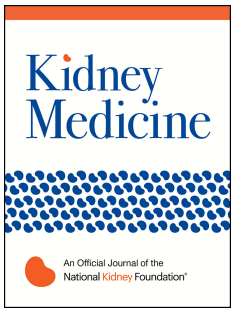

Treatment Options for Anemia in Kidney Transplant Patients: A Review

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Treatment Options for Anemia in Kidney Transplant Patients: A Review

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ABSTRACT

Anemia is common after kidney transplantation. The etiology may be multifactorial including both causes of anemia in the general population and more specific causes unique to the kidney transplant setting. Post-transplant anemia, particularly when severe, may be associated with adverse effects including graft failure, mortality, and a decline in kidney function. After careful investigation, having excluded or treated reversible causes of anemia, treatment of anemia in patients with a kidney transplant is based on iron supplementation and/or erythropoiesis stimulating agents though there are no specific guidelines on anemia management in this patient population. Iron therapy is often needed, but optimal and safe iron deficiency management strategies remain to be defined. Evidence suggests that erythropoiesis stimulating agents are safe and potentially associated with favorable outcomes. Better graft function has been reported upon ESA use targeting hemoglobin levels higher than those recommended in the general chronic kidney disease population with no apparent increased risk of cardiovascular events. These results require further investigation. Data on the use of hypoxia-inducible factor inhibitors are limited. Prevention and treatment of anemia in kidney transplantation can improve patients' quality of life, life expectancy, allograft function, and survival.

Key words: anemia – kidney transplantation – iron – erythropoiesis stimulating agent – graft failure – HIF-inhibitors

Introduction

Normocytic normochromic anemia represents a frequent complication in patients suffering from chronic kidney disease (CKD) and is associated with several adverse clinical outcomes (1). Successful kidney transplantation (KT) may potentially correct anemia. Yet up to 20-51% of kidney transplant recipients (KTRs) are anemic at various time points after transplantation (2-4). Post-transplant anemia is usually distinguished between early and late. Early anemia (up to six months after transplantation) has a prevalence of about 50%, whereas late anemia occurs after six months in 23-35% of transplanted patients (5, 6).

Post-transplant anemia is associated with reduced exercise capacity, cognitive decline, chronic fatigue, and impairment in quality of life (7, 8). Moreover, a growing number of observations indicate that anemia can be negatively associated with long-term clinical outcomes in KT including graft failure, mortality, and a decline in kidney function. It is thus reasonable to treat anemia in KTRs, probably starting as soon as possible after transplantation (5), although there are no proper or accurate guidelines for management of anemia in this patient population. KDIGO Guideline Transplant Recipients (9) and the position statement of the European Renal Best Practice Group (10) mention treating anemia in KT by following management guidelines for anemia in CKD.

The aim of the present review is to provide an update on post-transplant anemia in adult KTRs. Anemia in pediatric KTRs has recently been described elsewhere (11) and will not be discussed here.

Causes of Post-Transplant Anemia

There are many potential causes of post-transplant anemia (Box 1).

Allograft function strongly correlates with the prevalence and severity of anemia (12, 13). Erythropoietin (EPO) secretion by the graft occurs within a few days of transplantation, though it connects to effective erythropoiesis weeks after, through a second peak of EPO release depending on the recovery of kidney function (14). Serum EPO levels may fluctuate in KTRs according to kidney function level (15). EPO production decreases with the decline in GFR of the transplanted graft (13), and lower EPO levels are associated with poorer graft function (15). A rapid decrease in EPO levels can be caused by acute rejection episodes (16). Besides EPO deficiency, a EPO-resistant state may also be involved in the pathophysiology of post-transplant anemia, possibly related to risk factors persisting (iron deficiency, inflammation, hyperparathyroidism) or acquired in the posttransplant milieu (infections, myelotoxic drugs) (15).

Iron deficiency is highly prevalent in KT and may contribute to both early and late anemia. Increased iron consumption due to increased EPO production by the allograft, and blood loss (transplant surgery, repeated sampling, use of anticoagulants, return of menstrual cycle, malignancies) may cause an absolute iron deficiency (17). On the other hand, low-grade inflammation, and use of mTOR inhibitors promote the upregulation of hepcidin, leading to reduced iron availability (functional iron deficiency) for erythropoiesis (17). Folate and vitamin B_{12} deficiency can also be detected because of poor dietary intake, requiring nutritional supplementation (18).

Several pathogens, mainly viruses, may increase the risk of anemia by direct bone marrow suppression or indirect effects such as increased inflammation causing impaired erythropoiesis (19, 20). The time of infectious disease onset is usually in the first few months after transplant surgery, consistent with the stronger immunosuppression therapy

at that period (21). However, parvovirus B19 infection, strongly suggested by a very low percentage (<1%) in the reticulocyte count, may occur as early as within 2 weeks after KT (22).

Medication-induced anemia may be considered when other etiologies are at least apparently absent (12); an algorithm to manage drug-induced anemia in recipients of solid organ transplant has recently been suggested (23). Immunosuppressive drugs (calcineurin inhibitors, mTOR inhibitors, anti-thymocyte globulin, antimetabolites), antivirals (ganciclovir and valganciclovir), and antimicrobials (trimethoprim-sulfamethoxazole), can, directly or indirectly, suppress the bone marrow causing anemia (6, 23). Several other drugs that may be used in KTRs can cause hemolytic or megaloblastic anemia (24). Chronic use of proton-pump inhibitors may impair intestinal iron absorption resulting in iron deficiency (25). Other medications associated with anemia in KTRs are renin-angiotensin system (RAS) inhibitors (13). After RAS activation, angiotensin II enhances erythropoiesis by increasing EPO secretion through tubulointerstitial ischemia (26), stimulating erythroid progenitors (27), and reducing hepcidin (28). While the RAS contribution to erythropoiesis may be imperceptible in the general population (29), RAS blockade may have a hematocrit-lowering effect in patients with immunosuppression (30). Such action by RAS inhibitors is exploited in the treatment of posttransplant erythrocytosis (12, 31).

Consequences of Post-Transplant Anemia

Decline of kidney function

Recent findings indicate that KTRs with anemia may experience a decline in eGFR over time. In a retrospective analysis comparing eGFR at 2 years and at 6 months,

patients with late post-transplant anemia showed a decline by 2.26 ml/min/1.73 m^2, while patients without anemia had an increase by 3 ml/min/1.73 m^2 (4). The difference between the two groups proved statistically significant ($P<0.05$).

Further evidence concerning an association between post-transplant anemia and eGFR decline, in particular the role of anemia correction on the decline rate, is reported below in the section on erythropoiesis stimulating agent (ESA) therapy.

Graft failure

A meta-analysis addressing the effect of anemia on graft survival including eleven observational studies and 11,632 KTRs reported a consistent association between anemia and poor graft outcome (32), as confirmed by several subsequent studies (2, 4, 33-35). During a mean follow-up time of 5.4 years, KTRs with both early (6 months) and late (2 years) anemia had a significantly higher percentage of graft failure at 4 years than did patients without anemia (4). In a cohort of 1139 KTRs (412 anemic), during a median 5.5 year follow-up the presence of severe anemia (Hb <11 g/dl) was significantly associated with death-censored graft failure, the association being weaker for mild anemia (2).

A retrospective analysis on the association between graft survival and temporal changes in Hb values during the first 90 days after surgery, rather than Hb values at specific time-points, showed that KTRs with no Hb increase (> 0.5 g/dl/month in at least one interval) had an increased risk of death-censored graft failure (the primary outcome of the study). It should be noted that neither rate nor timing of the Hb increase correlated with the primary outcome (36).

Cardiovascular complications

Cardiovascular disease (CVD) is frequent after KT and comprises the leading cause of mortality (37). Anemia is a modifiable risk factor for CVD development in KTRs (38).

Post-transplant anemia proved a potentially modifiable correlate of de novo congestive heart failure (CHF), which in turn was a predictor of death (39, 40). Anemia also proved an independent risk factor for left ventricular growth 1-5 years after transplant, and both anemia and left ventricular hypertrophy are associated with an increased risk of mortality (41). An inverse association between Hb concentration and E/e', an echocardiography index of left ventricular filling pressure, was reported in KTRs (42). These results suggest that, through the increase in left ventricular stiffness and pressures caused by the impairment of left ventricular relaxation, anemia may contribute to heart failure in KTRs (42).

A recent meta-analysis and systematic review demonstrated a significantly increased risk of CV death and major adverse cardiovascular events in anemic KTRs as compared to those without anemia (35).

Mortality

Studies examining the association of post-transplant anemia with mortality yielded conflicting results. In a prospective cohort study, at the end of the follow-up period of 4 years anemia was associated with an increased risk of mortality (43). A retrospective analysis showed that every increase by 1 g/dl in Hb levels reduced mortality by 18% (44). Another retrospective series reported an association between post-transplant anemia at 12 months and an increased risk of mortality (45). Likewise, anemia shortly after KT (3-12 months) was associated with an increased risk of mortality up to 10 years'

follow-up independently of kidney function (46). Both early and late PTA was associated with higher mortality at 4 years (4).

Other studies, however, did not confirm the association of post-transplant anemia with mortality. These include two retrospective studies, one with a follow-up of 8 years (3) and the other involving 887 KTRs evaluated at 12 months (47) and a prospective cohort study with a follow-up of 5 to 6 years (48).

One possible explanation for the discrepancies between studies examining the correlation of post-transplant anemia and mortality is that in studies showing no association, most patients had mild anemia (mean Hb > 11 g/dl). Thus, in a cohort study of 1139 KTRs the association between anemia and mortality was related to severity. While severe anemia (Hb <11 g/dl) proved to be strongly associated with mortality, mild anemia was not (2).

Treatment of Post-Transplant Anemia

The approach to anemia in a KTR should begin with a diagnostic workup to search for any underlying reversible cause (Figure 1). Having excluded or treated reversible causes of anemia, the recommended treatment for post-transplant anemia is iron preparations and/or ESAs.

Iron therapy

Data on how iron deficiency affects the clinical outcome of KT are limited. Better graft function and graft survival was associated with higher ferritin concentration (49). By contrast, no association between graft failure and the percentage of hypochromic erythrocytes (an indicator of iron status) was found in 438 KTRs (50). However, an independent association between the percentage of hypochromic erythrocytes and all-

cause mortality was reported (50), while in another trial- iron deficiency was independently associated with all-cause mortality even in the absence of co-existing anemia (51). Potential mechanisms include direct effects on cardiac and skeletal muscle metabolism. Iron deficiency may compromise cardiac and skeletal muscle cell function by decreasing intracellular oxygen availability and impairing the Krebs cycle (17). Furthermore, iron deficiency stimulates the expression and concomitant cleavage of fibroblast growth factor 23 (FGF23) (52). FGF23 proved an independent risk factor for graft loss and cardiovascular and all-cause mortality in KTRs (53, 54), likely due to off-target effects of high FGF23 levels (17). Whether FGF23 may represent an intermediate between iron deficiency and adverse outcome in KT remains to be elucidated.

There have been few studies addressing iron supplementation in KTR, and it remains unclear whether intravenous (iv) iron is better than oral iron. Oral iron preparations may be preferred for their ease of administration and low cost. However, the occurrence of gastro-intestinal side effects, impaired intestinal absorption, and poor patient adherence restrict the effectiveness of oral iron. Newer oral iron agents (ferric maltol, ferric citrate, and sucrosomial iron), which are better tolerated and more effective than traditional iron salts (55), have not been evaluated in KTRs. However, oral iron may be harmful to the gut microbiota (56), and recent studies suggest that the host microbiota profile exerts an important effect on KT outcome (57). Compared with oral preparations, iv iron has a higher capacity to correct iron parameters and to increase Hb levels, with a similar safety profile in both dialysis and nondialysis CKD patients (58). In a small retrospective study, administration of 800 mg iv iron sucrose was associated with a significant increase in Hb levels and a reduced eGFR decline (59). No increased risk of

infection was associated with iv iron (polymaltose) as compared to oral treatment (ferrous sulfate) (60). Newer iv iron agents (ferric carboxymaltose, ferric derisomaltose) allow for fewer infusions and reduced risk of serious hypersensitivity reactions (55). The safety and tolerability of iv ferric carboxymaltose has been demonstrated (61). One potential concern when using iv iron polymaltose and ferric carboximaltose is that hypophosphatemia may worsen due to a sharp change in the metabolism of FGF23 (62). This risk is especially present in KTRs who continue to have elevated PTH levels after KT. Out of 23 KTRs who had received up to 1000 mg ferric carboxymaltose, however, only one patient required short-term phosphate supplementation (63). Understanding the patient-related clinical impact of hypophosphatemia induced by iv iron requires further investigation (64).

Iron supplementation may be beneficial in KTR, and iv administration may comprise a reasonable choice (5). However, several issues are still unresolved. It remains to be definitively established how far iron depletion/administration affects long-term clinically significant outcomes. The role of iv iron in conjunction with ESA administration needs to be further clarified (65). Also, no effective treatment regimen to counteract disturbances of iron metabolism in KT has been devised. A proactive high-dose iv iron regimen proved to be safe and superior to a low-dose iv iron administered reactively in a recent study in HD patients (66), but no such therapeutic strategy has been investigated in the setting of KT. Thus, prospective studies are warranted to define optimal and safe iron deficiency management strategies in KT.

ESA therapy

ESA therapy has revolutionized the care of anemic patients with CKD (1) but is currently thought to be underutilized in KTRs (65). The results of randomized controlled studies (RCTs) focusing on improvement of Hb levels and graft outcome in ESA-treated KTRs are summarized in Table 1.

In early post-transplant anemia, the first RCT enrolled patients with Hb < 12 g/dl in the immediate post-transplant period who were randomized to subcutaneous epoetin beta thrice weekly to target Hb > 12.5 g/dl, or else to placebo. No difference between groups was observed in graft function or Hb level at the 3-month end of the study, though the ESA group reached the Hb target faster, had a higher Hb increase from baseline, and required fewer blood transfusions (67). Another RCT including patients with Hb between 8 g/dl and 10 g/dl in the first post-operative week who were randomized to receive either 3 doses of subcutaneous EPO biosimilar or placebo, showed that after 6 months, while the Hb level was comparable between the two groups, lower serum creatinine and higher creatinine clearance were found in the intervention arm (68). More recently, KTRs with anemia 3 months posttransplant were randomized to epoetin beta targeting Hb levels 11.5-13.5 g/dl or to no treatment (69). After 2 years, Hb concentration was significantly higher in the ESA treated group, while eGFR and rate of progression (eGFR slope) did not differ between groups. Treatment with ESA improved some quality of life scores (69).

In late post-transplant anemia, the Correction of Anemia and Progression of Renal Insufficiency in Transplant patients (CAPRIT) study examined the 2-year effect on graft survival and quality of life of normalizing Hb levels (target 13-15 g/dl) versus partial Hb correction (10.5-11.5 g/dl) by using subcutaneous epoetin beta (70). The Hb

normalization group showed a reduced decline in estimated creatinine clearance (2.4 vs 5.9 ml/min/1.73 m^2 in the partial correction group), a lower rate of progression to kidney failure, and higher death-censored graft survival. Quality of life also significantly improved in the full-correcting group (70). Tsujita et al. (71) conducted a 3-year study in KTRs treated with either darbepoetin alpha or epoetin beta pegol (subcutaneous or iv), comparing the effect on graft function decline rate (primary efficacy endpoint) of sustained maintenance of high Hb levels (12.5-13-5 g/dl) as opposed to maintenance of low Hb values (10.5-11.5 g/dl). The average decline in eGFR was significantly greater in the low Hb group (5.1 ml/min/1.73 m^2) than in the group with high Hb levels (1 ml/min/1.73 m^2) (71). More recently, 153 KTRs randomized to either a high (≥12.5 g/dl) or a low (<10.5 g/dl) Hb target and to either cholecalciferol or control (2 x 2 factorial design) received subcutaneous methoxy polyethylene glycol epoetin beta as ESA (72). Changes in creatinine-based eGFR over a 2-year period comprised the primary outcome of the study. Among patients who completed the study period, the decline in kidney function was smaller in those with high Hb levels than in the low Hb group (-1.6±4.5 vs -4±6.9 ml/min/1.73 m^2; $p<0.05$), with no difference between the cholecalciferol and the control group (72).

The results of these studies suggest that in KT anemia is associated with a decline in eGFR, and that correction of anemia may effectively reduce the rate of decline. This is discordant with a previous meta-analysis reporting the absence of reno-protective effects by ESA in the post-transplant setting (73). Major drawbacks have been identified in that study, however, including heterogeneity and different primary endpoints (65).

In a rat model of KT, correction of Hb using EPO prevented histologic signs of chronic allograft nephropathy through the regulation of intragraft expression of antioxidant, antiapoptotic and angiogenic properties (74). Interestingly, blood transfusion normalizing post-transplant Hb had no impact on allograft injury, suggesting that the reno-protective effect of EPO outweighed the correction of anemia itself (74). In in vitro murine models, and in a prospective clinical study in CKD stage 4 ESA-treated patients, EPO exhibited immunomodulating properties which are needed for spontaneous kidney allograft acceptance (75). Early clinical studies, however, did not show any tissue-protective benefit from using ESA in the post-transplant setting (73, 76), which might be explained from several methodological angles (36). Thus, the potential reno-protective role of ESA in KT awaits better definition in adequate future studies.

Recommendations based on the level of evidence indicate that use of ESA in early post-transplant anemia should be considered using a case-by-case approach, while ESA should be used in late anemia with a target Hb level between 12.5 and 13.5 g/dl to achieve better graft survival, caution being required in patients with a high risk of malignancy (65). This Hb target is quite similar to the Hb target of 12-13 g/dl recently recommended by a panel of experts (6). It should be noted that the recommended Hb target in KTR is higher than the recommended target suggested in the general CKD population by KDIGO (Hb level of 11.5 g/dl) and KDOQI (Hb level of 11 g/dl) guidelines (77, 78). The practice of targeting lower Hb levels in CKD has been guided by the undesirable results of large-scale studies regarding the safety and efficacy of ESA therapy targeting high Hb targets in CKD patients (79-81).

Though results concerning cardiovascular complications at higher Hb target levels in KT need to be interpreted with caution due to some study limitations, the evidence gathered so far in KTRs treated with ESA has not shown an increased cardiovascular risk. In the CAPRIT study, no cardiac disorders (heart failure, arrhythmia, myocardial infarction) or stroke occurred in the full-correction Hb group, while some cardiovascular events occurred in the group with a lower Hb concentration (70). Cardiovascular disorders were not noticed in the study by Tsujita et al. (71). The study by Obi et al. showed no increased incidence of stroke in KTRs randomized to the high Hb target arm (72). Moreover, no adverse cardiovascular effects or thrombotic events were observed in a 2-year trial in KTRs receiving epoetin beta with an Hb target of 11.5-13.5 g/dl (69). The apparent discrepancies between the non-transplanted CKD population and KTR may be explained by the different setting. Chronic allograft nephropathy and CKD are fundamentally different entities in terms of pathophysiology and outcome (70). Also, a chronic allograft kidney may prove superior to the kidney of a non-dialysis CKD patient in terms of histopathology, hemodynamics, and immune biology (71).

The actual evidence suggests that use of ESA in KTRs is safe and associated with a possible favorable outcome. Different types of ESA showed comparable efficacy in correcting anemia, though long-acting ESAs may be more practical in managing PTA, while there is no preferable way (subcutaneous or intravenous) for ESA administration. The optimal use of ESA from the viewpoints of dosage and Hb target needs further clarification.

Blood transfusion

Red blood cell transfusion is common in KTRs, particularly in the first few months after transplant (12, 82). A study including more than 12,000 KTRs however reported an association between early transfusion and transplant failure defined as graft loss or death with a functional graft (82). Receiving transfusion within one month from KT was associated with reduced graft survival and increased risk of antibody-mediated rejection and infections at one year (83). Furthermore, transfusion may have a pro-thrombotic effect predisposing to venous thromboembolism (84). A recent retrospective cohort study described a significantly increased risk connected with receiving transfusion after transplantation: namely venous thromboembolism, including deep venous thrombosis or pulmonary embolism; the risk increased as the number of transfusions increased (85). Notably, venous thromboembolic events in KT are associated with graft loss and death (86).

Blood transfusions cannot be considered as an alternative strategy to managing post-transplant anemia because they still carry some risks, expose patients to large Hb-level fluctuations, and have limits of availability (1). The current evidence emphasizes the need for judicious use of transfusion in KT, weighing the risk-benefit balance, and considering other methods of anemia correction such as optimizing iron stores or ESA use (85).

Hypoxia-inducible factor inhibitors

Oral hypoxia-inducible factor-prolyl hydroxylase (HIF-PH) inhibitors are now available to manage anemia in people with CKD. This novel class of erythropoietic drugs increases endogenous EPO levels, stimulating transcription of the erythropoietin gene in kidney and hepatic tissue, and seems to reduce hepcidin levels and improve iron

homeostasis (87). Thus, inhibition of HIF may comprehensively, and via different mechanisms, regulate pathological factors associated with the anemia of CKD. Among HIF-PH inhibitors, 16oxadustat was authorized for use in CKD anemic patients (regardless of dialysis or not) by the European Medicines Agency in 2021, whereas daprodustat has just been approved by the US Food and Drug Administration for dialysis patients prevalent from 4 months.

Data on the use of HIF-PH inhibitors in KTRs are limited. This may be mainly due to a theoretical increased cancer risk (e.g., upregulation of vascular endothelial growth factor, angiogenesis, etc.), in an immune suppressed population already prone to develop malignancies (65). A prospective, observational study in KTRs with Hb < 11 g/dl evaluated the effect of 16oxadustat (20-100 mg) administered thrice weekly (88). Target Hb was 11-13 g/dl, and ESAs were used if Hb levels were < 10 g/dl. Twenty-five out of 31 enrolled patients completed the study period of 20 weeks, with seven cases of early PTA. Mean Hb levels increased progressively from 9.8 g/dl at baseline, plateauing after 20 weeks at a value of 12.4 g/dl. Iron deficiency requiring iron supplementation was observed at 8 weeks, and twelve patients received ESAs. Complications leading to dropout included reduced Hb levels in 3 patients, gastrointestinal symptoms in 2 patients, and myocardial infarction in 1 patient (88). Li et al. examined 21 KTRs (six ESA-treated) admitted to hospital for complications after KT with Hb < 10 g/dl; they monitored the effect of 16oxadustat thrice weekly at a weight-based starting dose (89). Eleven patients were withdrawn from 16oxadustat before the study ended (10 weeks), due to initial or later nonresponse (n=6) or upon reaching the Hb target. In patients completing the study, the Hb level significantly increased from 6.9 to 10.4 g/dl, and the treatment response rate

(Hb increase > 1 g/dl) was 71.4%. No obvious adverse reactions were noticed (89). In 5 KTRs with late post-transplant anemia, who switched from epoetin beta pegol to 17oxadustat 100 mg thrice weekly for a 9-month period Hb levels increased in all patients after just 1 month, and a satisfactory improvement in anemia was maintained thereafter. However, Hb overshooting was observed, with 1 patient suspending roxadustat after 1 month and 3 patients needing a drug dosage decrease. No serious complications were observed (90).

From the current evidence on the use of HIF-PH inhibitors in KT it is advisable to start with a low dose and slowly increase the titration as well as supplementing iron due to increased iron utilization (20). Randomized controlled studies are needed to elucidate the long-term efficacy and safety of HIF-PH inhibitors in anemic KTRs.

Conclusions

Anemia in KT needs to be carefully investigated and appropriately treated. An increasing body of evidence indicates that the presence of anemia, particularly when severe, may be associated with adverse effects on graft function and patient health. Upon correction of a treatable cause, iron administration and ESA use comprise the mainstay of treatment for late PTA. Correction of anemia in KTR by iron/ESA is usually well tolerated and of potential clinical benefit. HIF-PH inhibitors may represent a further therapeutic approach in the near future. Several factors remain to be established, however, including target Hb level, proper iron therapy, and the safe use of ESAs. Resolving such issues will improve management of the anemic status occurring in kidney transplant patients.

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BOX 1. Main Causes of Anemia in Kidney Transplantation

Early Anemia

- IRON DEFICIENCY
- IMMUNOSUPPRESSION INDUCTION
- INFECTIONS
  - Viruses causing aplastic anemia (parvovirus B19, Epstein-Barr virus, cytomegalovirus, adenovirus, BK virus, herpesviruses, varicella-zoster virus)
  - Indolent infections (bacterial, fungal, viral, parasitic)
- ALLOGRAFT QUALITY
  - Ischemia time
  - Delayed graft function
  - Extended donor criteria
- ACUTE REJECTION
- AGGRESSIVE HYDRATION (dilutionary effect)

Late Anemia

- ALLOGRAFT DYSFUNCTION
- IRON DEFICIENCY
- IMMUNOSUPPRESSIVE TREATMENT
- INFECTIONS
  - Late-viral (cytomegalovirus, hepatitis B virus, hepatitis C virus)
  - Community-acquired pathogens
- DRUGS
  - Renin-angiotensin system inhibitors
  - Proton pump inhibitors
  - Antimicrobials
- ACUTE REJECTION
- VITAMIN B12 AND FOLIC ACID DEFICIENCY

TABLE 1. Randomized controlled trials focusing on improvement of Hb levels and graft outcome in ESA-treated kidney transplant patients

Author	Patients (N)	Intervention	Target Hb	Follow-up	Kidney Outcome	CV Outcome	Comments
Early PTA							
Van Biesen[67]	ESA (n = 18); Control (n = 22)	Subcutaneous epoetin beta (100 U/kg) 3x/wk	> 12.5 g/dL	3 mo	No difference in graft function	NA	No difference in Hb but faster target Hb and fewer blood transfusions in ESA group
Nafar[68]	ESA (n = 20); Control (n = 20)	Subcutaneous biosimilar PD-poietin (2000 U) 3x in the first post-operative wk	-	6 mo	Lower serum creatinine and higher creatinine clearance in ESA group	NA	No difference in Hb
Pile[69]	ESA (n = 26); Control (n = 27)	Subcutaneous epoetin beta	11.5-13.5 g/dL	2 y	No difference in kidney function	No increase in CV morbidity or thrombotic events	Improved vitality and mental health domains in quality of life SF-36 score in ESA group
Late PTA							
Choukroun[70]	Hb normalization (n = 63); partial Hb correction (n = 62)	Subcutaneous epoetin beta (dose steadily increased)	13.15 g/dL (normalization group); 10.5-11.5 g/dL (partial correction group)	2 y	Reduced decline in estimated creatinine clearance, lower rate of kidney failure, higher graft survival in normalization group	No CV complications (heart failure, arrhythmia, myocardial infarction, stroke) in normalization group; some CV events in partial correction group	Improved quality of life in normalization group
Tsujita[71]	High Hb (n = 64); low Hb (n = 63)	Subcutaneous or IV darbepoetin alpha or epoetin beta pegol	12.5-13.5 g/dL (high Hb group); 10.5-11.5 g/dL (low Hb group)	3y	Slower decline of graft function in high Hb group	No cardiac disorders in high Hb group	

Obi[72]	High Hb target (n = 74); low Hb target (n = 79)	Subcutaneous methoxy polyethylene glycol epoetin beta	≥12.5 g/dL (high Hb group); <10.5 g/dL (low Hb group)	2 y	Lower decline of kidney function in high Hb group	No increased incidence of stroke in high Hb group	

ESA, erythropoiesis stimulating agent; Hb, hemoglobin; CV, cardiovascular; N.A., not available; IV, intravenous.

Figure Legends

Figure 1. Clinical approach to evaluating anemia in a kidney transplant recipient.

PPI, proton-pump inhibitors; RASI, renin-angiotensin system inhibitors.