Long-Term Management of Post-Transplant Anemia and Erythrocytosis

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Post Transplant Erythrocytosis (PTE), defined as a hematocrit above 55% in transplant recipients, is a well recognized but poorly understood phenomenon affecting 10 to 15% of renal allograft recipients during the first three years after successful transplantation. The pathogenesis of PTE is multifactorial. While initial studies support inappropriate erythropoietin production by either the native kidney or the renal allograft, recent data suggest that other factors may be involved. Regardless of its pathogenesis, the high incidence of thromboembolic events associated with PTE necessitates aggressive implementation of treatment. In contrast, anemia occurs in 12 to 20% of patients after successful renal transplant, but has usually received modest attention despite its important effect on the quality of life for allograft recipients. Iron deficiency, hemolysis, inappropriate erythropoietin production, and suppression of bone marrow by immunosuppressive drugs or infection are the major contributors to post-transplant anemia. In this article, we review the diagnosis and therapy of both of these conditions in the well transplant patient.

POST-TRANSPLANT ERYTHROCYTOSIS:

An increase in the hematocrit of >55% patients after renal transplantation.

Post-Transplant Erythrocytosis

Post-transplant erythrocytosis (PTE) is defined as a hematocrit above 55% in transplant recipients. It affects 10 to 15% of patients with excellent allograft function[1,2] and occurs predominantly during the first 3 years after transplant.[1-6] Risk factors for the development of PTE are smoking, diabetes, and a rejection free course.[4]

Etiology. The etiology of PTE is complex. PTE has been attributed to transplant hydronephrosis or renal artery stenosis with secondary inappropriate secretion of erythropoietin by either the native kidney or the transplant renal allograft.[2,3,7-11] Nevertheless, not every patient with PTE has an elevated or even detectable plasma erythropoietin level, which suggests that the pathogenesis of PTE is multifactorial. For example, in a study of 20 patients with PTE, four patients had elevated erythropoietin levels while seven had normal levels.[3,11] Dagher et al performed selective catheterization of veins of native and transplanted kidneys and demonstrated excess erythropoietin production from the native kidneys.[23] The systemic effect of this finding is unknown in view of decreased blood flow to end-stage kidneys. Wickre et al studied the influence of pretransplant hematocrit, duration of pretransplant dialysis, renal transplant function, rejection, transplant renal artery stenosis, urinary tract obstruction, smoking, diabetes mellitus, retention of native kidneys, splenectomy, parathyroidectomy, immunosuppression, and liver enzymes abnormality on the development of PTE in patients maintained on azathioprine and prednisone. The incidence of PTE was 17.3%. Smoking was the most significant risk factor. It acted synergistically with diabetes and absence of rejection.

Alternate pathogenic mechanisms for post-transplant erythrocytosis may involve cytokines, insulin-like growth factors (IGF-1), and androgens. These mediators can act on erythroid progenitor cells, either independently or in conjunction with erythropoietin significantly enhancing its effect on erythropoiesis. Other cytokines such as interleukins (IL-1 and IL-2), and Tumor Necrosis Factors

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(TNF-α) have an inhibitory effect on erythropoiesis.[12-14] IL-1α and β, TGF-β and TNF-α also modulate the erythropoietin response to anemia and cause a dose dependent inhibition of erythropoietin production.[13] Other studies indicate that factors other than erythropoietin may act as primary stimuli for erythrocytosis. For example, abnormalities of insulin like growth factors similar to that seen in polycythemia vera have also been described in PTE.[1,48]

Several studies describe the influence of the immunosuppression drugs' type and dose on PTE. In one study, the incidence of PTE was noted to be higher in cyclosporine treated patients.[15-17] Cyclosporine blocks the production of IL-2, removing the inhibitory effect of IL-2 on erythropoiesis.[15-17] This observation prompted many clinicians to discontinue CSA in patients with erythrocytosis or to change to azathioprine for its myelosuppressive effect since other authors have found that the mean azathioprine dosage correlates inversely with the development of PTE.[32] MacDougall et al reported that the incidence of PTE was significantly higher in CSA and prednisone treated patients (14-20%) compared to the AZA and prednisone treated group (1-4 %).[15,16] In contrast, some investigators have found that patients not receiving AZA develop PTE, and that the average dose of AZA in PTE was identical to control group without PTE.[4]

HEMOLYTIC UREMIC SYNDROME (HUS):

A disorder characterized by microangiopathic hemolysis, thrombocytopenia and renal failure. Post-transplant, it can be due to calcineurin inhibitors.

Diagnosis and Symptoms. PTE is often asymptomatic, and the diagnosis is usually suspected when the hematocrit measurement is elevated on several occasions. When patients are symptomatic, their complaints are secondary to the expanded blood volume and increased viscosity, which increase exponentially as the hematocrit exceeds 55%. Symptoms include headache, lightheadedness, tinnitus, visual disturbances, weakness or fatigue.[2,18] Thromboembolic complications of hyperviscosity can occur at any site with increasing frequency if the patient becomes dehydrated. Hypertension is also very prevalent in this population. Studies have shown that erythrocytosis contributes to hypertension in renal allograft recipients. This contribution depends on the history of longstanding pre-transplant hypertension, since vascular dilatation, which is a normal adaptive mechanism to the increased viscosity caused by erythrocytosis, is impaired in patients with chronic hypertension.[21] Spieker et al described 18 hypertensive patients with PTE and stable renal function. Repeated phlebotomies over a three months period to lower the hematocrit to below 45% resulted in a decrease in blood pressure with no significant change in heart rate. The antihypertensive medications were also tapered. The cessation of phlebotomy at a later stage was followed by recurrent rise in both the hematocrit and blood pressure.[21]

The differential diagnosis of erythrocytosis includes polycythemia vera (PV), relative (spurious) and secondary erythrocytosis. PV and secondary polycythemia are referred to as true erythrocytosis representing an absolute increase in red blood cell (RBC) mass (Table 1). PV or Vaquez disease is a myeloproliferative disorder associated with trilineage marrow hyperplasia. It must be considered in any man with a hematocrit above 54% and in any woman with a hematocrit above 49% when associated with elevation of all of he three components of peripheral blood (RBC, WBC, and platelets) and splenomegaly. There are however no reports of de novo PV post-transplant. Erythropoietin synthesis is adequately suppressed in PV.

Since the hematocrit is the ratio between RBC per unit volume of whole blood, an increase in hematocrit caused by decreased plasma volume is referred to as spurious or relative erythrocytosis. This is seen with stress (Gaisbock syndrome), diarrhea, burns, or diuretic therapy.

Secondary erythrocytosis is caused by either abnormal erythropoietin production or by decreased tissue oxygenation. Renal cysts or neoplasms may independently secrete erythropoietin. In other situations such as pulmonary disease or high altitude, tissue hypoxia stimulates erythropoietin production. Chronic pulmonary hypertension leads to erythrocytosis as a result of inadequate oxygenation of blood circulating through the lungs. This creates a vicious cycle as the ensuing polycythemia with its associated increase in blood viscosity progressively worsens the pulmonary hypertension. Ayerza syndrome is characterized by slowly developing asthma, dyspnea, cyanosis and polycythemia and represents right-sided heart failure resulting from pulmonary hypertension.[29]

True and relative erythrocytosis can be distinguished by measurement of red blood cell mass with the isotope dilution technique. A sample of the patient's RBCs is labeled with a radioactive tracer, usually chromium, and reinfused. The red cell mass

Table 1 | **CLASSIFICATION OF ERYTHROCYTOSIS**[18]

Primary	Polycythemia Vera
Secondary	Increased erythropoietin production by tumors or cysts Decreased tissue oxygenation due to lung disease, pulmonary hypertension, carboxyhemoglobin, high altitude, hypoventilation syndromes, and abnormal hemoglobins
Relative	Stress Hemoconcentration secondary to diarrhea, diuretics, or burns

can then be calculated from the degree of dilution of the isotopically labeled red cells. It is important to allow time for the equilibration of the labeled cells. Serial blood samples should then be taken over a period of approximately 90 minutes to ensure that the equilibration is complete and that the RBC mass is not underestimated.[30]

An elevated erythropoietin level suggests that erythrocytosis is a secondary event, but does not establish a cause. A normal erythropoietin level does not exclude primary or secondary erythrocytosis. In those with compensated hypoxia for example, the erythropoietin level is usually within normal limits secondary to the compensatory effect of erythrocytosis on tissue hypoxia (Fig. 1A). Arterial oxygen saturation (SaO_2) is a sensitive indicator of tissue hypoxia but SaO_2 can also be misleading with high oxygen affinity hemoglobins and carbon monoxide intoxication.

Differentiating between the different causes of polycythemia and establishing an exact etiology can, therefore, be a challenging task that may not influence management. PTE patients represent a heterogeneous group with very similar clinical presentations and complications. A detailed history and list of medications are readily available and an extensive diagnostic work-up to exclude causes that are not clinically apparent is usually unwarranted.[4] It is reasonable, however, to obtain an ultrasound or other imaging study of the allograft and the native kidneys to rule out renal cell carcinoma.

Treatment. The high incidence of PTE and the risks of associated thrombotic events should encourage awareness and aggressive implementation of therapeutic modalities. Wikre et al reported thromboembolic complications such as stroke, transient ischemic attack, pulmonary embolus, or deep vein thrombosis in 11 of 53 (21%) patients with PTE compared to none in 50 matched controls.[4]

Treatment of reversible causes of PTE such as smoking cessation and discontinuing diuretic therapy should be considered first,[2] taking into consideration that spontaneous resolution of PTE is infrequent, occurring in fewer than 20% of patients and likely indicates worsening allograft function.[4,19] An extensive work up is usually not indicated (Fig. 2).[2]

Phlebotomy. Phlebotomy is the initial modality of treatment in any symptomatic patient because it may have an immediate effect. It may be combined with intravenous fluid or plasma infusion. Because of the toxicity of ACE-I in pregnancy, it is the treatment of choice for women contemplating pregnancy. The goal of therapy is to reduce the blood viscosity and to improve blood flow to the different organs.

Phlebotomy should be performed by slow removal of small volumes of blood under continuous blood pressure monitoring throughout the procedure. Serial phlebotomy should not, however, be considered the standard of care for every patient with PTE. It is not always a benign procedure and is time-consuming for both the patient and the medical staff.[9,20,21] Kiraly et al reported systolic hypotension in three patients with polycythemia and history of cardiovascular disease after removal of 400 to 1000 ml of blood. In two patients, acute myocardial infarction and in a third cardiovascular collapse and death were temporally related to the phlebotomies.[28]

Blood viscosity changes slowly with phlebotomy, and rapid phlebotomy can result in hypoxemia. The determination of blood viscosity values at different hematocrit levels allows the estimation of blood flow rates. The rate of oxygen transport can then be calculated from the blood flow rate and oxygen content and is represented by an arc shaped curve (Fig. 1A).[29] At a low hematocrit, the reduced hemoglobin translates into reduced oxygen content and transport, while at an elevated hematocrit, the increased viscosity reduces oxygen transport despite increased blood oxygen content. In primary and secondary polycythemia, the concomitant hypervolemia shifts the oxygen transport curve up and to

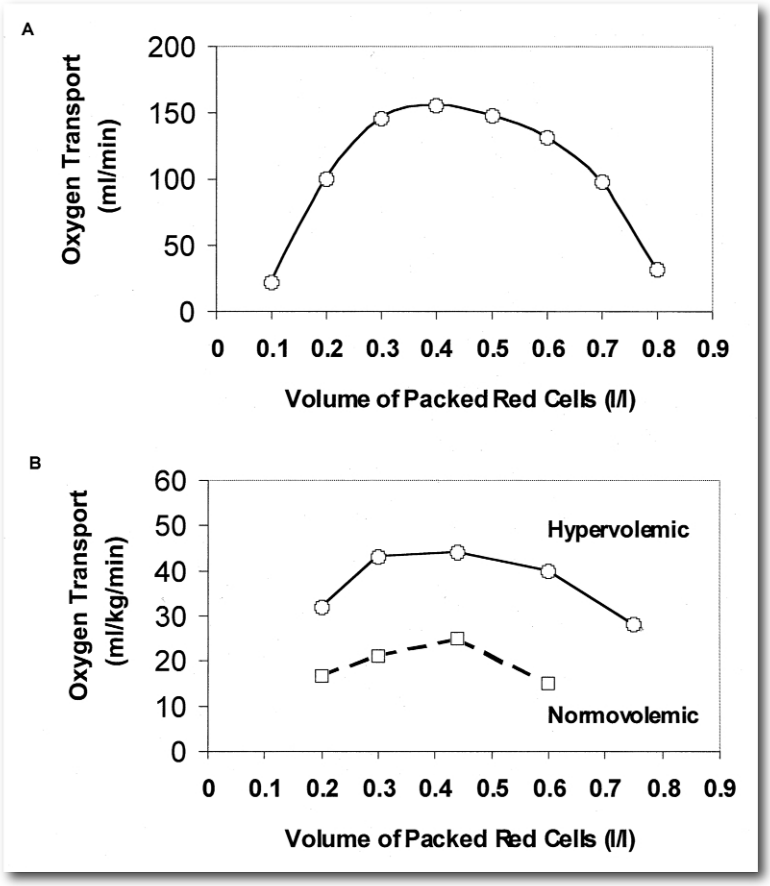

Figure 1. (A) Arterial oxygen transport at different volumes of packed red cells or hematocrit, and thus different viscosity. (B) Systemic oxygen transport as calculated from the cardiac output measured in normovolemic and hypervolemic canines. (Adapted from Murray et al. J Clin Invest 1663; 42:1150-1155.)

the right. In contrast, decreased total blood volume shifts the curve down and to the left adversely affecting oxygen transport (Fig. 1B).[29] This concept becomes very important when phlebotomy is performed. Time should always be allowed for hemodilution to occur between phlebotomies, and saline or plasma expanders should be given. Patients will otherwise be shifted from the hypervolemic beneficial curve to the hypovolemic adverse curve resulting in possible ischemia.[29]

In relative polycythemia, with decreased plasma volume, phlebotomy should be avoided as it will further contract blood volume and impair tissue perfusion.

Native nephrectomy. Native nephrectomy has also been used to decrease erythropoietin production and different studies described different rates of success. PTE recurred in few patients within 24 months post nephrectomy.[23-25] In one study, bilateral nephrectomies were more common in the control group with no PTE, however this difference did not reach statistical significance.[4] Native nephrectomy should therefore be reserved for patients whose PTE work-up reveals a suspicious renal lesion.

Theophylline. Theophylline inhibits activation of adenosine A-2 receptor, the stimulation of which facilitates the synthesis, release, and bone marrow response to erythropoietin.[1,2] Theophylline, however, has a narrow therapeutic window and its use is associated with many side effects such as irritability, restlessness, insomnia, and gastrointestinal disturbances. Studies have also found its effect to be

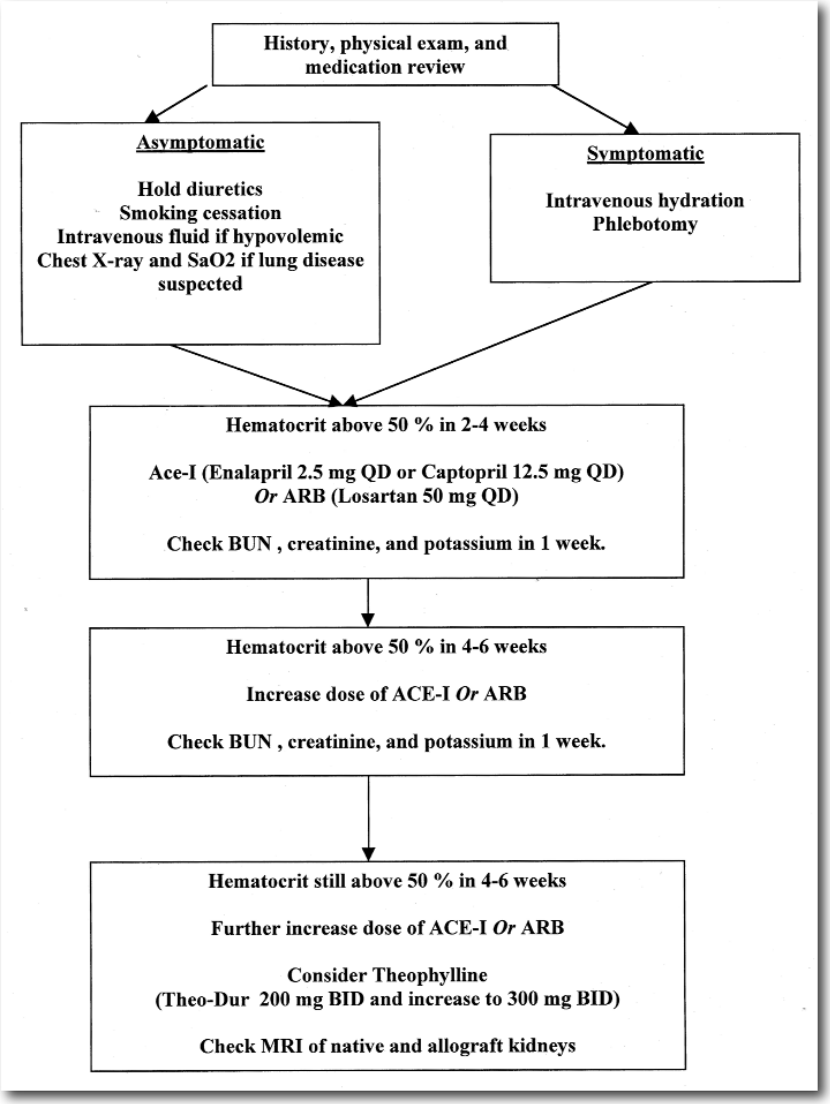

Figure 2. Recommendations in managing post-transplant erythropoieses (PTE).

unpredictable despite many reports of a 10-15% reduction in hematocrit in 6-8 weeks.[1,25] In one study, nine patients with an average hematocrit of 56 received 600 mg per day of theophylline. The hematocrit was reduced to an average of 52% but remained above 51% in 5 patients.[1,22] Withdrawal of theophylline caused the hematocrit to revert back to pre-treatment values.

Angiotensin converting enzyme inhibitors (ACE-I) . Although often avoided post transplant due to their possible adverse effect on kidney function and contribution to hyperkalemia, ACE-I are now widely used to control PTE and are very well tolerated. This reflects the fact that PTE usually accompanies excellent graft function. Low dose of an ACE-I starting with 2.5 mg of enalapril or 12.5 mg of captopril reduces hematocrit to near normal levels within 6 weeks.[2] As with theophylline, ACE-I corrects but does not cure PTE, and the withdrawal of ACE-I results in gradual rise in hematocrit with or without rise in erythropoietin levels.[1,26,27] The mechanism by which ACE-I decrease the hematocrit

is unknown. Decreased erythropoietin production appears to be a possible explanation. However this fails to account for the fact that patients with suppressed erythropoietin also respond to ACE-I, and that erythropoietin levels could remain constant during the treatment. Angiotensin II has been shown to enhance erythropoietin-stimulated red blood cell proliferation in vitro, and may increase proliferation of erythroid progenitors.[49] Angiotensin receptors blockers (ARB) are equally effective in treating PTE. Losartan (50 mg/day) produced a significant drop in hematocrit in 6-8 weeks.

Post-Transplant Anemia

Anemia, defined as hematocrit less then 35% in women and less then 38% in men, is common in patients with renal failure primarily as a result of inadequate erythropoietin (EPO) production from the diseased kidneys. Anemia however still occurs in 12 to 20% of patients after successful renal transplant,[35,39] but has usually received a modest attention despite its effect on the quality of lives of allograft recipients. Soon after transplant, and as the allograft function is established, many patients report increasing level of energy. Although this improved level of well being is likely due to clearance of uremic toxins; in some cases, it may in part be a result of increasing hematocrit. Persistence of anemia hinders such feelings of well being. Iron deficiency, hemolysis, bone marrow suppression by immunosuppressive drugs or infection, and inappropriate EPO production are major contributors to PTA. Minor factors are deficiencies of vitamins B-12 and folate, and effect of aluminum on the bone marrow, a common finding when aluminum was used as a phosphate binder.

Iron Deficiency. It is established that administration of EPO to dialysis patients causes an increase in the RBC mass with a rapid decrease in iron stores. Successful renal transplantation corrects anemia at least partly because endogenous production of EPO is regained. One should expect therefore a similar depletion of iron stores post-transplant. Occult gastrointestinal blood losses should also be ruled out in view of the adverse effects of corticosteroid immunosuppression and the high prevalence of arteriovenous malformations in renal patients.

Moore et al reported iron deficiency to develop in the majority of patients during the first 6 months following transplant.[38] In another study, 16 patients with successful renal transplant showed marked decrease in their serum ferritin as their hematocrit rose. Four patients developed microcythemia.[36] Ferritin however, being an acute phase reactant, did not correlate well with serum iron or hematocrit[39] and is considered inaccurate in measuring iron deficiency in this population.

Inappropriate erythropoietin production. Relative EPO deficiency in allograft recipients with preserved renal function may suggest inability of the transplant kidney to respond adequately to anemia or defective regulation of EPO release.[39] This is a diagnosis of exclusion in patients with successful transplant and absence of rejection. Nampoory et al reported 12 patients with PTA after excluding all recognized causes of anemia. All patients except two had inappropriately low levels of EPO which indicates decreased EPO production by the transplant kidney. This was supported by adequate response to EPO administration in five patients.[40] Two patients in the same study[40] had higher EPO levels than what would be expected for a similar degree of anemia what suggests a phenomenon of functional EPO deficiency or EPO resistance similar to that seen in anemia of chronic disease or in other solid organ transplants.[33,34]

Immunosuppression. Azathioprine (AZA) affects purine nucleotide synthesis and is a potent myelosuppressant. Saito et al reported a trend towards macrocytic and hyperchromic changes in anemic patients on AZA similar to vitamin B12 or folate deficiency.[35] This was more frequent when AZA was commonly used and doses were maintained at higher levels. Wickramasinghe et al reported macrocytosis in 74% of renal transplant recipients receiving 3mg/kg/day of AZA.[43]

Mycophenolate mofetil (MMF) inhibits the type II isoform of inosine monophosphate dehydrogenase needed in the de novo pathway of purine synthesis and was recently described to cause anemia with or without associated leukopenia.[45] Arbeiter et al reported a patient with erythroid aplasia that resolved when MMF was discontinued. Causes of anemia such as iron deficiency and bleeding were ruled out. There were no signs of parvovirus B19 infection by PCR and CMV and EBV serologies were negative. MMF was restarted four months later and anemia recurred.[46]

Anemia was also reported in 27-37% of patients receiving sirolimus during clinical trials.[51] This can usually be managed with erythropoietin.

Suzuki et al described a patient with pure red cell aplasia (PRCA) induced by tacrolimus (FK506). The mechanism by which tacrolimus causes PRCA is unclear, however substitution with CSA caused resolution of the anemia.[47]

ACE–I and ARB. As described earlier, angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) cause anemia and are used for the treatment of PTE. Angiotensin II may stimulate erythropoiesis through effects on AT1 receptors. In anemic patients, discontinuing these medications causes improvement in hematocrit within 6-8 weeks.

Hemolysis. Hemolytic uremic syndrome (HUS), a disorder characterized by microangiopathic hemolysis, thrombocytopenia, and renal failure, is a serious complication of organ transplant. Reports describe an incidence of 0.5 to 3.4% in renal patients usually occurring within one year after transplantation.[44,45] In one study, 90% of patients with HUS were renal transplant recipients. The cause was attributed to cyclosporine A (CSA) or tacrolimus therapy that triggered an immune-mediated vascular endothelial damage and secondary thrombogenesis.[41] Infections with CMV, *E. coli* 0157:H7 and *Shigella dysenteriae* had no statistical correlation to HUS in transplant patients.[41] Diagnosis is usually suspected when anemia is associated with thrombocytopenia, renal dysfunction, and hemolysis evident by increased direct bilirubin, lactate dehydrogenase and reticulocyte count, decreased haptoglobin, and presence of schistocytes on peripheral blood smear.

The treatment of post-transplant thrombotic microangiopathy consists of discontinuing or reducing the triggering factor (CSA or tacrolimus), plasmapheresis, steroids, and conversion to other immunosuppressive agents. Plasmapheresis or plasma exchange allow the removal of the offending platelets aggregating factors and are therefore more effective than plasma infusion. Despite treatment however, the incidence of renal allograft loss due to HUS is 43% and mortality is 12%.[41]

Infections. Parvovirus B19 infection is an underestimated cause of anemia in transplant patients. It accounts for 6.3% of hypo-proliferative anemias in this population and should be suspected when anemia is associated with normal renal function, decreased reticulocyte count, and minimal response to erythropoietin.

Parvovirus B19 is a single stranded DNA virus that causes erythema infectiosum or fifth disease, arthritis and aplastic anemia. Infection is biphasic and the initial symptoms such as fever and myalgias are non-specific and coincide with viremia. It is only during the second phase that symptoms specific to parvovirus B19 such as rash, slapped cheeks appearance and arthralgias manifest. Immunoglobulins M (IgM) appear first and are followed a few days later by IgG. This antibody response correlates with clearing of the infection.[44] The role of cellular immune response in controlling the infection is not clear.

The receptor to parvovirus is a p antigen that is present on the erythroid precursor cells eventually causing lysis of these cells. In a normal host, the immune response controls the infection in 1 to 2 weeks, and the lysis of the erythroid precursor cells causes a transient anemia. In patients with high blood turnover such as sickle cell disease and thalassemia, anemia is more severe but still resolves with clearance of the infection. It is in the immunocompromised patients however that viremia persists leading to a chronic infection and severe bone marrow aplasia affecting the erythroid precursor cells and occasionally other hematopoietic stem cell lines. IgM may not be present and detecting B19 DNA by PCR makes the diagnosis.[37]

Patients have been treated with different regimens of intravenous immunoglobulin (IV Ig). Bertoni et al treated successfully four patients with 400 mg/kg/day of IV Ig for 15 days.[42] Another study reported normalization of both the reticulocyte count and hematocrit within six weeks after a two day treatment with 1 gm/kg/day of IV Ig.[37]

Recommendations. The initial serology in evaluating PTA should include iron studies, vitamin B12 and folate levels, and a reticulocyte count. Iron deficient patients receive iron supplements and are evaluated for occult blood loss. Infections such as parvovirus B19, hepatitis, Epstein-Barr virus, and cytomegalovirus should be included in the differential diagnosis of anemia and reticulocytopenia in transplant patients. Caution should be used in oral iron replacement for patients taking mycophenolate mofetil. Iron may chelate the mycophenolate, restricting gastrointestinal absorption, and lead to markedly diminished levels of mycophenolic acid. Iron should be taken after there is adequate time for absorption of mycophenolate.[50] Patients with increased reticulocyte count should

have lactate dehydrogenase (LDH), haptoglobin, and blood examined for schistocytes to rule out hemolysis or hemolytic uremic syndrome (HUS) especially in the setting of a low platelet count. If the reticulocyte count is decreased, bone marrow suppression by the immunosuppressive drugs or infection is suspected. Inappropriate production of erythropoietin is a diagnosis of exclusion in stable allograft function, but is a major factor in a failing renal transplant.

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