

## Management of renal anemia

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**SUMMARY:** Peco-Antic A. Management of renal anemia. Turk J Pediatr 2005; 47 (supplement): 19-27.

Normochromic normocytic anemia is common in children with chronic renal failure (CRF) when their glomerular filtration rate is below 35 ml/min/1.73 m<sup>2</sup> BSA, but it may develop earlier in some forms of renal disease. An inadequate erythropoiesis due to insufficient erythropoietin synthesis in the kidneys is the main cause of renal anemia. Other reasons include reduced red blood cell lifespan, chronic blood loss, iron deficiency, inhibitors of erythropoiesis, and malnutrition.

The presence of anemia contributes to many of the symptoms of uremia, including decreased appetite, decreased energy, poor cardiac function, and poor school performance. Therefore, correction of anemia dramatically improves the life of the child with CRF. Presently, the goal of anemia management is to maintain hematocrit concentrations at 33% to 36% and a hemoglobin concentration of at least 11 g/L. This can be accomplished by intravenous or subcutaneous administration of recombinant erythropoietin (rHuEPO, 100-300 U/kg/week) and iron preparations. If adequate iron stores cannot be maintained with oral therapy (2-3, max 6 mg/kg/day), intravenous iron should be administered.

In order to optimize anemia management in children with CRF, future research should be concentrated on the normalization of hemoglobin early in the course of CRF, and the long-term effects on the child's development.

*Key words:* anemia, chronic renal failure, children, erythropoietin.

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### Introduction

Anemia of chronic renal failure (CRF) was recognized more than 150 years ago<sup>1</sup>. It is hypo proliferate, normocytic anemia that correlates with the degree of uremia<sup>2</sup>. Decline in hemoglobin (Hb) concentration rate may start early, at levels of creatinine clearance of around 70 ml/min in men and 50 ml/min in women, and progresses relentlessly<sup>3</sup>. When closer to terminal renal failure (TRF), the majority of the patients develop chronic anemia, which can be severe unless treated.

There is increasing evidence that early and complete anemia correction may slow down the progression of CRF, thus preventing cardiovascular and overall morbidity, and improving survival in the dialysis population<sup>4-8</sup>. However, the data have so far been insufficient to generally recommend the complete correction of renal anemia<sup>9</sup>. Prospective, multi-center

trials are needed to establish a clear target hematocrit (Hct)/Hb range and the renal anemia management period (RAMP)<sup>10,11</sup>, to determine the best erythropoietin product, as well as the significance of adjuvant therapy for optimal renal anemia management. The current practice is that every patient with CRF must be treated individually to ensure the safest, and most cost- and dose-effective therapy<sup>12-14</sup>. Contrary to a large number of studies of the optimization of renal anemia management in adults, the anemia present in children with CRF has received remarkably little attention. Recently, the European Pediatric Peritoneal Dialysis Working Group (EPPWG) produced the first guidelines for the management of anemia in children on peritoneal dialysis<sup>15</sup>. However, the current practice in the treatment of anemia in pre-dialysis, hemodialysis and transplanted pediatric patients is based largely on an extrapolation from adult studies and

small pediatric trials. This paper will discuss the pathophysiology of renal anemia and the optimization of its management in children.

#### Causes Enal Anemia

The causes of renal anemia are outlined in Table I and include a moderately reduced red blood cell (RBC) lifespan, blood loss, and impaired erythropoiesis. RBC lifespan decreases with worsening uremia to as little as one-third of normal value<sup>16</sup>. It may be shortened due to corpuscular (reduced resistance of RBC to mechanical, osmotic or oxidative stress) and extra-corpuscular (uremic plasma factors may contribute to premature RBC destruction) factors<sup>17-19</sup>. Patients with CRF may regularly lose blood from hemodialysis, diagnostic sampling and the gastrointestinal tract. In pediatric pre-dialysis patients, and probably also patients on peritoneal dialysis, mean daily intestinal blood losses are about 6 ml/m<sup>2</sup> BSA. For pediatric hemodialyzed patients, mean gastrointestinal blood losses increase to 11 ml/m<sup>2</sup> BSA, and dialyzed-associated blood losses are about 8 ml/m<sup>2</sup> per treatment<sup>20</sup>. The factors contributing to the failure of erythropoiesis are central to the development of renal anemia<sup>21</sup>. Of these, the most important is inadequate erythropoietin (EPO) production. EPO stimulates hematopoietic stem cells to mature to erythroid cells, fosters addition of iron to hem moiety and prevents apoptosis of progenitors<sup>22</sup>. Unlike other factors that stimulate erythropoiesis, particularly the insulin-like growth factors (IGF-I and II)<sup>23</sup>, EPO is the only erythroid growth factor known to regulate erythropoiesis according to the dictates of oxygen demand<sup>21</sup>. The major site of EPO production (90%) is in type I fibroblastic cells in the peritubular interstitium of the renal cortex and the outer medulla<sup>24</sup>. Hypoxia activates the transcriptional hypoxia inducible factor (HIF-1) that promotes the expression of the EPO gene and its transcription. In CRF there is a failure of the mechanism that adjusts EPO production to the oxygen transport capacity of the blood due to the destruction of a subpopulation of renal fibroblasts that normally produce EPO, and the transformation of these EPO-producing fibroblasts into matrix-producing myofibroblasts<sup>21</sup>. The contributing factors include the absence of paracrine signals

from the tubular cells adjoining the EPO-producing cells, and increased expression of the inflammatory mediators in the kidney.

**Table I.** Causes of Renal Anemia

<i>Shortened red cell lifespan</i>
• Extracorporeal factors
• Corpuscular factors
• Hypersplenism
<i>Blood loss</i>
• Hemodialysis
• Diagnostic blood sampling
• Occult gastrointestinal blood loss
<i>Inhibition of erythropoiesis</i>
• Inadequate erythropoietin (EPO) production
• Iron deficiency
• Folate deficiency
• Hyperparathyroidism
• Inadequate dialysis treatment
• Inflammatory reactions

#### *Inadequate Erythropoietin Production in Children with CRF*

In pediatric patients with CRF, a linear correlation has been found between Hct and glomerular filtration rate (GFR)<sup>2</sup>. However, there has been no relationship detected either between GFR and serum EPO levels, or between the degree of anemia and serum EPO levels<sup>2</sup>. In contrast to the inverse relationship between the serum EPO concentration and Hct present in non-renal anemia, in children with CRF, serum EPO levels are within normal values for hematological normal individuals, but are inappropriately low for the severity of anemia of CRF. A lack of correlation between EPO levels and Hct in CRF appears to be related to the multifactor origin of renal anemia, i.e. the factors that influence EPO production independent of changes in Hct, such as underlying renal disease; altered Hb-oxygen affinity; altered state of protein metabolism or protein malnutrition; serum levels of renin, angiotensin II, and aldosterone; extent of hemolysis; and biochemical milieu within the kidney<sup>2</sup>. The observation that mean serum EPO levels for anephric children have measurable EPO levels only slightly lower than those of normal children is important for a better understanding of the mechanism of the anemia of TRF and indicates that extra-renal sites (liver) can be triggered to produce EPO

when anemia is severe<sup>25</sup>. Children with CRF have been found to have ten-fold higher serum EPO levels during the episodes of spontaneous acute hypoxic stress than during stable-state of CRF<sup>2</sup>. These findings suggest that the tissue-oxygenation-EPO-Hct feedback mechanism operates at a lower set point in patients with CRF in comparison with normal subjects.

#### *Consequences of Renal Anemia*

In pediatric patients with CRF, anemia generally becomes manifest at a GFR below 35 ml/min/1.73 m<sup>2</sup> BSA, but it may develop earlier in some forms of renal disease<sup>26</sup>. The presence of anemia is partially or wholly responsible for many symptoms that have been historically attributed to uremia (Table II). Thus, correction of

**Table II.** Manifestations of Chronic Renal Failure Caused by Anemia

Pallor
Reduced exercise tolerance and weakness
Exertional chest pain and shortness of breath
Impaired concentration and impaired cognition
Headache and insomnia
Malaise/depression and lethargy
Anorexia
Intolerance to cold
Tendency to bleeding
Cardio-respiratory disturbances
Gastro-intestinal disturbances
Impaired immune system
Endocrine/metabolic abnormalities
Neuromuscular disturbances
Musculoskeletal symptoms
Impaired libido/impotence

anemia leads to increased appetite<sup>27,28</sup> and exercise tolerance<sup>27,29</sup>, improved school performance or IQ<sup>30,31</sup>, ameliorated insulin and lipid abnormalities<sup>32</sup>, and diminished blood transfusion requirements<sup>27,33</sup>. The relationship between anemia and left ventricle hypertrophy (LVH) has been well documented<sup>34</sup>; for every 0.5 g/dl decrease in Hb, left ventricular growth increases by 32% (p=0.004). Early correction of anemia can result in the regression of LVH<sup>35</sup>. The presence of renal anemia independently predicts the future risk of hospitalization<sup>36</sup>; patients with anemia are hospital-free for a median of 13.3 months, compared with a median of 21.5 months (p=0.0593) for

those with higher Hb levels<sup>36</sup>. Furthermore, it has been found that anemia predicted mortality in adult patients who progress to TRF independent of age, diabetes mellitus, cardiac failure, hypoalbuminemia, serum creatinine, mean arterial pressure, or echocardiographic heart disease. For every 1 g/dl decrease of Hb, the relative risk of mortality increases by 18% (p=0.019)<sup>37</sup>. The association between anemia and hospitalization risk has been recently reported also for pediatric patients with CRF<sup>38</sup>. Not only is the baseline Hct of less than 33% associated with a greater mean number of hospitalization days within the initial year of dialysis, but also with a significantly greater probability for hospitalization of 30 days or more during that year, irrespective of dialysis modality and after adjusting for death, change in dialysis modality, and transplantation<sup>38</sup>. In the same study, the multivariate analysis demonstrated anemia to be associated with a 52% higher risk of death (adjusted relative risk 1.52, 95% confidence interval 1.03-2.26, p=0.037). Cardiopulmonary disease has been the primary reported cause of death associated with anemia, accounting for 22% of cases<sup>38</sup>.

#### *The Renal Anemia Management Period (RAMP)*

Despite the evidence that management of renal anemia in its early stage plays an important role in delaying or halting progression of CRF and its associated co-morbidities<sup>4-8</sup>, anemia is often under-recognized and under-treated<sup>39</sup>. The United States Renal Data System (USRDS) has revealed the mean Hct value of children to be less than 30% at initiation of dialysis, in large part reflecting suboptimal anemia management during the pre-dialysis period of CRF in children<sup>40</sup>. According to the recent North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) data, 40-60% of children with CRF (total 1992) have not attained the recommended Hct<sup>41</sup>. Compared to day 30, the prevalence of anemia was lower at six months of dialysis, but still exceeded 40%. Similarly, the first pediatric reports of End-Stage Renal Disease Clinical Performance Measures Project (CMP) have shown that 37% of the 516 patients aged 15.5±1.8 years had mean Hb of <11 g/dl<sup>42</sup>. The patients on dialysis <6 months were more likely to be anemic (67%). The problem of renal anemia is even worse in underdeveloped countries. In Yugoslavia in

2001 more than half of the pediatric patients with CRF (54%) had Hb concentration of <11 g/dl<sup>43</sup>. Although published data about transplant patients are limited, they have shown anemia in the pediatric population to be present in about 60 to 82.2%<sup>44,45</sup>. To call attention to the need to improve outcomes for patients with CRF and possibly lower the economic burden by correcting anemia earlier, the renal anemia management period (RAMP) has been developed<sup>10,11,46</sup>. The RAMP is the time after onset of chronic kidney disease when anemia develops and requires early diagnosis and treatment. Pediatric nephrologists are those who should provide vital consultation on early guidelines for appropriately diagnosing and managing anemia in children with CRF.

#### *Evaluating Renal Anemia in Children*

Anemia in children with CRF should begin to be evaluated when Hct and Hb are consistently below the lower normal range for the child's age and sex. The European Best Practice Guidelines (EPBG)<sup>47</sup> have recommended a work-up for the diagnosis of anemia in children whenever the Hb concentration is a) <11 g/dl (Hct <33%) in pre-pubertal, and b) <12 g/dl (Hct <37%) in post-pubertal patients.

Evaluation of anemia begins with a good general clinical examination to assess its possible causes (chronic blood loss, nutritional deficiencies) and its clinical impact<sup>47</sup>. Basic laboratory evaluation of anemia should consist of measuring the following: 1) Hb concentration and Hct level, 2) RBC indices including mean corpuscular volume (MCV) and mean corpuscular Hb concentration (MCHC), 3) absolute reticulocyte count, 4) iron stores-serum apoferritin concentration (SAF), 5) iron supply for erythropoiesis including transferrin saturation (TSAT), or even better when available, the percentage of hypochromic red blood cells (HCRBC) and reticulocyte hemoglobin content (CHr), and 6) C-reactive protein (CRP) as a marker of inflammation. MCV and MCHC are readily available laboratory tests, but do not become diagnostic until moderate-to-severe iron deficiency anemia is present. TSAT is the calculated value of the quantity of circulating transferrin-bound iron available to the maturing erythroid precursor (reported as serum iron) divided by the total available circulating transferrin

binding sites (reported as transferrin binding capacity, TBC). Although TSAT and SAF are widely available and are commonly used measures for iron status, these markers of iron stores do not always provide the most reliable or accurate information, especially when isolated determinations are utilized<sup>48,49</sup>. Recently, HCRBC has been introduced as a sensitive tool in the diagnosis of iron deficiency in dialyzed patients. However, it can be influenced by inflammation, and its cut-off value for functional iron deficiency has a wide variation, from 3.7 to 10% in different series<sup>50</sup>. Furthermore, because of the longer life span of mature RBC, HCRBC fails to provide the relevant information on rapid change in iron utilization. With the advent of a novel automated flow-cytometry technique that is a part of a red cell auto analyzer, measurement of CHr allows extremely early and objective information on erythropoietin activity in anemia. CHr has been proposed as a surrogate marker of iron status and an early predictor of response to iron therapy<sup>51</sup>. Flow cytometry further assesses the maturation of reticulocytes in low-, middle- and high-fluorescence intensity regions. Reticulocyte fluorescence intensity is directly proportional to the quantity of intracellular RNA, and thus expresses the function of cellular maturity. The most immature reticulocyte expresses high-fluorescence intensity regions (HFR). CHr and HFR have been proposed as surrogate markers of iron status and early predictors of response to iron therapy with the highest accuracy (sensitivity 96%-100% and specificity of 80%-100%)<sup>49,51</sup>. Unfortunately, the technique for measuring these parameters is not available everywhere.

#### *Target Hemoglobin Concentrations*

The choice of Hb targets for treating patients with renal anemia is still a matter of great debate<sup>12</sup>. The current practice aims for only partial correction of anemia, and this is a result of several contributing factors. First, initial studies aimed for partial correction of anemia<sup>52</sup>. Second, there is concern that complete correction of anemia in CRF patients may increase risk of adverse events such as arterial hypertension and vascular access thrombosis. Third, the US Normal Hematocrit Trial failed to live up to expectations, as the patients with the higher



Hct were at risk of higher incidence of death or non-fatal myocardial infarction<sup>9</sup>. Finally, but not of least importance, there are economic considerations due to costly life-long therapy (unless transplanted). Presently, the goal of anemia treatment is to maintain the Hct at 33% to 36%<sup>26</sup>. Exact target Hb concentrations of >11 g/dl should be tailored for individual patients<sup>12-14</sup>. For patients with cardiovascular disease, an Hb concentration limited to 11-12 g/dl is suggested<sup>12,47,55</sup>.

#### *Erythropoietin Therapy, Dosage and Mode of Application*

The gene for erythropoietin was identified in 1983 on the long arm of chromosome 7, cloned in humans in 1984<sup>54</sup>, and its recombinant product was tested in humans in 1984<sup>55</sup>. Since 1986, human recombinant erythropoietin (rHuEPO-epoetin) has been available for clinical use<sup>52</sup>. Before the advent of rHuEPO, renal anemia was treated with blood transfusion and androgens or anabolic steroids that are now only historical treatment in the light of their side effects. The introduction of rHuEPO treatment has dramatically improved the life of the children with CRF<sup>27-32,56,57</sup>. An optimal (80 to 100%) response to rHuEPO in pediatric patients with CRF has been achieved with a starting dose that ranged from 75 to 450 U/kg per week, and this effect was maintained with a dose of rHuEPO that ranged from 75-300 U/kg per week<sup>4,27,33,56,57</sup>. The effects of rHuEPO are dose-dependent; increase in Hb was higher and more rapid in patients administered a high-dose versus in those who received a low dose<sup>56</sup>. Generally hemodialysis (HD) patients require a higher dose of rHuEPO than those on peritoneal dialysis (PD), and this may be explained by the following: 1) spontaneous EPO production is higher during PD than during HD, 2) most PD patients have some residual kidney function, and 3) better clearance of middle molecules in PD may be beneficial in erythropoiesis. Sensitivity of biotechnologically produced erythropoietin, rHuEPO, has been shown to be lower in children, and a larger dosage must be used when compared with adults<sup>26,33,57</sup>. In pre-dialysis children or after renal transplantation, the starting rHuEPO dose of 25-50 U/kg body weight (BW) per week in 1-2 doses may be enough. For dialysis children it seems

reasonable to start with 50-100 U/kg BW 2 to 3 times per week. Children younger than five years of age may require a greater dose of rHuEPO on BW (up to 300 U/kg/week) than older ones<sup>58</sup>. Hb should increase at a rate of 1 g/dl per month to the target level and then the maintenance dose is determined individually<sup>53</sup>. If the increase of Hct is less than 2% over a two-to four-week period, the weekly dose should be increased by 50%. If the increase in Hct is more than 8% over four weeks, the weekly dose should be decreased by 25%. Maintenance doses vary from 300 U/kg per week for a child with BW less than 20 kg to 120 U/kg per week for a child with BW more than 30 kg<sup>15</sup>. There are two main routes of rHuEPO administration: intravenous and subcutaneous. The efficacy of rHuEpo is better (15-50%) when given by the subcutaneous route due to more favorable pharmacodynamics<sup>59</sup>. For pre-dialysis and transplanted patients, the subcutaneous administration of rHuEPO is preferred. In PD patients, rHuEpo should be administered using the subcutaneous or intraperitoneal route<sup>15</sup>. If intra-peritoneal administration is used, it is best to infuse rHuEPO into a dry abdomen or with a minimal amount of dialysate<sup>15</sup>. The most common adverse events of rHuEPO are summarized in Table III. They can be decreased with

**Table III.** Adverse Events in rHuEPO Treatment (Van Damme Lombaerts 1999)<sup>57</sup>

Hypertension
Clotting within the extracorporeal circuit
Arteriovenous fistula thrombosis
Iron deficiency
Hyperkalemia
Thrombocyte count increase
Hyperphosphatemia
Subjective complaints: headache
Pain at the injection site with subcutaneous administration
Influenza-like symptoms

rHuEPO: humanrecombinanterythropoietin.

appropriate procedures to control the anemia gradually and with careful monitorization of the treatment<sup>47,53</sup>. Arterial hypertension is usually a problem during the initial phase of correction of anemia, and necessitates close monitoring of blood pressure, adjustment

of rHuEPO dosage, and administration of antihypertensive therapy. To avoid clotting problems, the dose of heparin should be increased in HD patients. Hyperkalemia and hyperphosphatemia are probably related to the better appetite of the child and should be corrected by dietary adaptation and/or by potassium and phosphate binders.

Resistance to rHuEPO is defined as a failure to attain the target Hb while receiving more than 300 U/kg per week<sup>47</sup>. The following conditions should be evaluated and, if reversible, treated: iron deficiency, infection or inflammatory disease, severe hyperparathyroidism with marrow fibrosis, malnutrition, hemolytic disorders, folate or vitamin B12 deficiency, under dialysis, vitamin C deficiency, ACE inhibitors, aluminum toxicity and anti-rHuEPO antibodies<sup>15</sup>. Pure red cell aplasia (PRCA) is a severe but rare undesired effect of rHuEpo from induced anti-erythropoietin antibodies<sup>60</sup>. The incidence of rHuEPO-induced PRCA has increased since 1998 after the formulation of erythropoietin alpha was changed, and in most cases has been associated with subcutaneously administered rHuEPO product. As a result, subcutaneous administration of erythropoietin alpha is presently discouraged in many countries<sup>15</sup>.

#### *Iron Therapy*

Iron deficiency has been identified as the most important factor limiting the responsiveness to rHuEPO therapy<sup>49,61,62</sup>. Children with CRF are especially prone to iron deficiency due to increased iron requirements for growth and rHuEPO-facilitated erythropoiesis, which is associated with decreased iron intake and absorption, chronic blood loss, and iron sequestration secondary to chronic inflammatory processes. The cumulative annual iron losses approximate 1.6 g/1.73 m<sup>2</sup> BSA in HD pediatric patients, and 0.9 g/1.73 m<sup>2</sup> BSA in pre-dialysis pediatric patients, as well as in those on PD<sup>20</sup>. Approximately 43%-90% of patients undergoing HD experience iron deficiency<sup>41,63</sup>. Absolute and/or functional iron deficiency plays the main role in the development of post-transplant anemia<sup>45</sup>. Functional iron deficiency occurs when there is failure to release iron rapidly enough to keep pace with the demands of bone marrow for erythropoiesis, despite adequate or even

increased body iron stores. It is confirmed and resolved by administering iron in a readily available form intravenously<sup>49,62</sup>.

Iron deficiency can be prevented by concomitant use of iron supplementation when commencing rHuEPO therapy. Iron supplements are available in both oral and intravenous formulations, each with its unique advantages and disadvantages<sup>63</sup>. Oral products offer convenient administration, which is very important in children, but usually cannot really match the elevated demand for increased erythropoiesis due to insufficient gastrointestinal absorption in CRF, and gastrointestinal side effects that may also adversely affect a food intake and/or poor adherence to therapy. Intravenously (IV) administered iron is well tolerated by the majority of patients. The most serious adverse reaction is anaphylactic hypersensitivity, which occurs more commonly with the use of IV dextran than in other IV iron formulas<sup>64</sup>. Another potential reason for caution regarding the use of IV iron in children may be the risk of iron overload, thus careful monitorization of iron stores is required<sup>47,53</sup>. For optimal rHuEPO response, the goal should be to maintain serum iron in the normal range, SAF from 200-500 ng/ml (not to be persistently 800 ng/ml), TSAT of 30-40% (not to exceed 50%), HCRBC of more than 2.5% and CHr >28 pg<sup>49,53</sup>. The best erythrocyte and iron metabolism indices are changes in CHr (cut-off value of >1.2 pg) and HFR (cut-off value of >500/ $\mu$ l) at either two or four weeks during aggressive iron treatment<sup>51,62</sup>.

Administration of supplemental iron in children with CRF usually starts with oral therapy. If adequate iron stores cannot be maintained with oral iron in doses of 3 to a maximum of 6 mg/kg per day (in 2 to 3 divided doses, 1 to 2 h after food or other medications), IV iron therapy should be instituted<sup>15,53 57</sup>. To minimize the risk of anaphylactic reactions, it is advised to give a test dose prior to the first infusion of a full dose<sup>57</sup>. Oral iron therapy is usually insufficient in hemodialysis patients<sup>41</sup>. Studies in adults show that IV iron, especially in the form of maintenance therapy, can help achieve target Hb levels<sup>49</sup>. However, experience with IV iron therapy in children with CRF is based on a few small pediatric trials<sup>63,65-71</sup>. The pooled pediatric data suggest that IV iron increases Hb and/or Hct values, increases SAF

and TSAT, and reduces the use of rHuEpo, with moderate to large effect<sup>71</sup>. Iron dextran, sodium ferric gluconate, and iron sucrose are all effective, but no study has directly compared different products<sup>71</sup>.

### Conclusion

Anemia is one of the most common manifestations of progressive CRF in children, and can develop at any time after its onset, often well before terminal renal failure develops. It has been shown to be associated with the development of cardiac complications, increased hospitalization, and increased mortality. Early treatment of anemia well before kidney function deteriorates to the point of requiring dialysis is now the focus of interest. Future research in anemia management in children with CRF should be concentrated on three major areas: 1) target Hct >36%, 2) the use of IV iron, especially new sucrose-based products, and 3) the long-term effects of normalization of Hct/Hb on child development.

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