Effect of Red Cell Transfusions on Future Kidney Transplantation

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Summary
Red cell transfusions, erythropoiesis-stimulating agents (ESAs), and intravenous iron therapy all have a place in the treatment of anemia associated with CKD. Their relative merits and uses are subject to many clinical and nonclinical factors. New concerns associated with the use of ESA therapy make it likely that the use of blood transfusions will increase, refueling previous debates about their associated risks. Data on whether red cell transfusions increase sensitization to HLA antigens, rendering subsequent transplantation more problematic, are mainly derived from older literature. Older data suggested that women were more at risk of HLA sensitization than men, particularly those with previous multiple pregnancies, although recent U.S. Renal Data System data have challenged this. HLA sensitization prolongs the waiting time for transplantation and reduces graft survival. Leukocyte depletion of red cells does not appear to reduce the risk of HLA sensitization. This review summarizes much of the data on these issues, as well as highlighting the need for further research on the potential risks for blood transfusion in patients with CKD.

Introduction
Before the advent of erythropoietin therapy, patients with CKD had to cope with basal hemoglobin concentrations of 5 or 6 g/dl, with periodic red cell transfusions to abrogate severe symptoms of lethargy and poor physical capacity. Many of the patients became iron-overloaded, with organ dysfunction due to tissue iron deposition. Concerns about transmission of infectious agents also arose, along with many other complications associated with blood transfusion. In many younger dialysis patients who were ultimately hoping to receive a kidney transplant, there was a concern that blood transfusions could increase sensitization to HLA antigens, potentially make transplantation more problematic, and reduce graft survival.

This latter issue has been the subject of much controversy in recent years and was extensively reviewed by the current Kidney Disease Improving Global Outcomes Anemia Guidelines Work Group. It became apparent that some of the assumptions of the effect of red cell transfusions on HLA sensitization are indeed scientifically based; others are myths. The purpose of this review is to critically examine the literature concerning this issue over the past 30–40 years, and in particular to ascertain whether some of the assumptions in the 1970s are still valid in 2012.

Overview of Blood Transfusion Use in Patients with CKD
In the pre-erythropoietin era, high-volume blood transfusions were common practice for treating anemia of CKD. However, the realization in the 1970s that blood transfusions were immunogenic, leading to production of anti-HLA antibodies (which at the time of cross-match precluded transplantation), as well as the serious consequences of transfusion-induced hepatitis in the immunosuppressed graft recipient, prompted a policy of avoiding blood exposure. Within a few years, however, some reports indicated that nontransfused patients receiving cadaveric donor grafts had a 20%–30% lower 1-year graft survival (1). Subsequent registry data involving thousands of patients confirmed that in the precyclosporine era, lack of pretransplant blood transfusions was the single most powerful predictor of poor outcome (2). Opelz et al. reported that patients receiving pretransplant blood transfusions had a 20% improvement in graft survival under steroids and azathioprine than those who did not (3).

In view of these observations, efforts were made to define the optimal dose and timing for pretransplant blood transfusions. Opelz et al. reported that there was a dose effect, with some improvement after a single blood transfusion and the highest survival rates after receipt of 10–20 pretransplant blood units (1). Other investigators suggested not exceeding 2–6 transfusions (4–6). The type of blood (frozen, fresh, or washed packed red blood cells) made no difference; the leukocyte component was the only one that mattered (7). Administration of blood in the preoperative period had no beneficial effect (8). Preservation of blood with the agglomeration method resulted in a less immunogenic product, but one that was still capable of improving graft survival (9). Duration of the so-called transfusion effect was difficult to evaluate, but blood transfused within a year or two before
transplantation appeared to have a beneficial effect. As a consequence of these data, many transplant centers started to deliberately transfuse two to five units to potential recipients before transplantation.

In the 1980s, the beneficial effect of blood transfusions in kidney transplantation became less clear. Registry data showed significant improvements in graft and patient survival, mainly as a result of the additive effect of better HLA matching (10) and more powerful immunosuppression. The change in the transfusion effect during the early 1980s, before the introduction of cyclosporine, was signaled by a disappearance of the graded response to increasing numbers of blood units. Registry data indicated that the transfusion effect diminished to a 10% improvement by the 1980s (2,11) and had almost disappeared in the 1990s (12,13). Given the lack of efficacy and the risk of sensitization, routine pretransplant blood transfusions were no longer used in most clinical transplant centers (14). In an effort to overcome the difficulties associated with pretransplant blood transfusions, some transplant centers used alternative strategies to random transfusions, such as donor-specific transfusions (15), HLA-DR-matched transfusions (16), partially or totally HLA-matched donor transfusions (17), and the use of cytotoxic T-lymphocyte antigen 4 immunoglobulin to inhibit alloantibody responses to blood transfusions (18). To re-examine the transfusion effect, Opelz et al. performed the first randomized clinical trial of pretransplant blood transfusions on graft outcomes. A total of 423 prospective cadaveric kidney transplant recipients from 14 European centers were randomly assigned to receive three pretransplant packed cell transfusions (n=205) or transfusions without transfusions (n=218) (19). The graft survival rate was significantly higher in the transfusion recipients than in patients who did not receive transfusions (at 1 year: 90%±2% versus 82%±3%, P=0.02; at 5 years: 79%±3% versus 70%±4%, P=0.03). The beneficial transfusion effect was independent of age, sex, cause of CKD, prophylaxis with antilymphocyte antibodies, and preformed lymphocytotoxins. The authors concluded that even with the use of more potent immunosuppressive regimens, pretransplant transfusions are associated with improved graft outcomes of cadaveric kidney transplant recipients. The mechanism for the beneficial effect of blood transfusions still remains unclear. Consequently, despite the somewhat favorable results of this randomized trial, no consensus favored transfusion benefit over sensitization and infection risk.

The concern regarding transmission of viruses, including HIV, and the introduction in 1989 of recombinant human erythropoietin (r-HuEpo) therapy to maintain an adequate red cell mass were additional incentives to avoid blood transfusions in patients with CKD. In a retrospective analysis of hemodialysis patients awaiting transplantation before (group A) and 4 years after (group B) the introduction of rHuEpo, the total number of transfusions decreased by 34% during the study period, and the ratio of transfusions to hemodialysis treatments was reduced from 0.095 to 0.06 (P=0.001). Moreover, the number of patients sensitized as a consequence of blood transfusion decreased from 63% in group A to 28% in group B (P=0.0004). The overall incidence of sensitization decreased from 50% in group A to 36.5% in group B (P=0.008), which resulted in a significant reduction in the mean waiting time for transplantation (42.1±1.1 versus 15.4±2.4 months; P<0.001) (20). Other studies have also reported a lower risk of sensitization with the use of r-HuEpo instead of blood transfusions (21–23). More current data from the United States Renal Data System (USRDS) indicate that the proportion of hemodialysis patients undergoing transfusion in an outpatient center was just 0.37% in 2008 and 7% overall (24).

Among transplant recipients, use of pretransplant blood transfusions has declined from 49% in 1991 to 15% in 2008. Transfusions are slightly more common among women than men (17.1% versus 13.4%) (24). Among wait-listed patients, blood transfusion use has remained rather stable since 1995. Approximately 30% of transplant candidates in 2007 had received at least one blood transfusion within 3 years of being added to the list. Moreover, blood transfusion use is greater among patients highly sensitized at the time of transplant (panel-reactive antibody [PRA] ≥ 80%) (24).

Several clinical trials published between 2006 and 2010, including CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency), CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta), and TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) have raised significant concerns regarding the safety of treating anemia of CKD with erythropoiesis-stimulating agents (ESAs) (25–28). Specifically, normalization of hemoglobin in patients with CKD has been associated with no benefit in terms of cardiovascular morbidity and mortality, as well as an increased risk of stroke and cancer in patients with a history of or current malignancy. Furthermore, recent post hoc analyses of two of these ESA trials have suggested, although not proved, that high doses of ESA may cause toxicity, particularly in conjunction with achievement of high hemoglobin levels (28–31). These concerns have led to renewed interest in blood transfusions for treating anemia in patients with CKD.

**Evidence for Blood Transfusions Causing Increased HLA Sensitization**

The risk of HLA sensitization after blood transfusion has changed over time, at least in part because of changes in blood transfusion practices and use of more precise methods to measure allosensitization. In the early 1980s, Opelz et al. examined the risk of sensitization in 737 hemodialysis patients (Figure 1, A and B), of whom 331 were followed prospectively (Figure 1C) (32). Approximately 90% of all transfusions were given as packed cells and the remainder as whole blood or frozen blood. About 10% of the packed cell units were washed packed cells. Because sensitization rates did not differ with the various types of blood (whole/frozen/washed packed cells), the data were combined. Antibodies were detected by the lymphocyte cytotoxicity test.

Overall, approximately 28% of transfused patients followed prospectively developed HLA antibodies; of these, 18% developed reactivity to 10%–50% of the panel, 7% to 50%–90%, and <3% to >90% with up to 20 transfusions (Figure 1C). Ninety percent of the men remained...
Figure 1. Lymphocytotoxic antibody reactivity against random donor test panel in relation to the number of blood transfusions. Fractions of patients reacting against <10%, 10%-50%, 51%-90%, and >90% of the panel donors are plotted. All 737 patients were undergoing long-term hemodialysis and were waiting for a first kidney transplant. Numbers of patients after 2, 5, 10, 15, and 20 transfusions are indicated at top of graphs. (A) Male and female patients. (B) Female patients categorized by the number of previous pregnancies. (C) Lymphocytotoxic antibodies in patients who were studied prospectively throughout the course of treatment (32).
essentially unresponsive (<10% antibody reactivity against the panel) and 10% developed reactivity to 10%–50% of the panel (Figure 1C). In contrast, after 10 transfusions, 6% of the women demonstrated >90% reactivity, 23% showed 51%–90% reactivity, 11% showed 10%–50% reactivity, and only 60% were “unresponsive” (Figure 1C). These and other data suggested that the main drivers of HLA sensitization after red cell transfusion are previous pregnancies and previous transplantation. Men seemed to have a much lower risk of HLA sensitization after transfusion than women, and women with multiple pregnancies seemed to have a much greater risk of HLA sensitization than nulliparous women.

Studies performed in the last two decades showed that the risk of sensitization with blood transfusion was apparently lower than previously reported, with an overall response rate ranging from 2% to 21% (19,33,34). A possible explanation for this lower sensitization rate is that red blood cell transfusions in recent years are less immunogenic because they contain fewer leukocytes as a result of more widespread use of blood filters (see below).

Other conclusions that can be drawn from previous studies include the following: (1) washed red blood cells do not appear to be less immunogenic than nonwashed red blood cells (32); (2) no consistent reduction in sensitization has been demonstrated with donor-specific (33) and DR-matched (35) transfusions; and (3) higher numbers of blood transfusions have been associated with an increased risk of sensitization in some studies (11,36) but not in others (32,37).

Further data relevant to this issue are found in the 2010 USRDS annual report (24). This report suggests that the risk of sensitization with blood transfusions is substantial. For example, compared with patients who have never received a blood transfusion, patients who received transfusions have a 2.38 odds of a PRA $\geq$ 80%. Interestingly, in this analysis the risk of being highly sensitized at the time of transplantation was higher for men than for women (Figure 2) (24). The 3-year cumulative incidence of transfusion in wait-listed patients was highest among patients who were highly sensitized at the time of transplant (PRA $\geq$ 80%) (38).

Effect of Leukocyte Depletion on Risk of HLA Sensitization after Blood Transfusion

Leukocytes often contaminate cellular blood components and have been implicated with several adverse effects of blood transfusions. The most common adverse effects are mediated by immune mechanisms and include graft-versus-host disease, reactivation of viral or bacterial diseases, immunosuppression, and allosensitization to HLA antigens. The latter may result in red blood cell alloimmunization, transplant rejection, febrile reactions, and refractoriness to platelet transfusions (39). Despite mounting evidence regarding the adverse consequences of leukocyte contamination of blood products, it continues to be a matter of debate whether the evidence is compelling enough to justify the cost of universal prestorage leukoreduction of blood products (40–47). Despite the debate, many European countries have already adopted universal leukoreduction of blood products. In the United States, approximately 75% of blood is leukoreduced.

Previous studies have also reported that leukoreduction of blood products is ineffective in decreasing sensitization in previously transplanted patients and in potential kidney transplant candidates (48–50). A possible reason for this finding is that the number of HLA molecules contributed by the red blood cells is similar to that of the leukocytes (51).

Effect of Increased HLA Sensitization on Waiting Time for Transplantation

Increased PRA titers due to blood transfusions and other factors are associated with longer waiting times for finding compatible donors and may completely preclude transplantation. For example, the median wait time for patients with a 0% PRA was 2.5 years in 2005, whereas for patients with a PRA of 1%–19% and 20%–79% the median wait times were 2.9 and 4.3 years, respectively. Not unexpectedly, wait times for highly sensitized patients (those with a PRA $\geq$ 80%) listed in 2005 were still to be observed in 2010 (24). Consequently, the distribution of PRA values among wait-listed patients tends toward higher levels of sensitization with longer periods from the date of listing,
reflecting the difficulty of finding suitable donors for highly sensitized candidates. As an example, the percentage of patients with PRA $\geq 80\%$ increased from 7.5\% at listing to 13.3\% at 5 years after listing (24).

It is important to note that waiting times in the United States have a large regional variation. Compared with a national average of 2.1 years, median waiting times for adults who underwent transplantation in 2008 exceeded 3 years in Alabama, Hawaii, New Jersey, California, and Illinois. Likewise, projected median wait times for listed adults in California and Alabama were 7.2 and 9.3 years, respectively (24). Thus, in these venues the sensitized patient will probably die on dialysis, making transfusions even more problematic.

**Effect of HLA Sensitization on Outcomes after Renal Transplantation**

Not being transplanted or having to wait longer for transplantation is associated with lower survival (52,53). Indeed, receiving a transfusion while on the transplant wait list in the first 5 years is associated with a nearly five-fold higher risk of dying and an 11\% reduction in the likelihood of ever receiving a transplant (24). The risk of sensitization is therefore not trivial (54). Furthermore, even after transplantation, the presence of preformed HLA antibodies is associated with an increased risk of early and late graft loss (55–58). Recent data also suggest that pre-existing donor-specific HLA antibodies identified by Luminex single-antigen assay at the time of transplantation are associated with a higher incidence of antibody-mediated rejection and inferior graft survival (59).

It is important to note, however, that the strength and specificities of anti-HLA antibodies of sensitized patients allow for estimation of the percentage of donors who will be crossmatch-incompatible for a candidate. For that reason, the United Network for Organ Sharing recently introduced a new measure of sensitization for transplant candidates, the so-called calculated PRA (60). Under this scheme, kidney transplant candidates who are sensitized to $\geq 20\%$ of potential deceased donors have access to HLA-matched kidneys from anywhere in the United States. Those with calculated PRA of $\geq 80\%$ are assigned

**Figure 3.** Clinical algorithm to guide the use of red cell transfusions in patients with CKD. ESA, erythropoiesis-stimulating agent.
### Table 1. Indications for Blood Transfusions

<table>
<thead>
<tr>
<th>Indication</th>
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<tr>
<td>When rapid correction of anemia is required to stabilize the patient’s</td>
<td>Red cell transfusion in patients with acute hemorrhage is indicated when there is: (1) rapid acute hemorrhage without immediate control; (2) estimated blood loss of &gt;30%–40% (1500–2000 ml) with symptoms of severe blood loss; and (3) estimated blood loss &lt;25%–30% with no evidence of uncontrolled hemorrhage if there are recurrent signs of hypovolemia despite colloid/crystalloid resuscitation. In patients with certain comorbid factors, transfusions may be necessary with less blood loss (69). Studies evaluating the importance of anemia and the role of transfusion in the setting of an acute coronary syndrome (i.e., unstable angina, myocardial infarction) have reached differing conclusions. The American College of Cardiology/American Heart Association and American College of Chest Physicians guidelines did not make any recommendations concerning the potential benefit or risk of blood transfusion in the setting of an acute coronary syndrome (70,71). Although anemia occurs frequently in patients with heart failure, limited data are available on treatment of anemia in this population. Correction of anemia has not been established as a routine treatment in heart failure, as noted in the 2005 American College of Cardiology/American Heart Association guidelines, the 2006 Heart Failure Society of America guidelines, and the 2008 European Society of Cardiology guidelines (72–74). General indications for red cell transfusion may be applied to patients with acute coronary syndrome and/or heart failure; however, careful attention to volume status is indicated when there is coexistent renal impairment.</td>
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<tr>
<td>condition (e.g., acute hemorrhage, unstable coronary artery disease)</td>
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<tr>
<td>When rapid preoperative hemoglobin correction is required</td>
<td>Criteria have been proposed for the administration of perioperative transfusions, as follows (69): Red cell transfusions are generally not recommended when hemoglobin level is ≥10 g/dl in otherwise healthy person. Red cell transfusions should be given when hemoglobin level is &lt;7 g/dl. When hemoglobin level is &lt;7 g/dl and the patient is otherwise stable, 2 units of packed red cells should be transfused, following which the patient’s clinical status and circulating hemoglobin should be reassessed. High-risk patients (those age &gt;65 years or those with cardiovascular or respiratory disease) may tolerate anemia poorly and may be transfused when hemoglobin level is &lt;8 g/dl. For hemoglobin level 7–10 g/dl, the correct strategy is unclear. Patients with chronic anemia (e.g., those with bone marrow failure syndromes or hemoglobinopathies) may be dependent on red cell replacement over a period of months or years, which can lead to iron overload. Approximately 200 mg of iron are delivered per unit of red cell; this iron is released when hemoglobin from the transfused red cell is recycled after red cell death. Given the progressive loss of red cell viability that occurs during storage, the “freshest available” units should be selected to maximize post-transfusion survival. Hemosiderosis can produce organ damage when the total iron delivered approaches 15–20 g, the amount of iron present in 75–100 units of red cells, as occurs in conditions such as thalassemia or sickle cell disease. The issue of red cell transfusion in patients with congenital or acquired hemolytic anemia is more complex. ESAs should be used with great caution, if at all, in patients with CKD with active malignancy, a history of malignancy, or a history of stroke.</td>
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<tr>
<td>When symptoms and signs related to anemia are present in patients in whom ESA therapy is ineffective (e.g., those with bone marrow failure, hemoglobinopathies, ESA resistance)</td>
<td></td>
</tr>
<tr>
<td>When symptoms and signs related to anemia are present in patients in whom the risks of ESA therapy may outweigh the benefits</td>
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ESA, erythropoiesis-stimulating agent.
additional priority points when a compatible kidney is the best option (61).

On the other hand, novel immunosuppressive protocols incorporating intravenous immunoglobulin and plasmapheresis enable successful transplantation for sensitized patients (62–65). Although encouraging, these protocols are available to only a small proportion of sensitized potential recipients and will probably do little to address the disparity in access to transplantation.

As an alternative to desensitization protocols, paired kidney exchanges enable kidney recipients who have willing living donors to swap incompatible kidneys for compatible ones (66). However, for most broadly sensitized patients, neither of these two options is feasible (61). Clearly, transplanting compatible kidneys is the best approach, and, thus, strategies to prevent allosensitization are likely to have a greater impact for patients with CKD.

Conclusions and Recommendations

The older data suggested that the risk of allosensitization with blood transfusions is low when they are given to transplant-naive male patients or nulliparous female patients who have not received repeated transfusions in the past. Patients who have lost a previous kidney graft and multiparous women, on the other hand, were thought to be at high risk of developing broadly reactive antibodies, especially after blood transfusions. More recent data from the USRDS, however, have challenged this and have suggested that men may be at higher risk than was previously believed. Despite some uncertainties, the available data support the premise that blood transfusions are sensitizing events that can cause an increase in HLA antibodies, and thus, should be minimized or avoided if possible in all potentially transplantable patients with CKD.

Although the evidence is conflicting, the majority view is that leukoreduction of blood products is ineffective in decreasing sensitization in previously transplanted patients and potential kidney transplant candidates. Increased PRA titers due to blood transfusions are associated with longer waiting times for finding compatible donors and may completely preclude transplantation. Not being transplanted or having to wait longer for transplantation is associated with lower survival. Furthermore, even after transplantation, the presence of preformed HLA antibodies is associated with an increased risk of early and late graft loss.

Despite the risks associated with HLA allosensitization, the introduction of calculated PRA and the emphasis on strengths and specificities of donor-specific antibodies as opposed to non-donor-specific antibodies have resulted in a paradigm shift regarding the management of sensitized patients for transplantation. Furthermore, desensitization protocols and paired kidney exchanges offer additional options, although they are limited to only a small proportion of sensitized potential recipients.

The decision to transfuse patients with CKD should be based on a careful analysis of benefits and risks (Figure 3). Individualization of anemia management has appeared as a consistent theme throughout several recent guideline and recommendation documents, and this is highly pertinent to the use of red cell transfusions in patients with CKD. Thus, in certain acute situations (e.g., acute severe hemorrhage), the use of blood transfusions is mandatory and may be life-saving (Table 1). In other clinical scenarios (such as when major surgery is planned and the preoperative hemoglobin level is < 7 g/dl), the balance of benefit versus risk may also favor transfusion. In the critical care setting, in which anemia is common, data from a randomized, controlled trial showed that a restrictive transfusion strategy (transfusing red cells at a hemoglobin level < 7 g/dl) is at least as effective as and possibly superior to a liberal transfusion strategy (transfusing red cells at a hemoglobin level < 10 g/dl) in critically ill patients, with the possible exception of patients with acute myocardial infarction and unstable angina (67). Recommendations following a recent systematic review on the management of anemia in heart disease, however, suggested that in acute coronary syndromes, the use of blood transfusions to correct anemia when the hemoglobin level is 8–9 g/dl is questionable (68). In chronic anemia, when blood transfusions to correct anemia when the hemoglobin level is 8–9 g/dl is questionable.

A relevant factor in this situation is the likelihood of the patient being listed for kidney transplantation. In an older patient in whom kidney transplantation is contraindicated because of severe cardiovascular disease, for example, the threshold for using blood transfusions might be lower. However, in a 29-year-old, otherwise fit mother of two who is contemplating kidney transplantation, greater efforts should probably be made to avoid the use of transfusions, given the risk of allosensitization and subsequent outcomes. Conversely, in patients at high risk of serious complications with ESAs (those with previous or current malignancy, or previous stroke), and in those who require high doses of ESA to achieve a certain hemoglobin level, the balance of benefits and risks may favor transfusion.

Clearly, further research is needed to confirm the older data on the risk of allosensitization after blood transfusion and to continue searching for alternative ways to reduce sensitization with blood products. In the short term, this is likely to take the form of prospective observational studies monitoring the use of transfused blood in patients with CKD and collecting data on HLA sensitization and subsequent transplant outcomes. In the longer term, there is also a pressing need for randomized, controlled trials, although the design, funding, and implementation of such trials will not be straightforward.

Disclosures

None.

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