, CHF, CVA	0.03 (lower Hb)
CREATE (2006)	1432	13-15 v 10.5-11.5	Epoetin Beta	15-35	Composite of 8 CV events, CKD progression	NS CV events 0.03 CKD progression
TREAT (2009)	4038	13 v 9	Darbepoetin Alfa	20-60	Death, CV event , ESRD	NS

Current Guidelines



Investigating ACKD

- Haemoglobin
- eGFR
- Red cell indices (MCV/MCH/MCHC)
- Vit B_{12}
- Folate
- Ferritin
- Transferrin Saturation (%)
- C-reactive protein (CRP)
- Nutritional status
- Assessment of occult blood loss

Management of ACKD……

- Correction of haematinic deficiency

(Vit B_{12}, folate, **iron**)

- **Erythropoiesis-stimulating agents**
- Blood transfusions
- Nutrition
- Dialysis Adequacy
- Treatment of additional causes

(bleeding, infection)

Teamwork – the key to success

Iron deficiency

- Decreased availability of iron
  - Anorexia
  - Reduced dietary intake of iron
  - Malabsorption
  - Phosphate binders (Ca^{2+}, Mg^{2+}), PPIs
  - CKD (chronic inflammation, cytokines)
  - Hepcidin (reduced absorption & release of stored iron)

- Increased iron losses
  - G.I tract
  - Dialysis (extracorporeal blood losses)
  - Haemolysis (blood pump trauma, contamination, overheating, autoimmune)
  - Drugs (penicillin, cephalosporins, methyldopa, quinidine)
  - Menorrhagia
  - Blood loss (platelet dysfunction)

ACKD-Iron Deficiency

- **Hb<11g/dl & serum ferritin <100µg/l**
- Common in stages 3B, 4 & 5

  absolute (ferritin <100µg/l)

  functional (ferritin >100µg/l, Tsat% <20%)
- Serum ferritin
  - **Target: >200µg/l**
  - Review iron dosage at 500µg/l
- Transferrin saturation (TSAT%)
  - **Target: >20%**

  (unless ferritin >800µg/l)

Iron Treatment

- Oral iron:
  - Simple, cheap, poor absorption rare in children
  - GI side effects
  - elemental iron; 3-6mg/kg bd/tds (max 200mg)
- IV iron:
  - Not licensed in children (Ferinject- < 14yrs)
  - Intolerance/non-concordance/ineffectiveness of oral iron
  - Rapidly replenishes iron stores (ferric hydroxide)
  - Anaphylaxis risk
  - (MHRA, 2013)

- **20mg/ml; max 7mg/kg single dose**
- **max 3mg/kg (200mg) x3/week**
- ***slow injection 200mg*** (1ml/min)
- Iron deficit calculated

- **50mg/ml; max 20mg/kg infusion**
  15mg/kg injection
- ***slow injection 500mg*** (5mins)
- ***slow injection 1000mg*** (15mins)

Erythropoiesis-stimulating agents

- Erythropoietin – glycoprotein (amino acids and sugars)
- Erythropoietic agents (s/c, IV)
  - Epoetin alfa (Eprex-HDpts- x3/week, Tx)
  - Epoetin beta (NeoRecormon)
  - Darbepoetin alfa (Aranesp-fortnightly/monthly, pre-Dx, PD, Tx)
  - Methoxy polyethylene glycol-epoetin beta (Mircera-pre-monthly)
  - BIOSIMILARS
  - HIF-PHI (phase 3)

History of ESA therapy

- 1957 kidney identified as principle source of erythropoietin
- 1976 Human EPO isolated
- 1983 EPO gene cloned
- 1986 First clinical report of EPO use in dialysis patients
- 1990 Recombinant human EPO licensed for the treatment of renal anaemia in Europe
- 1996 First clinical study of darbepoetin alfa
- 2001 Darbepoetin alfa licensed
- 2007 Mircera licensed
- BIOSIMILARS

They all work !

They have all transformed the lives of CKD patients !

Monitoring

- Hb (optimum response, rise of 1g/dl/ month in correction phase)
- Aim to keep rate 1-2g/dl
- Bloods 2-4/52 (induction),1-3 mths (maintenance)
- Target Hb 10.0 – 12.0g/dL (9.5-11.5 if <2yrs)
- Adjust dose >11.5g/dl or < 10.5g/d l(>1 or <10 if <2yrs)
- Individualised therapy
- Blood pressure
- Iron stores
- Side effects
- **ESA resistance**

Optimising Hb levels

- Correcting Hb to ‘normal’ not recommended
- Patient-centred care- preferences, symptoms & co-morbidities
- Patient education
- Coordinating care
- **Aspirational range 10-12g/dl**

- **Consider accepting lower Hb levels if:**

-high doses of ESAs are required

-range not achieved despite escalating ESA doses

- **Consider accepting higher levels if:**

-they develop with iron therapy alone

-they develop with low doses of ESA

-patient may benefit (active lifestyle, demanding job)

-absolute risk of cerebrovascular disease low

Factors inhibiting ESA response

- Iron deficiency
- Infection/inflammation
- Blood loss
- Hyperparathyroidism
- Malnutrition (iron)
- Concordance/administration
- Haematological disorders/malignancy
- ACE inhibitors
- Aluminium toxicity

ESA resistance:
≥ 300u/kg/wk s/c epoetin
≥ 450/kg/wk IV epoetin
≥1.5µg/kg/wk darpbepoetin

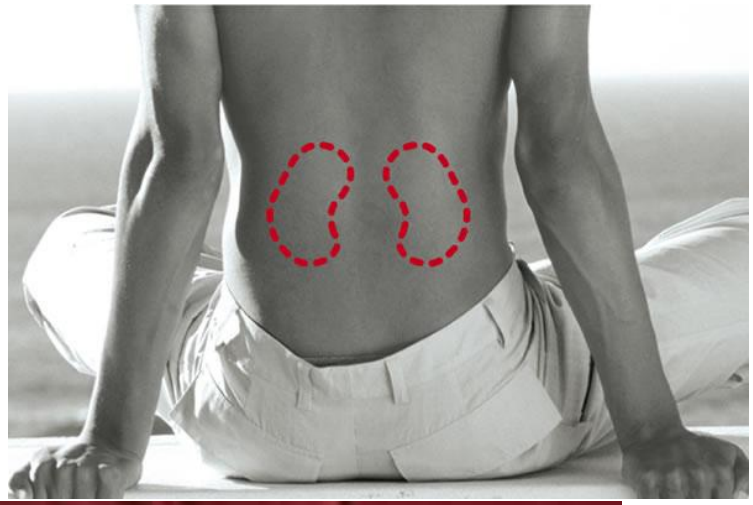
CKD Anaemia Management

- **Average iron dose**

1000mg iv Ferinject/year

- **Average ESA dose**

40µgx1/month sc Aranesp



- 0.45µg/kg/week (> 11yrs)
- 0.75µ/kg/fortnight (> 11yrs)
- 1.5µg/kg/month (adults only)
- High dose >100u/kg/week
- Pre- clinic review/60 day quark
- RCCT needed to assess Hb level as an outcome in pre-dialysis patients treated to Fe < 200 v 300-500

PD Anaemia Management

- s/c ESA
- high >125u/kg/wk
- **Oral**/IV Iron
- Monthly review
- Adequacy
- Peritonitis
- Nutrition
- > x2 likely Hb <11g/dl

HD/HHD Anaemia Management

- **Average iron dose**

50-100mg iv iron sucrose/week

- **Average ESA dose**

8300iu (3000iu x3/week) IV Eprex

- <50kg 4mg/kg/month
- >50kg 200mg/month
- starting dose 100-200u/kg/week
- high >175u/kg(max 500u/kg/wk)
- Monthly review
- PIVOTAL
- Access/Adequacy/Albuminaemia
- B12/folate deficiency

Tx (PTA) Anaemia Management

- s/c ESA
- Oral/IV Iron
- 3/12 post Tx
- Infection
- Immunosuppression
- GI blood loss
- Graft function/GFR

ACKD Summary

- Common complication of CKD
- Develops/progresses in line with GFR
- Associated with increased mortality & reduced QoL
- Investigate & treat if Hb<11.0g (<10.5 < 2yrs)/dl/pt symptomatic
- Consider other causes
- Iron replacement & ESA therapy main treatment
- European Commission regulations for IV Iron administration
- Nice (2011) Hb 10.0-12.0g/dl (10.5- 11.5 < 2yrs)
- Benefits/Risks
- Individualised management

Further Information

- Kate Taylor

kate.taylor@nuh.nhs.uk

0115 9691169 ext:55171

- Anaemianurse.org-ANSA
- NICE (2011) Anaemia Management in people with chronic kidney disease
- KDIGO (2012) Clinical Practice Guidelines for Anaemia in Chronic Kidney Disease