

# Understanding renal posttransplantation anemia in the pediatric population

Paul Joseph Galutira · Marcela Del Rio

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**Abstract** Advances in renal transplantation management have proven to be beneficial in improving graft and patient survival. One of the properties of a well-functioning renal allograft is the secretion of adequate amounts of the hormone erythropoietin to stimulate erythropoiesis. Posttransplantation anemia (PTA) may occur at any point in time following transplantation, and the cause is multifactorial. Much of our understanding of PTA is based on studies of adult transplant recipients. The limited number of studies that have been reported on pediatric renal transplant patients appear to indicate that PTA is prevalent in this patient population. Erythropoietin deficiency or resistance is commonly associated with iron deficiency. An understanding of the risk factors, pathophysiology and management of PTA in the pediatric renal transplant population may provide guidelines for clinicians and researchers in the pursuit of larger prospective randomized control studies aimed at improving our limited knowledge of PTA. Recognition of PTA through regular screening and evaluation of the multiple factors that may contribute to its development are recommended after transplantation.

**Keywords** Erythropoietin · Erythropoiesis-stimulating agents · Iron deficiency · Posttransplantation anemia · Renal transplantation

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P. J. Galutira  
Section of Pediatric Nephrology,  
University of Santo Tomas Hospital,  
Manila, Philippines

M. Del Rio (✉)  
Division of Pediatric Nephrology, Children's Hospital  
at Montefiore, Albert Einstein College of Medicine,  
Bronx, NY, USA  
e-mail: mdelrio@montefiore.org

## Introduction

Renal transplantation is considered to be the optimal renal replacement therapy for pediatric patients with end-stage renal disease (ESRD). Advances in the management of renal transplantation, particularly those related to immunosuppression therapy, have led to an increase in patient and graft survival. A well-functioning renal allograft is able to synthesize adequate amounts of erythropoietin (EPO) for erythrocyte synthesis. However, in patients with suboptimal graft function, posttransplantation anemia (PTA) may occur at any time in the posttransplant period, which may cause tissue hypoperfusion and hypoxia leading to cardiovascular morbidity and even potential graft loss. In this review, PTA will be defined and its prevalence determined. EPO production posttransplantation will also be discussed. Early recognition of possible risk factors to PTA which may lead to the appropriate intervention that will optimize the function of the newly transplanted kidney will be highlighted.

It can be said that the development of anemia in the posttransplant setting has received less attention than the occurrence of anemia in the chronic kidney disease (CKD) and dialysis patients. It can also be argued that PTA is an issue that have been overlooked since the focus of renal transplantation is on the prevention of rejection and the achievement of good renal function. However, with the improvement in allograft and patient survival rates, there has been a shift in emphasis towards the control of cardiovascular risk factors, which are relevant to the survival of the transplant patient.

Posttransplantation anemia may affect the patient's quality of life (QOL). Kawada et al. tested the administration of recombinant human EPO (rHuEPO-ad) and its positive impact on QOL [1]. In this study, the physical and mental QOL of their patients before and after rHuEPO-ad

were assessed and summarized as a physical summary score (PSC) and a mental summary score (MSC), respectively, using a 36-item short form (SF-36) which is an international questionnaire used to analyze the QOL. Before rHuEPO-ad, posttransplant patients had a preserved MSC but impaired PSC. The administration of rHuEPO for 6 months increased their hemoglobin (Hb), which was accompanied by an improvement of the PSC. Gheith et al. determined the impact of PTA on long-term patient graft survival and showed that chronic allograft nephropathy was significantly higher in the anemic group [2]. A 12-month PTA has been found to be associated with subsequent graft loss and patient mortality [3]. Furthermore, PTA is associated with an increased risk of congestive heart failure and left ventricular hypertrophy [4].

The definition of PTA varies among different studies and guidelines and is mostly based on the appropriate hemoglobin and hematocrit level for age and sex [e.g., <13 g/dL for men and <12 g/dL for women; with hematocrit level of >2 standard deviations (SD) below published means for age] and/or EPO dependency [5–10]. This definition is mainly applicable to adult transplant patients. In the pediatric population, the diagnosis of anemia is made when the observed hemoglobin concentration is <5th percentile of normal when adjusted for age and sex.

The reported prevalence of PTA, mainly in the adult population, varies among studies [6–17]. In a study by Turkowski-Duhem et al., PTA was defined as a hemoglobin level of <13 g/dL for men and <12 g/dL for women, with a prevalence of 35.5% (32 patients) and 25% (23 patients) at 6- and 12-months posttransplantation, respectively [6]. In a retrospective cohort study of 162 pediatric transplant recipients, Yorgin et al. [7] defined anemia as a hematocrit level of >2 SD below published means for age or as EPO dependency to maintain a normal hematocrit level. The study showed that 67% of the recipients were anemic at the time of transplant and that the prevalence increased to 84.3% in the first month posttransplant. From 6 to 60 months posttransplant, the prevalence of anemia remained high at 64.2–82.2% [7]. In another retrospective study, Mitsnefes et al. found out that anemia was present in 59 of 231 (25.5%) of their pediatric patients 1 year after renal transplantation [8]. In this study, anemia was defined as Hb <11 g/dL, as used in the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Anemia of Chronic Kidney Disease [9]. It was suggested that the increased incidence of PTA is related to modern immunosuppressive therapy and that it is more likely a marker of allograft dysfunction rather than its cause. Kausman et al. [10] studied 50 pediatric renal transplant recipients and found that the overall prevalence of PTA was 60%, including 30% who were severely anemic. In this study, anemia was defined as Hb <11 g/dL (age 2–6 years), Hb <11.5 g/dL

(age >6–12 years), or Hb <12 g/dL (age >12 years), and severe anemia was defined as Hb <10 g/dL [10].

### Risk factors for posttransplantation anemia

Table 1 lists the many risk factors for PTA. As can be seen, some of these (e.g., inadequate ESRD management, insufficient diet resulting to iron, vitamin B12, folate deficiency, and drug-induced factors) are shared with patients with CKD who do not undergo transplantation.

The use of immunosuppressive agents [e.g., tacrolimus (TC), azathioprine (AZA), mycophenolate mofetil (MMF)] with direct antiproliferative effects on the bone marrow is the most common risk factor for PTA [6, 10, 11, 16]. Peter et al. compared the rate of anemia in pediatric patients treated with TC vs. cyclosporine (CsA) [18]. Eighty-five children on CsA therapy were compared with ten patients on TC. A matched-pair analysis for creatinine clearance was performed, revealing equal values in both groups. CsA-treated patients showed a clearance of 48 mL/min/1.73 m<sup>2</sup>, while TC-treated patients had a clearance of 46 mL/min/1.73 m<sup>2</sup>. Hemoglobin was 10.3 and 10.4 g/dL in the TC- and CsA-treated patients, respectively, and there was no significant difference in the degree of anemia between the TC- and CsA-treated children. Among those children with functioning renal allografts, there was a positive correlation between the hemoglobin level and creatinine clearance.

Other common causes of PTA are blood loss, either secondary to the transplant surgery or multiple phlebotomy postoperatively or during outpatient follow-up for monitoring of the renal allograft, and an insufficient diet that results in iron, vitamin B12, and folate deficiency. Rejection episodes also contribute to PTA [19–21]. To increase our understanding of the molecular events underlying anemia in acute rejection, Chua et al. [22] analyzed the gene expression profiles of peripheral blood lymphocytes (PBL) from four pediatric renal allograft recipients with acute rejection and concurrent anemia using DNA microarrays. An ‘erythropoiesis cluster’ of 11 down-regulated genes was identified in these anemic rejecting patients that was involved in hemoglobin transcription and synthesis and in iron and folate binding and transport. Additionally, some alloimmune response genes, including immunoglobulins, were simultaneously down-regulated [22]. Kidney allograft recipients may also be particularly susceptible to anemia in the immediate postoperative period for several reasons. First, ESRD anemia management may not have been ideal. Second, an impaired EPO production or release by the transplanted kidney may occur secondary to a delayed graft function. Finally, if chronic EPO therapy is stopped, the decrease in hemoglobin level is more marked and the

**Table 1** Risk factors for posttransplantation anemia

	Risk factors for posttransplantation anemia
	Immunosuppressive agents (e.g., azathioprine, mycophenolate mofetil, tacrolimus)
	Blood losses (during surgery or laboratory procedures)
	Inadequate ESRD anemia management prior to transplantation
	EPO resistance
	Poor EPO production by the transplanted kidney
	Sudden discontinuation of chronic EPO treatment posttransplantation
	Insufficient diet resulting in iron, vitamin B12, folate deficiency
	Drug-induced (e.g., ACE inhibitors, angiotensin-II receptor antagonists)
	Rejection episodes
	Delayed or impaired graft function
	Advanced donor age
	Viral infection (e.g., parvovirus B19, cytomegalovirus, Epstein–Barr virus, HIV)
	Malignancy or lymphoproliferative disorder
	Repeat renal allograft

ESRD, End-stage renal disease; EPO, erythropoietin; ACE, angiotensin converting enzyme; HIV, human immunodeficiency virus

recovery more prolonged than if the dose is tapered [23–25]. Other risk factors include infections, and a unique example of infection is pure red cell aplasia due to infection with parvovirus B19, which exhibits tropism for erythrocyte precursors, resulting in maturation arrest at the pronormoblast stage [26, 27]. Cytomegalovirus can directly inhibit hematopoiesis by involving not only bone marrow stroma, but also hematopoietic precursor and stem cells [28, 29]. An additional risk factor for PTA is a repeat renal allograft. Hemoglobin levels have been found to be higher in patients who received a first kidney transplant ( $13.2 \pm 1.9$  g/dL) than in those who received a second ( $12.8 \pm 1.9$  g/dL) or third transplant ( $12.7 \pm 2.1$  g/dL) [11]. Advanced donor age (>60 years) is another risk factor [11]. There are a number of theoretical reasons why an EPO-resistant state may develop after renal transplantation. Some are associated with CKD, including iron deficiency, ongoing hyperparathyroidism, and chronic inflammation [30, 31]. The use of angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists has been associated with PTA [11, 16, 32]. One explanation that has been proposed for the development of anemia associated with ACE inhibitors is the possible lower production of EPO associated with impaired renal blood flow [33]. Another proposed explanation is a possible decrease in renal oxygen consumption determined by sodium absorption in the proximal tubules that is regulated by angiotensin II [34, 35].

### What happens to EPO production and erythropoiesis posttransplantation?

Erythropoietin is mainly produced by the peritubular capillary endothelial cells in the kidneys, with a small

contribution by the liver (<10%). After a successful renal transplant, EPO levels usually normalize, and active erythropoiesis ensues, creating a functional depletion of iron [36]. However, PTA may occur due to EPO resistance, which is characterized by high serum EPO levels relative to the hemoglobin value, or by EPO deficiency, which is characterized by low levels of both EPO and hemoglobin. In adult studies with immediate graft function, serum EPO levels may be detected as early as the first to third posttransplant day, remain elevated for 9–15 days after transplantation, and decrease thereafter [37]. This observation may be less applicable in our current transplant population because of the widespread use of erythropoiesis-stimulating agents (ESAs).

In recipients with delayed graft function, a biphasic pattern is observed, with a first peak of EPO occurring 4–6 days posttransplant that is not associated with reticulocytosis or change in the hematocrit values [38–40]. A lag phase between the initial rise in serum EPO levels and the onset of reticulocytosis may be attributed to uremic inhibitors of erythropoiesis that persist in the immediate posttransplant period. Low serum EPO levels increase 3–8 days after the onset of diuresis and well before the serum blood urea nitrogen and creatinine reach their nadir [37]. EPO resistance has been partly attributed to the inflammatory status induced by surgical intervention and to the occurrence of infectious complications [41].

### Iron deficiency anemia in the posttransplant setting

Iron deficiency anemia is common in the pediatric ESRD population and after renal transplantation. Iron may be depleted at the time of renal transplantation because of

chronic blood loss and inadequate dietary intake during dialysis. Female patients are more prone to iron loss with menstruation. Kausman et al. showed a high rate of iron deficiency (30%) in 50 pediatric renal transplant recipients and identified serum iron as the parameter of iron metabolism associated with anemia [10]. There has been a debate as to the ideal marker for iron deficiency, particularly for patients requiring ESAs. The most accepted parameters for iron deficiency include ferritin and transferrin saturation (TSAT) [12, 42]. However, there are no reported studies regarding the acceptable serum ferritin and TSAT in the renal transplant population. Newer alternative markers of iron status, such as reticulocyte hemoglobin content, percentage of hypochromic red cells, and soluble transferrin receptor may be of value [43].

At the present time, there are no definitive criteria for iron deficiency anemia in posttransplant patients, even in the presence of normal serum creatinine. Thus, the criteria to define iron deficiency anemia in children with CKD who are treated with ESAs, namely serum ferritin of <100 ng/mL and TSAT of <20%, are suggested for the pediatric renal transplant recipients [23]. Specific iron-marker cutoffs for the diagnosis of iron deficiency anemia in children with CKD not treated with ESAs do not exist. The same is true for transplant recipients who are not on ESAs.

### Approach to posttransplantation anemia management

The high prevalence of PTA rationalizes the use of iron and ESAs in the posttransplant period, avoiding unnecessary blood transfusions among renal transplant recipients. Most of the recommendations on renal PTA management are based on adult studies with limited data on the pediatric population [8, 10, 44]. The European Best Practice Guidelines for Renal Transplantation recommend treating PTA in the same manner as anemia in CKD, although there is little evidence to support this recommendation [45].

The anemia workgroup at the Lisbon Conference on the Care of the Kidney Transplant Recipient advised initiating therapy for anemia when the hemoglobin drops below 11 g/dL [25]. According to the 2007 update of the KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in CKD, the selected hemoglobin target in patients receiving ESAs should be in the range of 11.0–12.0 g/dL and not greater than 13.0 g/dL [46]. Unfortunately, the optimal hemoglobin to be achieved with anemia therapy is unknown in the transplant population.

Only a limited number of studies have focused on ESA therapy in children with PTA. Yorgin et al. [7] reported that the mean dose of ESA required to effectively treat PTA was  $144 \pm 121$  units/kg/week, a dose similar to that required to

treat adults. In their study, Mitsnefes et al. [8] were unable to evaluate the benefits of recombinant EPO therapy due to the low number of patients who were treated with EPO during the first year after transplantation. However, they did observe a more frequent use of EPO in children on TC, MMF, and prednisone therapy, which strongly suggests that the increase in PTA is related to the current use of these newer immunosuppressive agents [8].

Iron deficiency is the most common cause of hyporesponsiveness to ESAs, and pharmacological therapy with either an oral or parenteral iron preparation is recommended. Iron supplementation should begin via the oral route to maintain a TSAT >20% and a ferritin level of 100–800 ng/mL [25]. If oral supplementation is inadequate to maintain these parameters, parenteral iron should be administered. Vitamin B12 and folate supplementation may be required if insufficient levels are noted.

Oral iron is best absorbed if given on an empty stomach or with vitamin C-containing foods. If ferrous sulfate is used, the usual adult dose is one 300 mg tablet (containing 60 mg elemental iron) given three to four times daily. The pediatric dose is 2–6 mg/kg per day of elemental iron given in two to three divided doses [47, 48]. The side effects of oral iron therapy include constipation, diarrhea, nausea, and abdominal pain.

The parenteral administration of iron has been proven to be safe in pediatric ESRD patients on hemodialysis [49–53]. Potential side effects associated with intravenous (IV) iron administration include acute allergic reactions, such as rash, dyspnea, wheezing, and anaphylaxis. These side effects are predominantly seen in iron dextran as compared to the newer generation of IV iron (e.g., sodium ferric gluconate and iron sucrose) which are associated with less severe and less frequent adverse reactions [49, 54]. The cause of these immediate adverse reactions are not completely understood, but several mechanisms have been identified, including the direct release of mediators by mast cells, without stimulation by immunoglobulin E or immune complexes [55]. Warady et al. recommended that the starting dose of IV sodium ferric gluconate (SFG) complex be 1.0 mg/kg, not to exceed 125 mg, with adjustments made according to TSAT and/or serum ferritin levels [52]. Gillespie et al. analyzed data from 14 pediatric renal transplant recipients who received SFG for PTA during a 28-month period [56]. Patients received one to six doses of SFG to yield a total dose of 100–1000 mg or 2.7–23.7 mg/kg. The largest doses given during a single infusion ranged from 1.9 to 6.4 mg/kg. There was a modest, yet statistically significant, increase in mean hemoglobin and hematocrit values, while changes in TSAT and EPO dose were not statistically significant. Adverse events, including muscle pain, pain at the site of infusion, hypertension, foot numbness, and dizziness, were reported in three patients. Since IV iron

therapy results in a faster repletion of iron stores, does not require long-term patient adherence, and is relatively safe, its use may be beneficial for the treatment of severe iron deficiency anemia in transplant recipients [57]. More recently, newer IV iron preparations have appeared in the market, including ferumoxytol and ferric carboxymaltose. These latest IV iron preparations do not contain a requirement for a test dose, and a much higher dose of iron can be delivered as a single administration.

To decrease the incidence of iron deficiency anemia among transplant recipients, their diet should contain iron-fortified whole grains, seafood, dried beans, lean red meats, liver, spinach, and dried fruits such as raisins, prunes, dates, and apricots. There are two forms of dietary iron—heme and nonheme iron. The former is commonly found in animal food sources and is better absorbed than the latter, which is found in plant food sources. The recommended dietary allowances for iron for infants and children are the following: for infants 7–12 months old, males (M) and females (F)=11 mg/day; for children ages 1–3 years, M and F=7 mg/day; aged 4–8 years, M and F=10 mg/day; aged 9–13 years, M and F=8 mg/day; aged 14–18 years, M=11 mg/day and F=15 mg/day [58]. Signs of iron deficiency anemia include weakness, slow cognitive and social development, difficulty in maintaining body temperature, decreased immune function, and glossitis.

The use of iron supplementation and ESAs should preclude the need for blood transfusion, which should be limited to patients with symptomatic anemia or acute and severe blood loss. Blood transfusions expose a recipient to soluble and cell-bound antigens, which can activate the recipient's immune system, possibly leading to transfusion complications [59, 60]. Exposure to alloantigens, in particular leukocytes, can lead to T-cell activation and proliferation and to increased natural killer cell function. It can induce humoral immunity, as reflected by the formation of human leukocyte antigen alloantibodies. Thus, if needed, leukocyte-free blood products are used to prevent graft-versus-host reactions in transplant recipients.

### Future perspectives

Anemia is fairly common among pediatric renal transplant recipients. Larger prospective and randomized controlled trials are needed to improve our knowledge on PTA, in particular the determination of optimum hematologic status among pediatric renal transplant recipients. Recognition of PTA through regular screening and meticulous evaluation of the multiple factors that may contribute to it are recommended. Clinical practice guidelines should be developed for the evaluation and management of this unique group of patients.

### Questions (answers are provided following the reference list)

1. In a functioning renal allograft, serum erythropoietin is detected within:
  - a. First 72 h posttransplantation
  - b. Day 4–5 posttransplantation
  - c. Day 6–7 posttransplantation
  - d. After 1 week posttransplantation
2. The most accepted parameters for monitoring iron deficiency anemia are the following:
  - a. Hemoglobin and ferritin
  - b. Ferritin and total iron binding capacity
  - c. Ferritin and transferrin saturation
  - d. Hemoglobin and transferrin saturation
3. The following are risk factors for posttransplantation anemia, except:
  - a. Sudden discontinuation of EPO treatment posttransplantation
  - b. Advanced donor age
  - c. Posttransplant lymphoproliferative disorder
  - d. Absence of rejection episode
4. The most common cause of unresponsiveness to an erythropoiesis-stimulating agent is:
  - a. Use of immunosuppressive drugs
  - b. Iron deficiency anemia
  - c. Use of ACE inhibitors
  - d. Viral infection
5. Based on the Report of the Lisbon Conference on the Care of the Kidney Transplant Recipient, the therapy for posttransplantation anemia begins when:
  - a. Hemoglobin drops below 10.0 g/dL
  - b. Hemoglobin drops below 11.0 g/dl
  - c. Hemoglobin drops below 12.0 g/dl
  - d. Patient becomes symptomatic

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#### Answers:

1. a
2. c
3. d
4. b
5. b