ANEMIA IN CKD

Pathophysiology & Evaluation

Prof. Ashraf MA Bakr

Vice president for Students Affairs, Mansoura University
Prof of pediatrics, Mansoura Faculty of Medicine
Consultant, Pediatric Nephrology Unit, Mansoura University Children’s Hospital
Mansoura, Egypt
Anemia is an inevitable yet treatable morbidity in patients with CKD.
Untreated anemia is associated with

**Quality of life**
- Fatigue
- Depression
- Sleep disturbances
- Exercise intolerance
- Impaired cognitive function

**Mortality in dialysis patients**
**Decline in GFR in pre-dialysis patients**
**Left ventricular hypertrophy**


Prevalence of complications according to CKD stage

- CKD 4+5: Hypertension, Anemia, Acidosis, Salt wasting, Hyperkalemia, Growth failure
- CKD 3: Hypertension, Anemia, Acidosis, Salt wasting, Hyperkalemia, Growth failure
- CKD 2: Hypertension, Anemia, Acidosis, Salt wasting, Hyperkalemia, Growth failure
- CKD 1: Hypertension, Anemia, Acidosis, Salt wasting, Hyperkalemia, Growth failure
The Magnitude of the problem increases with severity of illness

Non anemia

Anemia

Stage 5: 93
Stage 4: 87
Stage 3: 73
Stage 1: 31

Atkinson MA, et al., Pediatr Nephrol. 2010
DEFINITION

- Hemoglobin value less than 11 g/dl in pre-pubertal patients with CKD (age and gender independent definition).

- Recent revision states that anemia present in the pediatric CKD patient when hemoglobin is less than the 5th percentile of the normal (adjusted for age and gender).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Hemoglobin (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5-5</td>
<td>&lt;11.0</td>
</tr>
<tr>
<td>5-12</td>
<td>&lt;11.5</td>
</tr>
<tr>
<td>12-15</td>
<td>&lt;12.0</td>
</tr>
<tr>
<td>&gt;15 Male</td>
<td>&lt;13.0</td>
</tr>
<tr>
<td>&gt;15 Female</td>
<td>12&gt;0</td>
</tr>
</tbody>
</table>

Anemia in CKD
Regulation of Erythropoietin Synthesis

- Decrease in oxygen delivery to the kidneys
- Peri-tubular interstitial cells detect low oxygen levels in the blood
- Peri-tubular interstitial cells secrete erythropoietin (EPO) into the blood
Regulation of erythropoietin synthesis
Erythropoietin and CKD

1- Erythropoietin deficiency
Erythropoietin and CKD

2- Erythropoietin dysregulation

↓ consumption  ↑ oxygen pressure
Back to basics 1

- Erythropoietin
- Iron dependence
- Iron
- EPO dependence

Pluripotent Stem Cell → Burst-Forming Unit-Erythroid (BFU-E) Cells 
| Colony-Forming Unit-Erythroid (CFU-E) Cells | Proerythroblasts |
| Erythroblasts | Reticulocytes | RBCs

- About 3-4 Days
- About 10-13 Days
- About 21 Days
- About 1-2 Days
Back to basics 3

Iron homeostasis in health
Iron homeostasis in health
Iron homeostasis in CKD

1- Absolute iron deficiency

Absorption

Intake

Loss
Iron homeostasis in CKD

High hepcidin conditions:
Ferroportin degraded, iron accumulates intracellularly

Other mechanisms of anemia in CKD

1- *Uremic toxins*

RELATION BETWEEN INADEQUATE DIALYSIS AND EPO HYPORESPONSIVENESS

Klarenbach et al 2002

39% EPO requirements

Nocturnal dialysis
Other mechanisms of anemia in CKD

2- Hyperparathyroidism
Other mechanisms of anemia in CKD

3- Nutritional deficiencies

Quoted: Anemia in Chronic Kidney Disease. Pediatr Nephrol, 2018
Other mechanisms of anemia in CKD

4- Medications

- ACE inhibitors
- Nonadherence with anemia therapies
- Drug toxicity
- Pure red-cell aplasia associated with ESA

Quoted: Anemia in Chronic Kidney Disease. Pediatr Nephrol, 2018
Pathophysiology of anemia in CKD

Fe

Erythropoietin

Deficiency

Dysregulation
EVALUATION OF ANEMIA IN CKD
### Evaluation of anemia in CKD

#### Frequency

<table>
<thead>
<tr>
<th>Patients WITHOUT anemia when it is clinically advised AND</th>
<th>CKD 3</th>
<th>At least annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD 4 and CKD 5ND</td>
<td></td>
<td>At least once every 6 months</td>
</tr>
<tr>
<td>CKD 5HD and CKD 5PD</td>
<td></td>
<td>At least once every 3 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients WITH anemia &amp; WITHOUT treatment with ESA when it is clinically advised AND</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD 3-5ND and CKD 5PD</td>
</tr>
<tr>
<td>CKD 5HD</td>
</tr>
</tbody>
</table>

2B
In peritoneal dialysis

**NOT critical**

In hemodialysis

**Prior to mid-week hemodialysis session**

- Pre-dialysis sample underestimates the euvolemic Hb level
- Post- Pre-dialysis sample overestimates the euvolemic Hb level
1- Complete blood picture.

2- Measurement of iron status.
Evaluation of anemia in CKD

**Base line investigations**

- Complete blood picture
  - Full blood count (FBC)
    - Hb concentration
    - Red blood cell indices: MCH, MCV, MCHC
  - White blood cell count and differential count
  - Platelet count
  - Absolute reticulocyte count to assess bone marrow responsiveness (if indicated).

Anemia of CKD is normocytic normochromic

- Microcytosis: IDA or hemoglobinopathies
- Macrocytosis: Folate or vitamin B12 deficiency
- Hemolysis: Macrocetosis, ↑Ret. Count & +ve coombs’ test
Evaluation of anemia in CKD

Base line investigations

2- Measurement of iron status
A- Traditional iron measures

- Serum iron
- TIBC
- Serum ferritin
- TSAT
- MCV

Limitations

- Biological and analytical variability
- Inflammation
  - ↑ serum ferritin
  - ↓ TIBC → ↑ TSAT

Evaluation of anemia in CKD

Base line investigations

2- Measurement of iron status
B- Other iron measures

- %HRC
  - The percentage of circulating hypochromic RBCs (Hb<250 g/L)

- CHr
  - Reticulocyte hemoglobin content

- STRs
  - Soluble transferrin receptors

- ZPP
  - Zinc protoporphyrin

Limitations
- Lack of widespread availability.
- Cost
- Technical difficulties

Pediatric reference ranges for HRC & CHr have been established
Evaluation of anemia in CKD

Baseline investigations

2- Measurement of iron status

Wesley Hayes. Ped Neph, 2018
Evaluation of anemia in CKD

**Base line investigations**

Definition of iron depletion

<table>
<thead>
<tr>
<th>Marker</th>
<th>Prevalence&lt;sub&gt;a&lt;/sub&gt;</th>
<th>Sensitivity&lt;sub&gt;b&lt;/sub&gt;</th>
<th>Specificity&lt;sub&gt;b&lt;/sub&gt;</th>
<th>PPV&lt;sup&gt;c&lt;/sup&gt;</th>
<th>NPV&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin &lt; 200 ng/mL</td>
<td>44%</td>
<td>77%</td>
<td>38%</td>
<td>49%</td>
<td>68%</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>77%</td>
<td>38%</td>
<td>24%</td>
<td>87%</td>
</tr>
<tr>
<td>TSAT &lt; 20%</td>
<td>44%</td>
<td>61%</td>
<td>79%</td>
<td>70%</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>61%</td>
<td>79%</td>
<td>42%</td>
<td>89%</td>
</tr>
<tr>
<td>TSAT &lt; 20% and serum ferritin &lt; 100 ng/mL</td>
<td>44%</td>
<td>33%</td>
<td>98%</td>
<td>93%</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>33%</td>
<td>98%</td>
<td>80%</td>
<td>85%</td>
</tr>
<tr>
<td>%HRC &gt; 6%</td>
<td>44%</td>
<td>82%</td>
<td>95%</td>
<td>93%</td>
<td>87%</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>82%</td>
<td>95%</td>
<td>80%</td>
<td>95%</td>
</tr>
<tr>
<td>CHr &lt; 29 pg</td>
<td>44%</td>
<td>57%</td>
<td>93%</td>
<td>86%</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>57%</td>
<td>93%</td>
<td>67%</td>
<td>90%</td>
</tr>
</tbody>
</table>
International guide lines on iron assessment in CKD

2004

%HRC, TSAT, or CHr

2006 & 2007

Non-dialysis & PD: Serum ferritin & TSAT.
HD: Either CHr or TSAT + serum ferritin

2012

Ferritin and TSAT

2015

%HRC if processing of the blood sample is available within 6 h, or CHr if %HRC is not available
NOT routinely be considered for the diagnosis or management of anemia for patients with CKD.
Evaluation of anemia in CKD
Assessment of inflammation

- Plasma/serum C-reactive protein (CRP).
- Serum hepcidin. (Research tool).
Evaluation of anemia in CKD

Other investigations

- Serum B12 and serum folate concentrations
- Tests for hemolysis (plasma/serum levels of haptoglobin, lactate dehydrogenase, bilirubin, Coombs’ test)
- Tests for parasites
- Hb electrophoresis
The primary causes of the anemia in CKD are impaired erythropoietin production and hepcidin-mediated iron-restricted erythropoiesis.

Careful assessment of iron availability for erythropoiesis is important for children with CKD.

Traditional measures of iron, serum ferritin and TSAT, are not fit for this purpose.

Novel measures such as %HRC and CHr offer superior assessment.

No single parameter offers comprehensive assessment of body iron stores and bioavailable iron for erythropoiesis.
Quiz
MCQ

1- UK NICE guidance for assessment and management of anemia in people with CKD recommends measurement of iron status with:

A. CHr and TSAT
B. Ferritin, TSAT, and free serum iron
C. %HRC, or CHr/Ret-He if analysis of %HRC is not available within 6 h
D. None of the above
MCQ

2- Hepcidin mediates:

A. Endocytosis of ferroportin
B. Increased absorption of iron from the duodenum
C. Reduced release of iron from macrophages to plasma
D. A and C
MCQ

3- Iron-restricted erythropoiesis includes:

A. Absolute iron deficiency
B. Depletion of iron stores by ESA-stimulated bone marrow
C. Impaired iron trafficking with inflammation
D. All of the above
Thank you