Chapter 22: Hematological Complications

22.1: Perform a complete blood count at least (*Not Graded*):
- **daily for 7 days, or until hospital discharge, whichever is earlier;**
- **two to three times per week for weeks 2–4;**
- **weekly for months 2–3;**
- **monthly for months 4–12;**
- **then at least annually, and after any change in medication that may cause neutropenia, anemia or thrombocytopenia.**

22.2: Assess and treat anemia by removing underlying causes whenever possible and using standard measures applicable to CKD. (*Not Graded*)

22.3: For treatment of neutropenia and thrombocytopenia, include treatment of underlying causes whenever possible. *(Not Graded)*

22.4: We recommend using ACE-Is or ARBs for initial treatment of erythrocytosis. *(1C)*

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease.

Background

Hematologic abnormalities are common adverse effects of immunosuppressive medications and of transplant- or immunosuppression-related comorbidities. In addition, hematologic abnormalities can cause potentially life-threatening complications. Therefore, screening is warranted. In most laboratories, a complete blood count includes hemoglobin, white blood count (with differential) and platelet count. Anemia is defined as a hemoglobin <13.5 g/dL (135 g/L) in adult males, <12.0 g/dL (120 g/L) in adult females and <5th percentile for children (707). Neutropenia is defined as a neutrophil count <1500/μL (1.5×10^9/L). Thrombocytopenia is defined as platelet count <150 000/μL (1.5×10^{11}/L).

Erythrocytosis

Erythrocytosis or polycythemia is variably defined in the literature as hemoglobin >16–18 g/dL, or hematocrit >50–52%. Some report gender-specific hematocrit thresholds (men 53–55%; women 48–51%) and others require evidence of persistence over a specified time period or on multiple determinations (627,708–710). The Work Group has chosen to define erythrocytosis as hemoglobin >17 g/dL or a hematoctrit >51%.

Rationale

- In KTRs, anemia, neutropenia and thrombocytopenia are common.
- In KTRs, anemia is associated with morbidity and mortality, neutropenia with infection and thrombocytopenia with bleeding. In addition, these hematologic abnormalities may be an indication of treatable, but potentially life-threatening, underlying disorders.
- In KTRs, monitoring and identifying the underlying cause and treatment will reduce the morbidity and mortality of anemia, neutropenia and thrombocytopenia.

Anemia

The Work Group reviewed the KDOQI Guidelines on Anemia in CKD, and concluded that these evidence-based guidelines can and should guide anemia management in KTRs (707). Readers can find a detailed discussion of anemia in CKD in these guidelines. Anemia in the immediate posttransplant period is likely to be caused by pretransplant anemia and operative blood loss. The correction of anemia after transplantation is dependent on achieving hemostasis, immunosuppressive medications, iron deficiency, other causes of bone marrow suppression and factors affecting kidney function (e.g. DGF).

After the immediate posttransplant period, infections, rejection, immunosuppressive medications, other medications such as ACE-Is and ARBs (Table 31), hemolysis, and—less often—cancer, may cause or contribute to anemia. There is some evidence that KTRs may have a level of anemia greater than can be expected based on the level of kidney function, even without specific causes (711,712). When and how to evaluate anemia is well defined in the KDOQI guidelines for KTRs who are not actively bleeding, and have stable kidney function (707). Treatment should be directed at the underlying cause. Iron deficiency is common. There is evidence from a single small RCT that iron supplementation results in a higher hematocrit (44%) compared to no iron (36%) in KTRs (713).

Altering immunosuppressive agents to treat anemia should be considered, but may be difficult, especially in the early posttransplant period when acute rejection rates are highest and maintaining adequate immunosuppression is critical. Some, but not all, studies have identified anemia as an independent predictor of mortality in the intermediate posttransplant period (733–735). However, there are no RCTs showing that benefits of therapy with an ESA outweigh harm, or the optimal hemoglobin target, in KTRs.

Table 31: Medications associated with hematologic abnormalities

	Medications that cause hematologic abnormalities	
	Commonly	Uncommonly
Anemia	Azathioprine (714–717) MPA (718,719) Sirolimus (50) Leflunomide (720) ACE-I (721) ARB (721)	CNIs (722,723) OKT3 (722,723) Trimethoprim–sulfamethoxazole
Neutropenia	Azathioprine (714,715) MPA (718) Sirolimus (50) Leflunomide (720) Lymphocyte-depleting antibodies (8) Valganciclovir (724) Trimethoprim–sulfamethoxazole (725)	Rituximab (726) ACE-I (727) Ticlopidine/clopidogrel (728) Other antimicrobials (728)
Thrombocytopenia	Sirolimus (42) MPA (729) Azathioprine (729) Lymphocyte-depleting antibodies (8)	OKT3 (730) Valganciclovir (722,723) Ticlopidine/clopidogrel (731) Heparin (732)

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CNI, calcineurin inhibitor; MPA, mycophenolic acid; OKT3, muromonab (anti–T-cell antibody).

There are two small RCTs using ESAs in the early posttransplant period, but the overall effects on anemia were small (711,736). Another small trial showed that patients receiving ESAs before transplant, who attained normal hemoglobin levels, had outcomes that were no different than those with low hemoglobin levels (737). There is no evidence to support routine ESA administration in anticipation of anemia (see Supporting Tables 54–55 at http://www3.interscience.wiley.com/journal/118499698/toc).

The European Best Practices Guidelines for kidney transplantation recommend regular screening and careful evaluation of anemia (721). They also identify immunosuppressive agents, ACE-Is and ARBs as causative agents. They recommend following the European Best Practices Guidelines for anemia management, which recommend that an ESA not normally be discontinued in patients undergoing surgery or who develop an intercurrent illness (738). No recommendation was made on whether to continue or stop ESAs in the immediate posttransplant period. Patients with a failing kidney transplant should be followed as any other patient with failing kidney function.

Neutropenia

Many of the same factors responsible for anemia also cause neutropenia (Table 31). Although there are no RCTs on screening for these abnormalities, the potential consequences of not screening are severe. Infection is the second most common cause of death, after CVD, in KTRs (739). In the nontransplant population with iatrogenic neutropenia (absolute neutrophil count $<500/\mu L$ [$5 \times 10^8/L$]), patients are at increased risk for serious infection (740). A possible major contributor to neutropenia in KTRs is that kidney dysfunction may delay clearance of medications that can suppress leukocyte production by the bone marrow.

Medications are a common cause of leukocyte abnormalities. There are a number of RCTs that document leucopenia in the first 1–3 years after transplantation. Unfortunately, the definition of leucopenia differs among studies; therefore, direct comparison across trials is problematic. Different classes of immunosuppressive agents have differing effects on leucocytes. CNIs are not generally associated with leucopenia. In contrast, antiproliferative agents are an important cause of leucopenia. In early trials, azathioprine was associated with leucopenia (714,715). In the European Trial of MMF vs. placebo with CsA and prednisone, there was more leucopenia in the group treated with 2 g/day MMF (14%, n = 165) vs. placebo (4%, n = 166) (718). In the tricontinental MMF trial, there was slightly less (significance not stated) leucopenia in the arm treated with 2 g/day MMF (19%, n = 171) vs. the arm using 100–150 mg/day azathioprine (30%, n = 162) (729). In two trials evaluating the safety of EC-MPS vs. MMF, there were no significant differences in leucopenia (42,43). These study protocols included rules to reduce the dose or discontinue these agents in the presence of leucopenia, which likely limited the severity and overall incidence of very low counts.

In a Cochrane systematic review, mTORi were associated with more leukopenia (RR 2.02, 95% CI 1.12–3.66, by meta-analysis) than CNIs (50). No mention was made of differences in leucopenia in patients treated with sirolimus vs. placebo with CsA and prednisone, or in the meta-analysis comparing sirolimus to other antiproliferative agents (50,741). The Symphony trial compared

four interventions: standard-dose CsA and MMF (n = 384), low-dose CsA with MMF (n = 408), low-dose tacrolimus and MMF (n = 403) and sirolimus and MMF (n = 380) (30). At the end of 12 months, leucopenia occurred in 10.2%, 10.1%, 13.4% and 10.3% of patients, respectively ($p > 0.05$).

There is no evidence that IL2-RAs cause significant hematologic abnormalities. In contrast, lymphocyte-depleting antibodies are associated with more ($p < 0.001$) leucopenia (33%, n = 141) compared to the IL2-RA, basiliximab (14.6%, n = 137) (8). More leucopenia was demonstrated in a RCT comparing groups treated with lymphocyte-depleting antibodies with tacrolimus or CsA to one with tacrolimus and no lymphocyte depleting antibodies (7). Addition of steroids also has an impact on leucopenia. In one trial, leucopenia was seen more often (significance not stated) in the steroid-free (17.9%) and the steroid-withdrawal (16.5%) arms compared to the standard steroid arm (13.8%) (48).

Other medications commonly used in KTRs to treat comorbidities are associated with leucopenia. Valganciclovir was associated with more leucopenia compared to ganciclovir (8.2% vs. 3.2%) in a RCT of high-risk solid-organ transplant recipients (724). However, the alternative antiviral valacyclovir was not associated with more leucopenia compared to placebo in a RCT of CMV prophylaxis in KTRs, but drug-induced leucopenia in the treatment arm may have offset the CMV-induced leucopenia in the control arm (742). Combined therapy with antiviral and antiproliferative agents may increase the incidence of leucopenia (743).

The risk of neutropenia from trimethoprim–sulfamethoxazole in KTRs is unclear. There have been several small RCTs, and they did not report differences in the incidence of leucopenia (744,745). In a bone marrow transplantation study, prophylaxis with trimethoprim–sulfamethoxazole (vs. ciprofloxacin) was associated with a 6-day delayed recovery of neutropenia (746). Case reports of agranulocytosis have been reported with trimethoprim–sulfamethoxazole (725).

Thrombocytopenia

Many of the factors that cause anemia and leucopenia also cause thrombocytopenia (Table 31). There are also relatively uncommon conditions, such as recurrent or *de novo* thrombotic microangiopathy, that can cause kidney dysfunction, hemolytic anemia and thrombocytopenia (722,723). Thrombocytopenia is also associated with several medications used in KTRs. mTORi are associated with much higher RRs of thrombocytopenia compared to CNIs (RR 7.0, 95% CI 3.0–16.4) (42). Sirolimus also demonstrated more thrombocytopenia in comparison to azathioprine and MMF (RR 1.95, 95% CI 1.29–2.97) (50). Thrombocytopenia was also frequently observed in the tricontinental MMF trial (5% MMF 3 g/day; 9% MMF 2 g/day; 12% azathioprine, significance not stated) (729). In a (potentially underpowered) study comparing thymoglobulin to basiliximab induction, thrombocytopenia (platelet count <80 000/μL) was not significantly different (10.6% vs. 5.8%, $p = 0.19$) in the thymoglobulin group vs. the basiliximab group (8). Thrombocytopenia is also observed in patients with thrombotic microangiopathy associated with CNIs and, rarely, other medications such as clopidogrel and valacyclovir (722,723,731).

Other causes of leucopenia and thrombocytopenia include severe sepsis, viral infection (CMV, parvovirus B19) and other medications (716,717,719,720,726–728,730,732,747–753). Idiopathic thrombocytopenia has rarely been described after transplantation, and can be related to autoimmunity transferred from the donor (754). Transient thrombocytopenia has also been described in recipients of allografts whose donors had suffered disseminated intravascular coagulation (755).

Patients with low platelet counts are at increased risk of bleeding. Treatment of thrombocytopenia includes removing the offending drugs or treating other underlying causes. For example, case series have shown that parvovirus B19 associated hematologic abnormalities can be treated with intravenous immunoglobulin (751). Plasmapheresis has also been used to treat HUS/thrombotic microangiopathy that may be associated with thrombocytopenia (723). There are several case reports documenting the use of colony-stimulating factors (CSFs) to treat neutropenia in kidney transplant patients (756–758). However, there is potential for harm with treatment. One case report suggested that CSFs may have been associated with worsening graft function (758). There are clinical practice guidelines in the cancer literature that can be referred to for the use of CSFs (616). The review performed by the American Society of Clinical Oncology (616) found there is ample evidence that CSFs shorten the duration of neutropenia. There are, however, inadequate data to know whether or not there is benefit in afebrile neutropenic (absolute neutrophil count <1000/μL [1×10^9/L]) patients. There is evidence, though, that patients with febrile neutropenia (absolute neutrophil count <500/μL [5×10^8/L]) benefit from CSFs along with antibiotics if there is pneumonia, fungal infection, hypotension, sepsis syndrome or multisystem organ failure.

The European Best Practice Guidelines on kidney transplantation recommend regular screening and careful evaluation of neutropenia in KTRs (759). The combination of allopurinol and azathioprine should be avoided to prevent neutropenia (616). There are not likely to be any RCTs to determine when to give CSFs in KTRs. Guidance for their use will be derived mostly from local clinical practice and oncology guidelines (708). There are similar guidelines for

the treatment of thrombocytopenia with platelet transfusion (760).

Erythrocytosis

- Erythrocytosis is a well-known complication of kidney transplantation.
- In the general population, erythrocytosis is associated with morbidity (fatigue, dyspnea, thrombotic events, etc.) and mortality.
- In the general population, there is some evidence that correction is associated with a reduction in thrombotic events.
- In KTRs, adverse consequences of erythrocytosis may be less common than in the general population.
- In KTRs, treatment of erythrocytosis is effective and safe with angiotensin blockade.

The incidence of erythrocytosis varies from 8% to 22% among reports identified from earlier clinical practice guideline publications (627,708–710). More recent studies document that erythrocytosis still occurs in KTRs (761–765). Many studies do not differentiate between increased red cell mass or reduced plasma volume. Erythrocyctosis tends to occur within the first 2 years, but can occur much later. It may revert spontaneously in 20% or more of cases (709,710).

The mechanisms of erythrocytosis are unclear and are likely multifactorial. Sustained increases in erythropoietin have not been consistently found, but seem to be increased to a greater extent than expected for the level of hematocrit (766). Other proposed mediators of erythrocytosis include endogenous androgens, renin–angiotensin system activation and other growth factors (710). Identified clinical risk factors that have been reported include male gender, polycystic kidney disease, smoking, immunosuppression, reduced kidney function, absence of rejection, renal artery stenosis, hydronephrosis, hypercalcemia, longer duration of dialysis, higher pretransplant hemoglobin, angiotensin-converting enzyme genotype, hypertension and diabetes mellitus (709,710,761–765,767–778).

The consequences of erythrocytosis can be severe. Evidence for the adverse outcomes related to erythrocytosis arise mostly from observations in patients with polycythemia vera. Historical observations document 20% of polycythemia vera patients present with a thrombotic event, and subsequent thrombosis occurs in as many as 50%; however, the associated risk of thrombosis has been difficult to quantify (779,780). Patients with polycythemia vera have a reduced life expectancy, but this is, in part, related to malignant progression (781). In addition, a large study of elderly patients without polycythemia vera undergoing noncardiac surgery showed that an elevated hematocrit was associated with short-term mortality and cardiac morbidity (782).

In the general population, treatment of erythrocytosis is effective. In a large observational study of patients in the general population with polycythemia vera and a prior history of thrombosis, pharmacological therapy to reduce red cell volume was associated with a 53% reduction in recurrent thrombotic events (783). Many of the recurrences occurred in patients with inadequate treatment (hematocrit >45%).

In KTRs, erythrocytosis can be asymptomatic, or patients may complain of fatigue, headaches, plethora, dyspnea or blurred vision (709,767,776). The more serious consequences include increased risk of venous and arterial thrombosis (767,768,784). One small case control study found more thromboembolic events in patients with polycythemia (11 events in 53 patients) compared to those without erythrocytosis (0 in 49 matched controls) (767). Most other studies in KTRs either did not report adverse events, described no concurrent controls, or found no increase in adverse events (770,771,774). In a large registry analysis of KTRs, erythrocytosis was not found to be a risk factor for stroke (450). Since erythrocytosis is now readily treatable, and the potential consequences of not treating are severe (venous and arterial thrombosis), there are not likely to be any long-term RCTs to compare the effect of treatment vs. no treatment on outcomes.

There are a number of small RCTs of fair quality and case series demonstrating the use of ACE-Is or ARBs to reduce hematocrit by an absolute value of between 4% and 15% (785–797). Given the small sample sizes and the lack of data on critical clinical outcomes, there is only a low level of evidence (see Evidence Profile and accompanying evidence in Supporting Tables 56–58). In a RCT comparing enalapril (2.5 mg/day, n = 15) to placebo (n = 10), the hematocrit dropped by 6.6% in the treatment arm compared to only 1.3% in the control arm ($p = 0.004$) (788). In another small trial, 15 patients were randomized to an ACE-I (enalapril) and 12 patients an ARB (losartan) (796). Hemoglobin levels decreased significantly in both groups (174–149 g/L for enalapril and 171–159 g/L for losartan); however, the drop was greater ($p = 0.05$) with enalapril (32.6 g/L decrease) than losartan (17.0 g/L decrease). Theophylline has been found to be useful in the transplant population with dramatic absolute reductions in hematocrit of 8–12% (798,799). However, several trials have found that ACE-Is were superior when compared directly to theophylline (800–802). In the study by Trivedi et al., the hematocrit fell by 7.6% in the ACE-I arm (fosinipril, n = 9) and did not change significantly (rose by 2.3%) in the theophylline arm (n = 5) (802). Other strategies include phlebotomy and bilateral nephrectomy, but these are invasive and the latter can be associated with significant morbidity (803). Clinicians should

also be aware that both ACE-Is and ARBs are associated with small, reversible reductions in kidney function (557).

The European Best Practice Guidelines on kidney transplantation recommend that first-line treatment of erythrocytosis (>52% hematocrit in men and >49% in women) be ACE-Is or ARBs (708). The American Society of Transplantation states that erythrocytosis (>17–18 g/dL or hematocrit >51–52%) causes potentially life-threatening complications and is readily treatable.

Research Recommendations

- RCTs on the use of ESAs and the optimal hemoglobin in KTRs are needed.
- RCTs on the use of CSFs and target cell counts are needed.
- Studies are needed to document the incidence and severity of erythrocytosis with current drug regimens.
- Studies are needed to document the role of ACE-Is and ARBs in reducing the incidence of erythrocytosis.