Management of Renal Anemia

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Disclosure:
I have no relevant financial relationship to disclose for this presentation within the period of 36 months.
Anemia is highly prevalent in patients with chronic kidney disease (CKD) and commonly start at early stage of CKD.

Anemia complicating CKD not only impairs patients QOL, but also play a role as an independent risk factor for adverse cardiovascular outcomes so that associated with significant morbidity and mortality.

The availability of erythropoiesis-stimulating agent (ESA) has greatly changed the management of anemia in CKD patients.

Management of anemia in CKD aims to achieve hemoglobin target level, avoid blood transfusion with optimization of ESA therapy.
Outline of Presentation

- Prevalence and Impact of Anemia in CKD
- Pathophysiology of Anemia in CKD
- Evaluation of Anemia in CKD
- Treatment
  - Iron Therapy
  - ESA Therapy
Prevalence and Impact of Anemia in CKD

Pathophysiology of Anemia in CKD

Evaluation of Anemia in CKD

Treatment
  - Iron Therapy
  - ESA Therapy
Definition of Anemia in CKD

KDIGO Clinical Practice Guideline
For Anemia 2012

Men
• Hemoglobin < 13 g/dL

Women
• Hemoglobin < 12 g/dL

Based on this criteria, nearly 90% of patients with GFR < 30 mL/min have anemia
Increasing Prevalence of Anemia with Declining Kidney Function

Patients with anaemia (%)

The 3rd National Health and Nutrition Survey

GFR (mL/min per 1.73 m²)

Multi national cross-sectional survey in Europe. Concomitant conditions CVD, metabolic, mental health disorder experienced by both anemic and non-anemic ND-CKD. But such condition significantly increasing in anemic population.
# RISK FACTORS IN THE INITIATION AND PROGRESSION OF CKD

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Definition</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptibility</td>
<td>Increase susceptibility to kidney damage</td>
<td>Older age, family history of kidney disease, reduction in kidney mass, US racial or ethnic minority status, low income or education</td>
</tr>
<tr>
<td>factors</td>
<td></td>
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</tr>
<tr>
<td>Initiation</td>
<td>Directly initiate kidney damage</td>
<td>Diabetes, hypertension, autoimmune diseases, systemic and urinary tract infections, urinary stones, lower urinary tract obstruction, drug toxicity</td>
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<tr>
<td>factors</td>
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<tr>
<td>Progression</td>
<td><strong>Cause worsening kidney damage and faster decline in kidney function</strong></td>
<td>Higher level of proteinuria, higher blood pressure, poor glycaemic control in diabetes, smoking, anaemia?</td>
</tr>
<tr>
<td>factors</td>
<td>after initiation of kidney damage</td>
<td></td>
</tr>
<tr>
<td>End-stage</td>
<td><strong>Increase morbidity and mortality</strong> in kidney failure</td>
<td>Lower dialysis dose, temporary vascular access, anaemia, low serum albumin, late referral</td>
</tr>
<tr>
<td>factors</td>
<td></td>
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</tbody>
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Adapted from Levey et al Ann Intern Med 2003
LVH PREVALENCE AND RENAL FUNCTION

The most important consequences of anemia is LVH development.

Levin et al AJKD 1999
Prognosis Declines with CKD Progression
CKD patients not on dialysis

Hospitalisation

CV events

Death

Increasing event rate

Rates per 100 person-years

GFR (mL/min/1.73m²)

260
45–59
30–44
15–29
<15

260
45–59
30–44
15–29
<15

260
45–59
30–44
15–29
<15

Decreasing GFR

US renal registry 1996-2010
Prevalence and Effects of Anemia in CKD

Pathophysiology of Anemia in CKD

Evaluation of Anemia in CKD

Treatment
  - Iron Therapy
  - ESA Therapy
Erythropoietin
CD34
Stem cells
Progenitor cells (BFU-E, CFU-E)
Precursor cells (erythroblasts)
Reticulocytes

Iron

GM-CSF
IGF-I
IL-3
SCF
Apoptosis
Erythropoietin-dependent

~8–13 days
4 days

Besarab A. Nat Rev Nephrol 2010;6:699-710
Prolyl Hydroxylase Domain-Hypoxia-Inducible Factor (PHD-HIF) Oxygen-Sensing System

A Normoxic Conditions

B Hypoxic Conditions

Fishbane S. AJKD 2018;71: 423-35
Etiology of Anemia in CKD

- EPO Deficiency
- Iron Deficiency
- Reduced Erythrocyte lifespan
- 2nd Hyperparathyroid
- Inflammation/Infection
- Bleeding

KDIGO Clinical Practice Guideline for Anemia in CKD 2012
Outline

- Prevalence and Effects of Anemia in CKD
- Pathophysiology of Anemia in CKD
- Evaluation of Anemia in CKD
- Treatment
  - Iron Therapy
  - ESA Therapy
Four steps to effective anemia management in chronic kidney disease

1. Blood transfusions
2. ESA therapy
3. Iron management
4. Exclude other causes of anemia
Evaluation of Anemia in CKD

Focused history and physical examination

Laboratory evaluation

- Complete blood count
- Reticulocyte count
- Serum ferritin level
- Serum transferrin saturation (TSAT)
- Serum vitamin B12 and folate levels
- Stool for occult blood

KDIGO Clinical Practice Guideline for Anemia in CKD 2012
Prevalence and Effects of Anemia in CKD

Pathophysiology of Anemia in CKD

Evaluation of Anemia in CKD

Treatment
  - Iron Therapy
  - ESA Therapy
Address all correctable causes of anemia prior to initiation of ESA therapy:

- Iron deficiency
- Bleeding
- Infection
Iron deficiency is common in CKD: > 50 %

Adequate iron stores are essential for achieving maximum benefit from ESA treatment in CKD

Iron deficiency in CKD is the most common reason for hyporesponsive of ESA therapy

Correction of Iron deficiency can increase Hb level and reduce ESA dose

Agarwal R. Hemodialysis International 2017; 21:S78–S82
KDIGO Clinical Practice Guideline for Anemia in CKD 2012
Causes of Iron Deficiency in CKD

- Loss of iron through blood retension on HD apparatus
- Impaired iron absorption
- Accelerated erythropoiesis with ESA therapy will need more iron
- GI blood Loss: common in CKD patients.

Agarwal R. Hemodialysis International 2017; 21:S78–S82
Iron Indices:

- Transferin saturation
- Ferritin serum
Functional iron deficiency: The presence of adequate iron stores but an inability to sufficiently mobilize this iron to the circulatory.
Absolute Iron Deficiency

Low Transferin Saturation

AND

Low Iron Store

Tsat < 20 %

Ferritin < 100 ng/mL (pre-dialysis)
< 200 ng/mL (dialysis)

Both Transferin saturation and iron stores are low

KDIGO Clinical Practice Guideline for Anemia in CKD 2012
Infection and Inflammation

- Transferin is negative acute phase reactant protein $\rightarrow$ reduce serum level.
- Ferritin is positive acute phase reactant protein $\rightarrow$ the concentration will increase.

Agarwal R. Hemodialysis International 2017; 21:S78–S82
Iron Deficiency:

- % of red blood cell hypochrome: < 10%
- Reticulocyte Hemoglobin content (CHr): < 29pg
Oral or IV Iron in CKD ND

Randomized studies have reported inconsistent findings

Concern regarding adverse effect of IV Iron (infection, CV event, anaphylaxis)

For practical and safety reason oral iron is considered for CKD ND, IV for HD.

Ferrous sulfate 325mg (65mg elemental iron) 3x/day, between meals

Indication for IV Iron in CKD ND

- Severe Iron deficiency (TSat < 12%)
- Risk of ongoing blood loss (chronic GI loss)
- History of side effect to oral iron
- History of not responding to oral iron in the past

Chapter 2: Use of Iron to Treat Anemia in CKD

TREATMENT WITH IRON AGENTS

For adult CKD patients with anemia:
If TSAT is ≤ 30% and ferritin is ≤ 500 ng/ml (≤ 500 mg/l)

1. Not on iron or ESA therapy
2. On ESA therapy who are not receiving iron supplementation

We suggest a trial of IV iron in CKD HD patients (or oral in CKD ND patients, 1–3 month trial of iron therapy)
Chapter 2: Use of Iron to Treat Anemia in CKD

IRON STATUS EVALUATION

- 2.2.1: Evaluate iron status (TSAT and Ferritin) at least every 3 months during ESA therapy, including the decision to start or continue iron therapy.

- 2.2.2: Test iron status (TSAT and ferritin) more frequently when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of IV iron, and in other circumstances where iron stores may become depleted.
For adult CKD 5D patients, we suggest that ESA therapy be used to avoid having the Hb concentration fall below 9.0 g/dl by starting ESA therapy when the hemoglobin is between 9.0–10.0 g/dl. Individualization of therapy is reasonable as some patients may have improvements in quality of life at higher Hb concentration and ESA therapy may be started above 10.0 g/dl.
ESA Therapy

**ESA α, ESA β**
- 50-100 Units/Kg, 3x/week

**Darbepoetin**
- 0.45mcg/Kg/week or
- 0.75mcg/Kg/2 weeks

**CERA**
- 0.6 mcg/Kg/2 weeks or
- 50-75 mcg/2 weeks

**Target response at initial:** Hb ↑ 1-2 g/dL per month

KDIGO Clinical Practice Guideline for Anemia in CKD 2012
Kidney International (2016) 89, 971–973
Higher hemoglobin levels and quality of life in patients with advanced chronic kidney disease: no longer a moving target?

Christina M. Wyatt¹ and Tilman B. Drueke²

International clinical practice guidelines for the management of anemia in chronic kidney disease suggest target hemoglobin levels ≤ 11.5 g/dl (115 g/l), with individualized consideration of slightly higher hemoglobin targets to improve quality of life. An updated meta-analysis of randomized trials demonstrates no significant improvement in quality of life with erythropoietin-stimulating agent therapy targeting higher hemoglobin levels. Limitations of the available data suggest that individualized targets should nonetheless remain an option in future clinical practice guidelines.

Reevaluate ESA dose if:

• The patient suffers an ESA related adverse event
• The patient has an acute or progressive illness that may cause ESA hyporesponsiveness

KDIGO Clinical Practice Guideline for Anemia in CKD 2012
META-ANALYSIS

Meta-Analysis of Subcutaneous Versus Intravenous Epoetin in Maintenance Treatment of Anemia in Hemodialysis Patients

Anatole Besarab, MD, Carolina M. Reyes, PhD, and John Hornberger, MD, MS

- **Background:** Clinical and pharmacokinetic studies have shown that target hemoglobin or hematocrit levels can be maintained using a reduced recombinant human erythropoetin (epoetin) dosage by switching from intravenous (IV) to subcutaneous (SC) administration. **Methods:** We conducted a meta-analysis of comparative studies of epoetin administered IV versus SC to assess the relative costs of these administration routes. Twenty-seven prospective clinical studies involving 916 patients were included in the analysis. The average difference between IV and SC doses of epoetin and average difference in drug costs between administration routes were determined. **Results:** The average reduction in dose in patients treated with SC versus IV epoetin was 48 IU/kg/wk (P < 0.001), representing an average annual cost savings with SC administration of US $1,761 + $1,080 (SD) per patient. The
SC – Increased Efficiency

*Mean study duration = 82.3 days

What’s Next: Changing Paradigm of Anemia Treatment?

- The currently available treatment of anemia have some limitations.

- High dose circulating level of ESA is required to stimulate erythropoiesis, 7-30mU/mL.

- Unphysiologic administration of high dose ESA could mediate harm for patients.

- IV iron administration required to maintain iron status in hemodialysis patients might also has potential risk..

- HIF stabilizer, a new drug stimulate endogenous Erythropoietin production and enhance iron availability.
## Hypoxia Inducible Factor Stabilizers Under Development

<table>
<thead>
<tr>
<th>Company</th>
<th>Molecule</th>
<th>Drug name</th>
<th>Hase of development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrogen Astellas</td>
<td>FG-4592</td>
<td>Roxadustat</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Astra Zeneca</td>
<td>FG 4592</td>
<td>Roxodustat</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Glaxo SmithKline</td>
<td>GSK 1278863</td>
<td>Daprodustat</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Akebia</td>
<td>AKB-6548</td>
<td>Vadadustat</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Bayer</td>
<td>Bay 85-3934</td>
<td>Molidustat</td>
<td>Hase 2/3</td>
</tr>
<tr>
<td>Japan Tobacco Inc Inc</td>
<td>JTZ-951</td>
<td>Molidustat</td>
<td>Phase 1</td>
</tr>
</tbody>
</table>

Large phase 3 trials are now underway with several HIF activators. This agents also upregulate other hypoxia sensitive genes that are involve in angiogenesis.

Coyne DW. Kidney Int Suppl 2017;7:157-163
MANAGEMENT OF ANEMIA IN CKD

Anemia Evaluation
- History and Physical exam
- Hb < 10 g/dL
- Complete blood count
  - Reticulocyte count
- Iron status
  - Transferin saturation
  - Serum Feritin (SF)
- Stool for occult blood

Iron Therapy
- If Iron def. exist
  - Tsat < 30%
  - SF < 500 ng/mL
- IV or oral Iron

ESA Therapy
- ESA α, ESA β
  - Initial dose
    - 50-100 IU/Kg/Wk
  - CERA 0.6 ug/kgBW or 50-75 ug/2 week

Target Hb 10-11.5 g/dL (KDIGO 2012)
MANAGEMENT OF ANEMIA IN CKD

Anemia Evaluation

▪ History and Physical exam
▪ Hb < 10 g/dL
▪ Complete blood count
  • Absolute reticulocyte count
▪ Iron status
  • Serum Feritin (SF)
  • Stool for occult blood
  
  If Iron deficiency exists:
  
  • Tsat < 30%
  • SF < 500 ng/mL

▪ IV or oral Iron Therapy

Iron Therapy

▪ ESA Therapy
  
  Target Hb 10-11.5 g/dL (KDIGO 2012)
  
  • ESA α, ESA β
  Initial dose 50-100 IU/Kg/Wk
  • CERA 0.6 ug/kg/W or 50-75 ug/2 week

Thank You