IN THE NAME OF GOD

Anemia In kidney Transplant Recipients

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Approach to Anemia in kidney transplantation Recipient

- ✓ Anemia, usually defined as Hb <12 g/dL in women and <13 g/dL in men, is a **common finding before and after** kidney transplantation

- ✓ Anemia is present in almost 90 percent of patients within the **first month posttransplant**, the prevalence falls to 34 to 45 percent among patients **more than one year posttransplant**

- ✓ At the time of transplantation, most adult patients can be defined as anemic

Transplantation 2012; 93:923.
Up to date 2020

Approach to Anemia in kidney transplantation Recipient

- Mean Hb levels rise to above 11 g/dL by three months posttransplant and to above 12 g/dL at 6 to 12 months posttransplant.

- Development of acute or chronic allograft dysfunction is almost invariably accompanied by worsening anemia.

J Am Soc Nephrol 2002; 13:794
BMC Nephrol 2018; 19:252.

RISK FACTORS AND PATHOGENESIS

varies by **time from transplant** and by **patient characteristics**

Common risk factors for anemia:

- ❑ female gender
- ❑ age
- ❑ allograft dysfunction
- ❑ use of ACEI OR ARBs
- ❑ choice of immunosuppressive agents

❖ Several studies have found that **donor type**, plays **no role** in the occurrence of anemia

Early posttransplantation Anemia

- surgical blood loss
- frequent phlebotomy
- Dilutional anemia
- allograft dysfunction
- increased donor age
- iron deficiency
- **Elevated Interleukin -6 & Hepcidin**

- Ferritin measurements have inconsistently reflected iron stores among kidney transplant recipients and do not always correlate with anemia
- In general, EPO levels begin to rise **on posttransplant day 2 and reach a fourfold elevation for two to three weeks**
- Early EPO surges **may be inefficient** in correcting anemia since the hormone seems to be inefficient in this **persistent uremic setting**.
- Anemia may also correct in some patients despite relatively low EPO levels

Anemia following renal transplantation. Transplant Proc 2003; 35:302.

Cont…

Cold and warm ischemia times do not correlate with EPO levels.

patients with delayed graft function have a slower rise in EPO levels.

Interstitial fibrosis and tubular atrophy in the donor kidney at the time of transplant associate independently with anemia **at 12 months posttransplant.**

In the first three months posttransplant, endogenous erythropoietin production increases dramatically and low iron stores may contribute to persistent anemia.

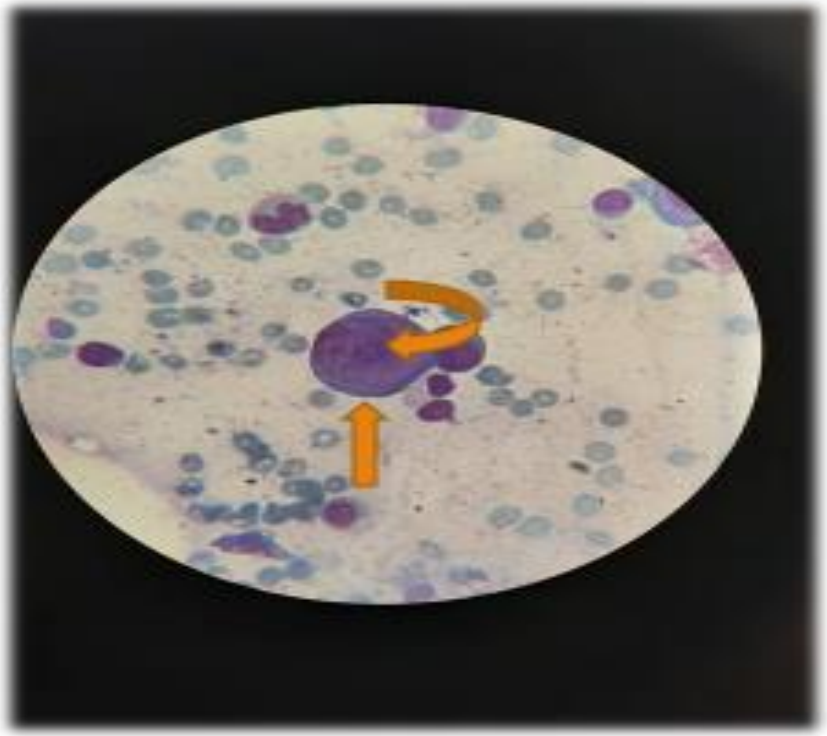
Am J Nephrol 2013; 38:267.

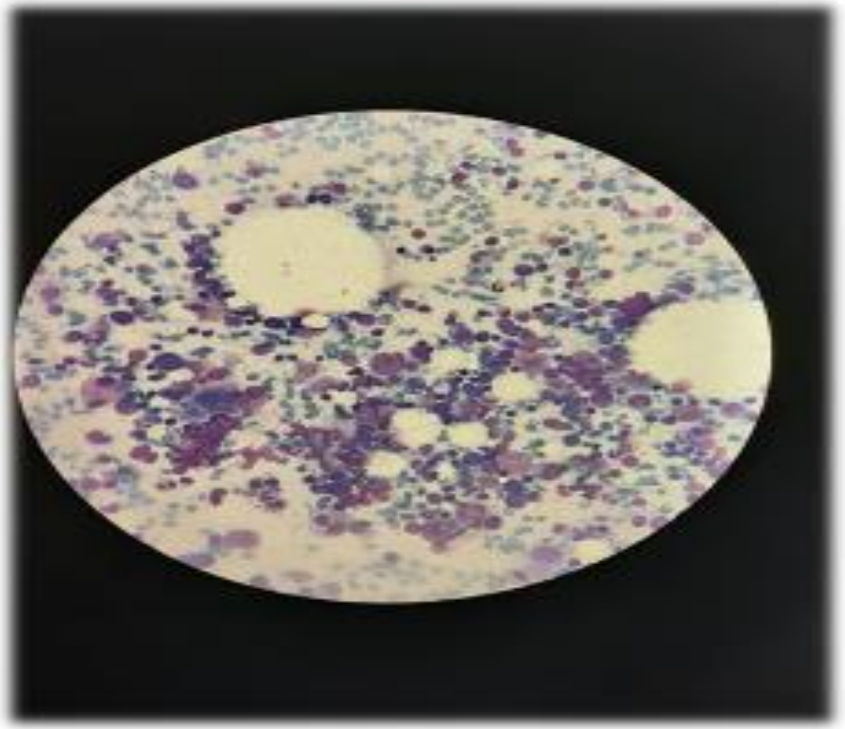
Later (>3 months) posttransplantation

- Immunosuppressive agents & Other medications
- Graft dysfunction and rejection
- Donor and recipient characteristics
- Comorbid conditions
- Nutritional abnormalities
- **Infections:**

parvovirus B19, EBV, CMV, BK virus (polyomavirus), varicella-zoster virus, tuberculosis, herpesviruses, and staphylococci.

parvovirus B19 Anemia





Bone marrow aspirate showing hypocellular with reduced erythropoiesis and maturation arrest. **Arrows pointing a giant pronormoblast with vacuole**

The underlying factors causing anemia in the setting of rejection

- ✓ suboptimal kidney function
- ✓ more intensified immunosuppression
- ✓ acute inflammation
- ✓ chronic inflammatory state leading to EPO resistance
- ✓ Elevated Interleukin -6

Acute rejection can lead to a rapid decrease in EPO levels that is reversible on treatment of rejection

Nephrol Dial Transplant 24: 1015–1023, 2009
Clin J Am Soc Nephrol 6: 1794–1801, 2011.

Immunosuppressive agents

1. **The antimetabolites** azathioprine, mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium (EC-MPS):

- ✓ cause marrow suppression and anemia
- ✓ the mean relative decrease in Hb concentration may only be 0.2 to 0.3 g/dL, respectively

2. Sirolimus:

- ✓ causes marrow suppression and anemia, particularly **early after initiation**, but the effect may lessen over time
- ✓ This effect on erythropoiesis **may be more severe than that observed with MMF**
- ✓ Anemia has also been associated with the use of the other available mammalian mTOR inhibitors, **everolimus**

sirolimus and tacrolimus and cyclosporine can also cause hemolytic anemia. They are associated with the hemolytic uremic syndrome

Am J Transplant 2004
Kidney Int 2009; 76:376

Pathophysiology 0f SLR-induced anemia

- Antiproliferative effect
- Increase in EPO resistance
- Chronic inflammatory state caused by IL10
- Functional iron deficiency mediated by hepcidin
- Anemia has been reported in as many as60% of patients receiving sirolimus

Cont…

- A decrease in MCV has also been described with **sirolimus**, which may be misinterpreted as evidence of **iron deficiency**

- In general, the calcineurin inhibitors do not cause marrow suppression directly and do not typically cause anemia.

- A positive correlation with **tacrolimus** use and anemia was reported in one study

Other medications

- ✓ The use of ACE inhibitors and ARBs has correlated with anemia in a dose-related fashion in kidney transplant patients
- ✓ Ganciclovir causes bone marrow suppression
- ✓ Trimethoprim-sulfamethoxazole causes myelosuppression and anemia.

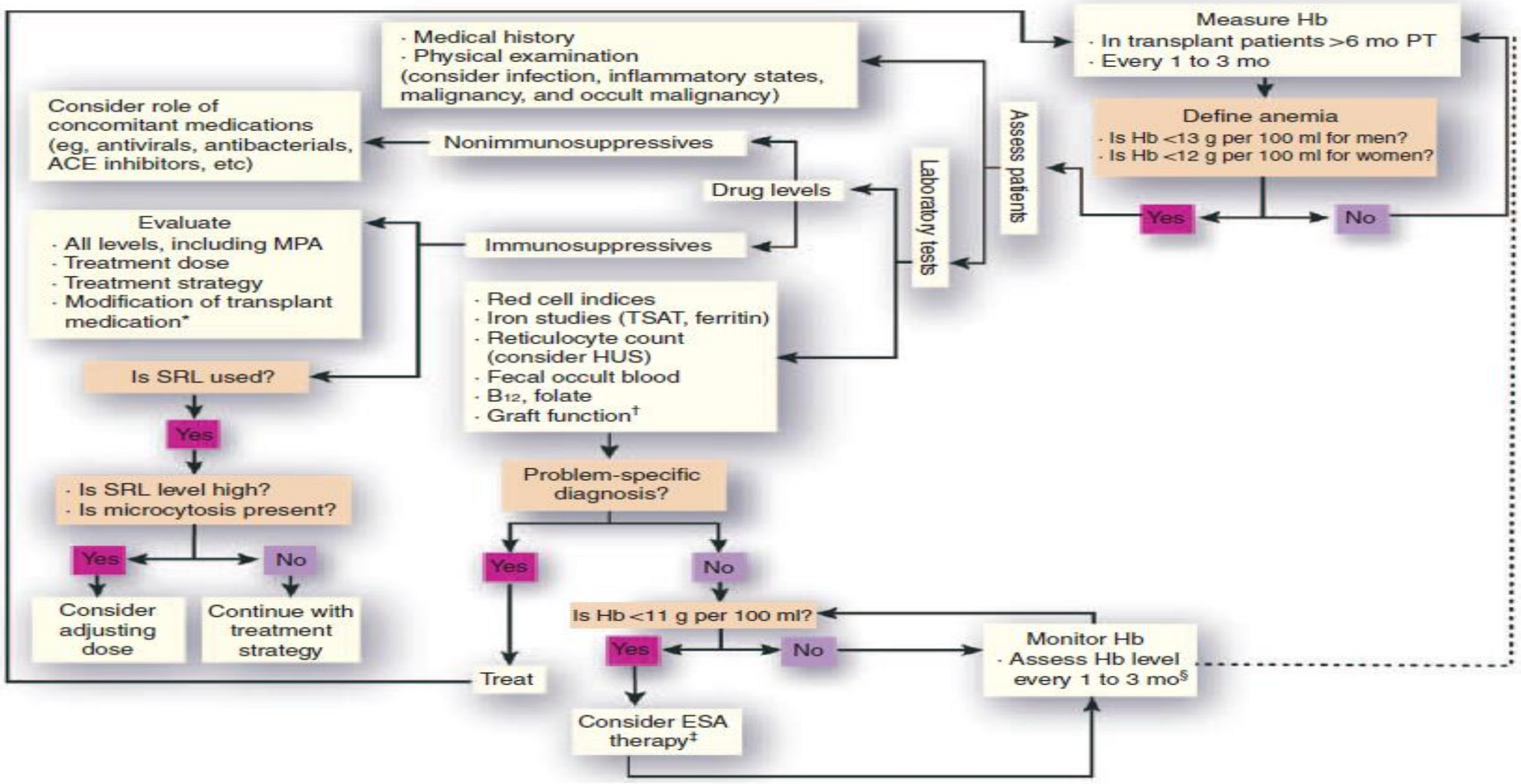
Comorbid conditions

- Hb concentrations have decreased with new diagnoses of heart failure, gastritis, peripheral vascular disease, cerebrovascular accident, and other comorbid conditions

- **polycystic kidney disease** is associated with greater EPO production, just as in **nontransplant CKD**, and is protective against anemia

- **secondary hyperparathyroidism has not been associated** with posttransplant anemia in larger retrospective analyses

A clinical approach for the management of



SCREENING

At most transplant centers, a CBC is obtained:

- at least **weekly** for the **first three months**
- every **two to four weeks** for **a year**
- **monthly to every three months thereafter**.

SCREENING…

- All patients **should have** an assessment of iron stores (serum iron, TSAT, serum ferritin).

- In patients who are **less than three months** posttransplant, **do not perform** a further diagnostic evaluation for anemia **unless** such patients develop worsening anemia.

- In patients whose Hb levels **fail to normalize** by **three months posttransplant**, or **new-onset anemia** perform a diagnostic evaluation for anemia.

DIAGNOSTIC EVALUATION

- Assessment for history of blood loss
- Assessment for symptoms and/or signs of infection (eg, fever, malaise)
- Assessment of dietary intake
- Assessment of medication history
- Assessment of kidney allograft function
- Reticulocyte count
- Iron studies
- Testing for blood in stool
- Testing for presence of hemolysis
- Testing for folate and vitamin B12 deficiency

do not routinely evaluate all anemic transplant recipients for infection with parvovirus B19 or other viruses.

DIAGNOSTIC EVALUATION…

- **The concurrent presence of leukopenia, thrombocytopenia, and/or acute renal allograft dysfunction suggests the following potential causes of anemia**:

- **Global myelosuppression** is commonly caused by immunosuppression, nutritional deficiency, and prophylactic medications but can also **be seen** in the setting of **viral infections.**
- **Hemolytic uremic syndrome** should be suspected when anemia is associated with renal dysfunction, thrombocytopenia, and evidence of microangiopathic hemolytic anemia.

- **the presence of anemia alone**, without leukopenia or thrombocytopenia, along with a **low reticulocyte count** and no nutritional deficiencies suggest **parvovirus B19 infection or possibly anti-erythropoietin antibodies**

TREATMENT

Target hemoglobin levels:

The optimal target Hb level for kidney transplant recipients is not well defined and may differ depending upon **renal allograft function**.

> Exp Clin Transplant. 2020 Feb;18(1):27-33. doi: 10.6002/ect.2018.0283. Epub 2019 Jun 10.

Treating Posttransplant Anemia With Erythropoietin Improves Quality of Life but Does Not Affect Progression of Chronic Kidney Disease

Taryn Pile [1], Martin Raftery, Raj Thuraisingham, Christopher J Kirwan, Steven Harwood, Muhammed M Yaqoob

Affiliations + expand

PMID: 31180297 DOI: 10.6002/ect.2018.0283

Conclusions: Treatment of anemia in kidney transplant recipients to a hemoglobin level of 11.5 to 13.5 g/dL with erythropoietin improves some quality of life scores. The treatment was safe and not associated with adverse outcomes. There were no changes in rate of decline of graft function.

Materials and methods: In this single-center exploratory, open-label randomized controlled trial, kidney trans-plant recipients with anemia 3 months posttransplant were either treated with epoetin beta to a hemoglobin target level of 11.5 to 13.5 g/dL (n = 28) or given no treatment (n = 27). Treatment effects on graft function and health quality of life were assessed.

TREATMENT

Use of iron

intravenous or oral iron provides better treatment among kidney transplant patients?

- In patients with iron deficiency, administer IV iron therapy rather than oral iron therapy.

- **oral iron** has been inadequate to replace or maintain adequate iron stores and **may bind with immunosuppressant medications, such as MMF/MPS**.

Dose separation 2 hour between MMF and iron

- Posttransplant erythrocytosis may develop in patients receiving oral iron supplementation.Hb often decreases **four weeks after iron discontinuation** in this setting

- Several IV iron formulations are available .All of these products are equally effective in treating iron deficiency

Use of ESAs

- **do not use ESAs in the immediate** transplant period.

- With anemia of CKD occurring **more than three months** posttransplant in the iron-replete patient, **may initiate** an ESA

- In patients who were previously receiving ESA therapy, **stop the ESA at the time of transplant** because of **hyporesponsiveness to ESAs** in the early posttransplant period, the **thrombotic and cardiovascular risks** of these drugs.

Use of ESA therapy in patients with delayed graft function is **controversial** and responsiveness to ESAs may be poor.

Use of blood transfusions

- avoid the use of blood transfusions, if possible, because of the risk of sensitization, which may increase the risk of rejection.
- if a blood transfusion is necessary, CMV-seronegative and/or filtered blood products are preferable.
- Irradiation of blood products is probably unnecessary

Treatment
Approach based on time from transplant

- ❑ Patients awaiting transplant
- ❑ Patients perioperative and early posttransplant
- ❑ Patients later (>3 months) posttransplant

Patients perioperative and early posttransplant

target Hb levels of >10 g/dL as these levels appear safe and may reduce cardiovascular events in the early posttransplant period

limit **RBC transfusions** to patients with an **Hb <7 g/dL or <8 g/dL in those with preexisting cardiovascular disease**

In patients with **an Hb <10 g/dL and evidence of iron deficiency** ([TSAT] ≤30 %and serum ferritin level ≤500 ng/mL) at the time of transplantation& immediately post-transplantation , administer IV iron (typically as **iron sucrose**)

ESA therapy in the immediate posttransplant setting shortens the time to improved Hb but has not been shown to improve clinical outcomes

IJKP TRANSPLANTATION

Effect of Erythropoietin on Kidney Allograft Survival
Early Use After Transplantation

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Fatemeh Pour-Reza-Gholi,[1,2] Fariba Samadian,[1,2]
Soudabeh Farhangi[1]

Materials and Methods. Forty kidney transplant candidates with a hemoglobin level of 8 g/dL to 10 g/dL were randomized to receive either erythropoietin (PD-Poietin) or placebo for the first posttransplant week. They were followed up for 6 months and serum creatinine levels, glomerular filtration rate (GFR), allograft rejection episodes, and graft loss were compared between the two groups.

Conclusions. Our findings suggest that **erythropoietin may have beneficial effects on graft function if administered early after transplantation.** Erythropoietin can be used for all kidney transplant recipients for protecting the allograft due to **its effects on tissue oxygenation.**

Patients later (>3 months) posttransplant

- ❑ Patients with stable graft function
- ❑ Patients with a failing graft

Patients with stable graft function

eGFR ≥45 mL/min/1.73 m^2

- In patients who are receiving **higher doses** of an antimetabolite (eg, MMF 1000 mg twice daily or EC-MPS 720 mg twice daily) **reduce the dose of the antimetabolite, typically by 50 percent, if anemia is severe**

- In patients who are receiving **ganciclovir** and/or **TMP-SMX,** make sure appropriately dose for the level of renal allograft function.

do not routinely dose reduce or discontinue these agents to treat anemia.

- If anemia persists : initiate an ESA in patients with an **Hb <9** g/dL and target Hb levels of 10 to 11.5 g/dL.

Observational studies have suggested that mortality **may be increased** with **Hb levels >12.5 g/dL**

Patients with a failing graft

- Patients with stage 4 to 5 CKD frequently become anemic, and ESA therapy may be required

- The management of anemia is **similar** to that in the **general CKD or ESRD** population, **except that higher doses of ESAs** may be required due to chronic inflammation.

- Initiate ESA therapy when the **Hg is 9 to 10 g/dL** and the iron stores appear adequate.

In patients with higher risks from ESA therapy, we generally avoid ESAs until anemia is more severe (Hb <9 g/dL)

- Patients who have returned to **dialysis** and are **resistant to ESAs may** benefit from **allograft nephrectomy**

Clin Kidney J 2013; 6:156

PROGNOSIS

- anemia was associated with an increased risk of mortality (Similar results were observed when anemia was defined as <11 g/dL).
- Hb levels, were negatively associated with graft loss.
- Randomized trials are needed to determine if ESA therapy for anemia improves survival in kidney transplant recipients.
- cardiovascular disease is the leading cause of death in diabetic kidney transplant recipients.

Am J Transplant 2007; 7:818.
Uptodate2020

SUMMARY

- ✓ Anemia, usually defined as Hb <12 g/dL in women and <13 g/dL in men, is a common finding **before and after kidney transplantation**

- ✓ The pathogenesis of anemia posttransplant varies by time from transplant and by patient characteristics.

- ✓ kidney transplant recipients should be regularly screened for anemia after transplantation with a CBC . a CBC is obtained **weekly for the first three months**, then **every two to four weeks out to one year** and then **monthly to every three months thereafter**.

- ✓ ***Persistent*** Anemia (ie, Hb levels that fail to normalize at **three months posttransplant**) or **new-onset** anemia should undergo a diagnostic evaluation to determine the cause of anemia.

- ✓ The general principles of anemia management in patients with CKD or ESRD also apply to the treatment of anemia in kidney transplant recipients. the selection of individual therapy depends upon **the severity of anemia and the presence of iron deficiency**


Have A
Nice Day !