Anaemia of Chronic Kidney Disease (ACKD)

Management on the move........

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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 < 5\textsuperscript{th} 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

Pluripotent stem cell
Myeloid progenitor
BFU-E
CFU-E
Erythrophoietin stimulation
Normoblast
Reticulocyte
Erythrocyte

Bone Marrow

Blood

7-10 days
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 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

Reduced $O_2$ levels in blood

Kidney (interstitial fibroblasts) releases erythropoietin

$O_2$

Red Blood Cell

More RBCs, increased $O_2$ carrying capacity

EPO acts on RBC precursor cells in bone marrow, stimulating proliferation and maturation

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

Infection/inflammation
Consequences of Anaemia

• Reduced $O_2$ utilisation

• Cardiovascular
  – $\uparrow$ stroke volume
  – $\uparrow$ heart rate
  – $\uparrow$ cardiac output
  – $\downarrow$ 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

Improvement in:

- quality of life
- exercise capacity
- cognitive function
- social activity participation
- sleep pattern
- sexual function
- appetite
- school attendance/capacity for work
- depression & fatigue
### Benefits (QoL) of Treating ACKD

**Well established QoL benefits of Hb >11g/dL**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RCTs</th>
<th>n</th>
<th>Evidence</th>
<th>Quality of evidence</th>
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<td><strong>Benefits in dialysis patients</strong></td>
<td></td>
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<tr>
<td>QoL generic</td>
<td>4</td>
<td>466</td>
<td>Benefit</td>
<td>Moderately high</td>
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<tr>
<td>QoL kidney-specific instrument</td>
<td>4</td>
<td>1,113</td>
<td>Likely some benefit</td>
<td>Moderately high</td>
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<td><strong>Benefits in non-dialysis patients</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>QoL</td>
<td>2</td>
<td>238</td>
<td>Likely some benefit</td>
<td>Relatively low</td>
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</table>

Benefits (Survival) of Treating ACKD

Survival in Stage 5 CKD increases with > Hb Levels

Treating ACKD: What Hb Target to Aim For?

Treatment targets
ACKD

- Renal Association Standards (2002): Hb ≥10g/dl
- European Best Practice Guidelines (2004): Hb >11g/dl
- NICE Guidelines (2006): Hb 10.5 – 12.5 g/dl
- Renal Association Guidelines (2007): Hb 10.5 – 12.5 g/dl
- NICE Guidelines (2011)
  - KDIGO Guidelines (2012): Hb 10.0 – 12.0g/dl
  - 9.5 -11.5 (< 2yrs)
<table>
<thead>
<tr>
<th>Study</th>
<th>N (pts)</th>
<th>Hb target (g/dl)Death, CV event</th>
<th>ESA</th>
<th>GFR range (ml/min)</th>
<th>Primary endpoint</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>CHOIR</td>
<td>603</td>
<td>13.5 v 11.3</td>
<td>Epoetin Alfa</td>
<td>15-50</td>
<td>Death, MI, CHF, CVA</td>
<td>0.03 (lower Hb)</td>
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<td>(2006)</td>
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<tr>
<td>CREATE</td>
<td>1432</td>
<td>13-15 v 10.5-11.5</td>
<td>Epoetin Beta</td>
<td>15-35</td>
<td>Composite of 8 CV events, CKD progression</td>
<td>NS</td>
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<tr>
<td>(2006)</td>
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<td></td>
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<td>0.03 CV events</td>
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<tr>
<td>TREAT</td>
<td>4038</td>
<td>13 v 9</td>
<td>Darbepoetin Alfa</td>
<td>20-60</td>
<td>Death, CV event, ESRD</td>
<td>NS</td>
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<tr>
<td>(2009)</td>
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</table>
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

Nurses

Pharmacists

GP’s

Patient

Dietitians

Carers

Hospital Doctors

Delivery company

We are here for you
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 darbepoeitin alfa
- **2001** Darbepoeitin 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/dl (>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 darbepoetin
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

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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