Managing Anaemia in End Stage Renal Disease

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Anaemia is virtually universal, irrespective of aetiology or stage in patients, with Chronic Kidney Disease, including transplant-associated CKD. Anaemia a multi-factorial risk factor for the progression of CKD to End Stage Renal Disease (ESRD), reduces the quality of life and is associated with significant morbidity and mortality. Degree of anaemia is a reflection of severity of chronic kidney disease. Anaemia develops earlier and more severe in anephric and diabetic patients. The WHO defines anaemia as a Haemoglobin level less than 13.0 g/dl in adult men and less than 12 g/dl in adult women. Erythropoietin deficiency along with absolute or functional deficiency of iron, accounts for nearly 90% cases of anaemia. India is leading in iron-deficiency anaemia in the world. With or without CKD, anaemia affects an estimated 2/3rd population in India, as per National Family Health Survey1.

Etiology of Anaemia

Consequences of Anaemia

1. Decreased Quality of Life
2. Decreased Exercise tolerance
3. Decreased Cognitive functions
4. Left Ventricular Hypertrophy
5. Congestive Heart Failure
6. Angina/Myocardial Infarction
7. Disturbed sleep pattern
8. Decreased Immune response

Beneficial Effects of Correction of Anaemia:

1. Lesser need of blood transfusion: Lesser risk of HIV/HCV, less chances of allo-antibodies (transplant rejection), less chances of Iron Overload
2. Improved Quality of Life and Work tolerance
3. Regression of LVH and Infrequent CHF
4. Reduced occurrences of Angina/WI

Diagnostic Evaluation of Anaemia in CKD

Anaemia in CKD is not due to isolated deficiency of EPO. Therefore, clinicians should first consider the evidence and degree of iron deficiency, so prevalent in India, when severity the anaemia is disproportionate to decline in GFR. The recommended laboratory evaluations find the degree and cause of anaemia, assessment of iron stores and iron availability for erythropoiesis.

1. Haemoglobin %:
   Severity of anaemia is assessed best by measuring Hb% concentration rather than Hematocrit, as latter measurement is relatively unstable and lacks standardization.

2. Iron Status:
   Knowing iron status before treating anaemia, assess the
potential contribution of iron deficiency to the anaemia. Iron status tests reflect:

A. **Serum ferritin**: The only available blood marker for Iron stores. S. ferritin level <25 ng/ml in men <12 ng/ml in women, suggest iron-store depletion as main contributing factor to anaemia. (Normal-100-200 ng/ml)²,³

B. **Transferrin saturation % (TSAT)**: (Normal >20%) Gives timely and reliable assessment of the adequacy of iron available for erythropoiesis. TSAT<16% suggests, Iron-deficient erythropoiesis as the most likely cause of anaemia.

C. **Serum Transferrin receptors (sTfR)**: Transferrin receptor and Serum ferritin are reciprocally linked to cellular iron content. It is typically increased in Iron deficiency anaemia, where Erythropoiesis is increased but decreased in CKD and aplastic anaemia. Soluble transferrin receptor (sTfR) has been introduced as a sensitive, early and highly quantitative new marker of iron depletion.⁴

Testing Hb%, S.ferritin, and TSAT together, every month during initial ESA treatment, then at least every 3 months during stable ESA treatment provides important insight into external iron balance and internal Iron distribution.⁵ The purpose of iron status testing is to evaluate anaemia and guide the use of iron agents to achieve and maintain targets of iron therapy during anaemia management. More frequent iron status evaluation may be required in the following clinical settings:

1. Initiation of ESA therapy
2. Monitoring response after a course of IV iron.
3. Correction of a less-than-target Hb% level during ongoing ESA therapy
4. Recent bleeding
5. Evaluation for ESA hyporesponsivinss.

**Management of Anaemia in CKD**

1. **Set optimal target range of Hb%**:

   Fixing the Hb target and selection of the Hb level at which ESA therapy is initiated, in the individual patient, should include consideration of potential benefits (including improvement in quality of life and avoidance of transfusion) and potential harms (including the risk of life threatening adverse events). Recommended Hb targets apply exclusively to patients receiving ESA. As per latest NKF-DOQI criteria, recommended Hb target is in the range of 11.0 to 12.0 g/dl.⁶ Cardiovascular outcomes in subjects randomized to a higher target Haemoglobin level > 13.0g/dl were studied in two large clinical trials Correction of Haemoglobin and Outcomes in Renal Insufficiency (CHOIR) and Cardiovascular Risk Reduction by Early Anaemia Treatment with Epoetin Beta (CREATE), showing no benefit in one study (CREATE) and harm in the other study (CHOIR).⁷,⁸

2. **Therapeutic Options**:

   I. **Erythropoiesis Stimulating Agents (ESA)**: The cloning of human EPO gene was in 1983 led to development of recombinant human EPO (rHuEPO), a biotechnological advance that revolutionized treatment of anaemia in CKD. Attempts to improve or ‘reengineer’ rHuEPO to meet the demands of additional erythropoiesis-stimulating agents (ESAs) are going on for along period of time. ESAs are essential in the management of anaemia of CKD. The term ESA applies to all agents that augment erythropoiesis, through direct or indirect action, on the erythropoietin receptors.⁹ All ESAs licensed for clinical use are protein based, bearing some structural resemblance to EPO itself. Protein-based therapies have a number of disadvantages, they are immunogenic (pure red cell aplasia caused by anti-EPO antibodies), heat unstable (must be stored at temperatures of approximately ⁴°C), and all are injectables, either IV or S/C. Currently available ESAs are:

   A. **Short acting**: Epoetin alfa, Epoetin beta, resemble closely the endogenous molecule, short acting (half-life =8.5 hrs).

   B. **Long-acting**: darb-Epoetin alpha second-generation molecule, long acting (half-life =23.5 hrs)

   C. **Choosing an ESA**: EPOs) have now been in clinical use for nearly 20 yr. Both products Recombinant Human Erythropoetin (rHuEPO) alfa and beta are synthesized in cultures of transformed Chinese hamster ovary (CHO) cells by gene encoding. rHuEPO’gene transfer ‘cDNA’Chinese hamster/hepatoma cell line. EPO-α, Darbepotein-α, EPO-β, EPO-γ, & EPO-δ are various genetically engineered erythropoietin available and used in different parts of worldwide.

   **Darbepoetin-Alpha**:

   Darbepoetin alfa is a hyper-glycosylated EPO analogue with an extended terminal half-life and a greater relative potency compared with rHuEPO at extended dosing intervals.¹⁰ This long acting erythropoiesis stimulating agent is effective, safe and more convenient than short-acting EPO-α & β. Early stage and CAPD patients may benefit even more from the extended periods between doses. There is a decrease in the dose over time with considerable cost benefits, especially relevant to Indian CKD population.

   Conversion formula: EPO-α, 200 Units = Darbepoetin- 1µg
Dose, Route and frequency of ESA administration:

- EPO-α -- 100-150U/kg/wk and Darbepotein-α -- 0.45 µg/kg/wk
- Frequency: Convenience favours less frequent weekly injections particularly in non-HD-CKD patients.

Hb% level monitoring and ESA dose adjustments: The frequency of Hb% monitoring in patients treated with ESAs should be at least monthly. In general, the objective of initial ESA therapy is a rate of increase in Hb% levels of 1-2 g/dl per month. The minimum interval between ESA dose adjustments is 2 weeks because the effect of most dose changes will not be seen within a shorter interval.

Adverse Effects of ESA Therapy:
- Worsening of Hypertension may require upward titration of antihypertensives, preferably Calcium channel blockers.
- Vascular access thrombosis,
- Inadequate dialysis,
- Seizures,
- Hyperphosphatemia

Newer Erythropoiesis Stimulation Therapies:

1. Continuous erythropoietin receptor activator (C.E.R.A.): It is a chemically synthesized ESA which differs from other epoteins, having a long half-life of 130 hr and low clearance, may be administered either intravenously or subcutaneously. CERA can correct anaemia and maintain stable Hb levels in patients with all stages of CKD. ARCTOS (Administration of C.E.R.A. in CKD Patients to Treat Anaemia with a Twice-Monthly Schedule) was first large-scale comparative darbepoetin alfa-controlled study, which demonstrated that subcutaneous C.E.R.A., administered (0.6 µg/kg/wk) once every 2 wk, was as effective and well tolerated as once weekly subcutaneous darbepoetin alfa, in CKD patients not on dialysis.

2. Peptide-Based ESA-Hematide: Hematide, is a pegylated synthetic dimeric EPO-mimetic peptide found to stimulate erythropoiesis. The potential advantages of this are greater stability at room temperature, a much simpler and cheaper manufacturing process, avoiding the need for cell lines and genetic engineering techniques. Antibodies against Hematide do not cross-react with EPO, hence this may be used in the treatment of PRCA.

3. Synthetic Erythropoiesis Protein (SEP): A 51-kD protein-polymer construct was synthesized using solid-phase peptide synthesis and branched precision polymer attached polymer moieties. As with darbepoetin alfa and CERA, this polymer stimulates erythropoiesis through activation of the EPO receptor, and with a longer circulating half-life than for EPO alone. A single subcutaneous administration of synthetic erythropoiesis protein (SEP) has been shown to vary in experimental animals and in mice it increased red cell production within 7 day at a dosage at which epoetin was ineffective.

4. EPO Gene Therapy: The ability to generate lower but continuous levels of EPO as a result of gene therapy is a potentially attractive area of research. It does not seem to matter by which cells and at which site EPO is into the circulation, and a number of delivery systems have released been investigated, including naked DNA, adenovirus transfection, use of artificial chromosomes and transplantation of autologous or allogeneic human cells. As with all gene therapy, there are many hurdles to overcome before this could be used in humans.

Pure Red Cell Aplasia
Cases of Antibody-Mediated PRCA were reported with s/c administration of an epoetin alfa, in prefilled syringes fitted with uncoated rubber stoppers containing polysorbate 80. Here antibodies neutralize both rHuEpo and endogenous erythropoietin. No case of antibody-associated PRCA has been documented in patients treated with only IV administration of ESAs. The characteristic sign of PRCA is almost complete cessation of erythropoiesis.

Diagnostic criteria of PRCA:
- Sudden rapid decrease in Hb level at the rate of 0.5 to 1.0 g/dL/wk, or requirement of red blood cell transfusions at the rate of approximately 1 to 2 per week, AND
- Normal platelet and white blood cell counts, AND
- Absolute Reti. Count less than 10,000/µL.
- Demonstration of anti-erythropoietin antibodies.

Treatment of PRCA: Discontinue the administration of any ESA. Most patients will require transfusion support. Hematide, a peptide-based erythropoietin receptor agonist is study found effective in the treatment of PRCA. Hematide does not cross react with anti erythropoietin (ant-EPO)antibodies, and will allow ongoing stimulation of erythropoiesis; this is the subject of current clinical research.

Resistance to Erythropoietin Therapy:
Resistance to the effect of ESAs is a common problem of grave significance associated with poor prognosis.
Whenever the Hb% level is inappropriately low for the ESA dose administered, we must re-evaluate the patient for Erythropoietin resistance/failure.

- A significant increase in the ESA dose requirement to maintain a certain Hb level or a significant decrease in Hb level at a constant ESA dose.
- A failure to increase the Hb>11 g/dL with epoetin-α greater than 500 IU/kg/wk.

Causes of Erythropoietin Resistance

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<th>Common causes</th>
<th>Uncommon causes</th>
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<td>Persistent iron deficiency</td>
<td>Pancytopenia/aplastic anaemia</td>
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<td>Frequent hospitalization</td>
<td>Hemolytic anaemia</td>
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<tr>
<td>Hospitalization for infection</td>
<td>Chronic blood loss</td>
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<tr>
<td>Temporary catheter insertion</td>
<td>Cancer, chemotherapy, or radiotherapy</td>
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<tr>
<td>Permanent catheter insertion</td>
<td>Inflammatory disease</td>
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<tr>
<td>Hypoalbuminemia</td>
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<td>Elevated C-reactive protein level</td>
<td>Infection</td>
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<td>ACE inhibitors</td>
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Iron Therapy in Anaemia of CKD:
The goals of iron therapy are:
(a) To achieve and maintain a target-range Hb level.
(b) To avoid depletion of storage iron.
(c) To prevent iron-deficient erythropoiesis,
(d) To minimize the dose of ESA

**A. Targets of Iron therapy**: Sufficient iron should be administered to generally maintain the following indices of iron status during ESA treatment:
- Patients on Dialysis: S. ferritin >200 ng/ml, TSAT >20%
- Patients on Conservative Therapy: S. ferritin >100 ng/ml, TSAT >20%

**B. Preferred Route: Oral OR IV Iron?** The preferred route is I.V in patients on Hemodialysis. The route can be either IV or oral for those on Conservative/CAPD. IV iron administration is found to be superior to oral iron in various RCT’s as: Oral Iron is poorly absorbed in patients with CKD and IV iron showed a greater Hb % level, lower ESA dose, or both compared to oral iron.

**C. Hypersensitivity Reactions**: There currently are 3 forms of IV iron that are widely available: iron dextran, iron gluconate, and iron sucrose. All forms of IV iron may be associated with acute adverse effects, occasionally severe, comprising of hypotension with or without other symptoms and signs. Anaphylactoid reactions appear to occur more frequently with iron dextran, and labile or free iron reactions occur more frequently with non-dextran forms of iron.

**D. Long term complications of Iron Therapy**: Increased susceptibility to infection and Oxidative stress.

**Adjuvants to Erythropoietin, ESA & Iron Therapy**
Aims of Add-on therapy are to enhance responsiveness to ESA hyporesponsive patients and to decrease cost by decreasing ESA doses.

**L-Carnitine**: Levo-carnitine (L-carnitine) is thought to be involved in the metabolic conversion of acyl coenzyme A, to the less toxic acyl-carn-itone, which accumulates in patients with renal. L-carnitine, has been postulated to have beneficial effects on anaemia, HD-related hypotension, myocardial dysfunction, impaired exercise tolerance and performance status, and impaired nutritional status. However NKF-KDOQI, found insufficient evidence to recommend use of L-carnitine in the management of anaemia in patients with CKD.

**Vitamin-C(Ascorbic acid)**: Vitamin C has been reported to increase the release of iron from ferritin and the reticuloendothelial system and increase iron utilization during heme synthesis. The long-term safety of IV ascorbic acid in HD patients remains undefined, the secondary oxalosis being the primary concern.

**Vitamin E**: Vitamin E has been considered as a potential adjuvant to ESA therapy based on the consideration that antioxidant properties of vitamin E may prolong red blood cell life span.

**Androgens**:
Before the availability of epoetin therapy, androgens were used regularly in the treatment of anaemia in dialysis patients. Still some nephrologist use this “Poor man’s Erythropoetin” in those who cannot afford costly Epoteins. The proposed mechanisms of action of these drugs include increased erythropoietin production from renal or non-renal sites, increased sensitivity of erythroid progenitors to the effects of erythropoietin, and increased red blood cell survival. Short-term and long-term toxicity of androgens limit their use, especially in women. NKF-DOQI strongly recommends that androgens should not be used as an adjuvant in CKD.
**Statins:**
Underlying inflammatory processes may be related to anaemia in patients with CKD, a growing body of literature indicates that there may be clinically important role for statins in enhancing epoetin therapy.

**Modifications of Dialysis Treatments:** Doubtful Efficacy
Changing patients with HD-CKD from standard bicarbonate dialysate to ultrapure dialysate, Membrane Type: low-flux to high-flux dialyzers, high-flux HD to Haemodiafiltration, Conventional intermittent HD to daily HD.

**CONCLUSION**
Identification and effective treatment of Anaemia in patients with CKD goes beyond the improvement in quality of life and Haemoglobin-in levels. Clinical introduction of recombinant human Erythropoietin has revolutionized the management of anaemia. Evaluation and management of pre-existing and/or concurrent iron deficiency and its treatment is even more relevant for Indian patients. Newer strategies are underway to use longer acting erythropoietic agents such as darbepoetin alfa and CERA. Cost of therapy is still a deterrent to majority of Indian patients.

**REFERENCES**
1. Lahariya C, Khandekar J. How the findings of National Family Health Survey-3(NFHS-3) can act as a trigger for improving the status of anaemic mothers and undernourished children in India: A review. Indian J Med Sci. 2007; 61:335-44