How important is transfusion avoidance in 2013?

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ABSTRACT

Prior to the advent of recombinant erythropoietin in the late-1980s, blood transfusions were the mainstay of anaemia management in patients with end-stage renal failure, many of whom required “top-up” transfusions every 2 to 4 weeks to relieve the debilitating symptoms of severe anaemia. Erythropoietin therapy, however, allowed for the first time, such patients to achieve a sustained correction of anaemia, and there was a dramatic fall in both the use of red cell transfusions in dialysis units, as well as the associated transfusional iron overload prevalent in dialysis patients. Avoidance of blood transfusions improved access to, and outcomes of, kidney transplantation, due to reduced HLA sensitization. In recent years, however, there have been safety concerns regarding the use of erythropoiesis-stimulating agents (ESAs), and there are now signs that the use of blood transfusions is once again increasing. The aim of this review is to reassess how important transfusion avoidance is in 2013, and whether we should still have the same concerns about HLA sensitization that we had 20 years ago.

INTRODUCTION

Prior to the 1990s, blood transfusions were the mainstay of anaemia management in patients with end-stage renal disease, with a large number of patients requiring ‘top-up’ transfusions every 2–4 weeks to relieve a constellation of severe debilitating symptoms, including profound lethargy, shortness of breath on mild exertion and poor physical capacity. The disadvantages and potential harm associated with this practice were well-recognized, and included the risk of transmission of infectious agents, sensitization to HLA antigens and transfusional iron overload [1]. The effects of the blood transfusions were transient, and chronic repeated transfusional support was the norm for many patients. The advent of recombinant human erythropoietin in 1990 transformed this situation, and allowed the vast majority of dialysis patients to achieve a sustained correction of anaemia to levels of haemoglobin that significantly reduced the need for regular transfusions. Three major consequences arose over the next decade or so: (i) there was a steady but progressive rise in haemoglobin concentration from a mean of ~9.5 g/dL to a mean of ~11.5 g/dL [2];

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INTRODUCTION

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(ii) the rate of use of blood transfusions in dialysis units fell by ∼50% between 1990 and 2000, as exemplified by data from the US Renal Data System Report 2009 (Figure 1) [2] and (iii) there was a dramatic reduction in transfusional iron overload in dialysis patients (and indeed functional iron deficiency became much more common than iron overload). From 2000 until the present day, the use of blood transfusions in dialysis patients has remained at these low levels, and the use of erythropoietin therapy, as well as intravenous iron supplementation, became increasingly widespread. Over the same period, a number of pivotal randomized controlled trials raised some safety concerns about erythropoiesis-stimulating agent (ESA) therapy [3–6], including an increased propensity to arterial thrombotic events such as stroke, as well as venous thromboembolism, and even exacerbation of malignancy. Regulatory advice, recommendations and guidelines have propagated a message that, while ESA therapy undoubtedly has a role in the management of anaemia and chronic kidney disease (CKD), greater care should be exercised regarding its use. Both the target haemoglobin (for patients receiving ESA therapy) and the trigger haemoglobin (the point at which ESA therapy is initiated) have gradually and progressively fallen and the likely implication of this is that once again there will be a rise in the use of blood transfusions in dialysis patients. Indeed, there is already preliminary evidence that this is happening. Two presentations at the National Kidney Foundation Meeting in May 2012 [7, 8] indicated a swing towards a greater use of red cell transfusions. Allan Collins presented the latest US Renal Data System (USRDS) data, indicating that the mean haemoglobin concentration in US dialysis patients fell 3.8% between 2009 and the first 9 months of 2011, from 11.39 to 10.96 g/dL [7]. There was a 19.2% drop in doses of ESA therapy and a 3.4% increase in the use of intravenous iron. The rate of blood transfusions increased slightly from 0.030 to 0.036 transfusions per patient per month [7]. There were similar findings from the Dialysis Outcomes and Practice Patterns Study (DOPPS) data presented by Bruce Robinson [8]. In this large global observational database, the median haemoglobin levels fell 0.08 g/dL between August 2010 and July 2011, and by an additional 0.37 g/dL up until October 2011. The median weekly ESA dose fell by 28% between August 2010 and December 2011. Intravenous iron use steeply increased from 57% of patients receiving iron in 2010 to 77% in December 2011. More worryingly, the rate of blood transfusions more than doubled from 2.21% of patients transfused per month in September 2010 to 4.87% of patients transfused per month in September 2011 [8]. Even ignoring the fact that blood products are a scarce resource in which there is often a short supply, should we be concerned if we have to administer more blood transfusions in our dialysis, or even non-dialysis patients?

The key questions for nephrologists regarding this issue in 2013 are surely the following:

(i) What are the risks of transfusion reactions or transmitted infections in the modern era with more stringent testing of donated blood?
(ii) Do blood transfusions increase the risk of HLA sensitization?
(iii) Is HLA sensitization ‘bad’ for the patient?

**RISKS OF BLOOD TRANSFUSION REACTIONS**

Immediate hypersensitivity reactions to blood transfusion are very rare, but are life-threatening. The risk of IgE-mediated anaphylaxis is estimated at 1 in 20 000 to 1 in 50 000 per unit of blood transfused [9]. The risk of fatal haemolysis is estimated at 1 in 1 000 000 [9]. Haemolytic reactions and transfusion-related acute lung injury are more common, estimated at 1 in 6000 and 1 in 5000, respectively [9]. Even more common, but less serious, are febrile reactions, which are believed to occur in ∼1 in 300 units of blood transfused and urticarial or other skin reactions in ∼1 in 50 to 1 in 100 [9]. All of these adverse events are believed to have an immunological basis,
and are usually idiosyncratic and unpredictable in the individual patient. Some patients develop red cell antibodies, which make cross-matching suitable blood problematic. In short, these adverse consequences of blood transfusions are sufficiently rare not to cause too much anxiety for the nephrologist, but can clearly be catastrophic for the individual patient who is involved.

The UK Transfusion Service initiated a survey a few years ago which examined the Serious Hazards of Transfusion [10]. A total of 3200 reports were obtained, of which 2464 were analysed. The findings indicated three deaths directly and solely caused by a blood transfusion. In a further 10 cases, the transfusion probably or possibly contributed to this adverse outcome. There were also 101 reports of major morbidity, with acute transfusion reactions being the single highest cause resulting in a serious outcome for 7.8% of cases reported [10]. Transfusion data from the US in 2010 documented 71 reports of a fatality in recipients of a blood transfusion, of which 40 were considered directly related to the transfusion [11]. Nearly half of these (45%) were caused by transfusion-related lung injury, 20% were caused by transfusion-associated circulatory overload, 10% were due to anaphylaxis and 18% were due to other transfusion reactions [11].

**BLOOD TRANSFUSION AND TRANSPLANTATION**

The impact of blood transfusion on accessibility to renal transplantation and the outcome of engraftment have swung full circle. Fifty years ago, it was recognized that blood transfusions were immunogenic, leading to the production of anti-HLA antibodies, which, in turn, caused a positive cross-match that precluded subsequent transplantation [12]. At the same time, there were serious concerns about transmission of hepatitis, and both these factors prompted a policy of avoiding exposure to blood transfusions at all costs. A few years later, however, some reports appeared in the literature suggesting that non-transfused patients receiving deceased-donor kidney transplants had a 20–30% lower 1-year graft survival compared with patients who had been transfused [13]. Subsequent registry data involving thousands of patients confirmed that in the pre-cyclosporin era, failure to transfuse a potential kidney recipient was the single most powerful predictor of a poor outcome [14]. Much of this observational research was led by Professor Opelz in Heidelberg, who reported that patients receiving a blood transfusion prior to renal transplantation had a 20% improvement in graft survival, compared with those who did not receive a transfusion [15]. Efforts were directed at trying to optimize the positive effect of a blood transfusion in terms of the number of units transfused [13, 16–18] and the type of blood administered (fresh, frozen and washed cells), in an attempt to optimize the 'transfusion effect'. For a while, many transplant centres adopted programmes, deliberately transfusing 2–5 units to potential recipients on the transplant waiting list.

In the 1980s, this beneficial effect of blood transfusions became less clear. Further registry data showed strong associations with graft and patient survival in relation to better HLA matching [19] and more powerful immunosuppression. By the 1990s, the ‘transfusion effect’ was finally discarded [20] and once again the desire to avoid blood transfusion appeared, now aided by the introduction of erythropoietin therapy. Nevertheless, there was a lasting legacy from a prospective randomized controlled trial published in 1997, again by Opelz and Terasaki [21], still suggesting a positive ‘transfusion effect’ in the 205 patients who were transfused compared with the 218 patients who did not receive a transfusion, with significantly greater graft survival rate at 1 year (P = 0.02) and 5 years (P = 0.03). Cox regression analysis showed that this effect was independent of a number of other factors, and was achieved in the era of modern immunosuppressive regimens [21].

**DO BLOOD TRANSFUSIONS INCREASE THE RISK OF HLA SENSITIZATION IN 2013?**

Shortly after erythropoietin therapy was introduced, a retrospective analysis of haemodialysis patients awaiting transplantation before (Group A) and 4 years after the introduction of recombinant erythropoietin (Group B) was conducted [22]. There was a dramatic reduction in the ratio of blood transfusions to dialysis sessions, from 0.095 to 0.06 (P = 0.001), and...
the number of patients sensitized as a result of blood transfusion decreased from 63% in Group A to 28% in Group B (P = 0.0004) [15]. The overall incidence of sensitization decreased from 50% in Group A to 36.5% in Group B (P = 0.008), which in turn resulted in a significant reduction in the mean waiting time for transplantation (42.1 ± 1.1 versus 15.4 ± 2.4 months; P < 0.0001) [22]. Thus, although not a randomized controlled trial, there was a strong temporal relationship between the introduction of erythropoietin and the reduction in blood transfusions impacting on HLA sensitization. Other studies from the early 1990s also reported a lower risk of HLA sensitization with the use of recombinant erythropoietin compared with blood transfusions [23–25], and data from the USRDS report in 2010 showed a gradual increase in the proportion of patients showing 0% panel antibody reactivity over the time period 1992–2008 (Figure 2) [26].

Twenty years on, can we still be as confident that blood transfusions negatively impact on HLA sensitization? In contrast to the number of studies of ESA therapy during this period, there has been remarkably little scientific data produced on the use of blood transfusions in CKD, and certainly no randomized trials. Several studies performed in the last two decades have shown that the risk of HLA sensitization with blood transfusion seems lower than previously reported, with an overall response rate ranging from 2 to 21% [21, 27, 28]. Possible explanations that have been offered for this lower sensitization rate is that red cell transfusions are now less immunogenic, containing fewer leucocytes than previously due to the widespread use of blood filters. Other factors that may impact on the risk of red cell transfusions have included the presence of washed cells versus non-washed cells, matching of the transfusion, and the volume of transfusions administered. Washed red blood cells do not appear to be less immunogenic than non-washed red blood cells [29], donor-specific [27] and DR-matched transfusions [30] have not been consistently shown to reduce HLA sensitization, and there is controversy regarding the number of blood transfusions impacting on the risk of HLA sensitization, with some studies showing a relationship [31, 32] and other studies showing no such relationships [29, 33].

USRDS data from 2010 suggest that the risk of sensitization with blood transfusions remains substantial [26]. The report examined factors impacting on the development of a panel reactive antibody level >80%. Compared with patients who had never received a blood transfusion, patients who had received a transfusion at any stage had an odds ratio of having a PR > 80% of 2.38. Interestingly, in this analysis, the risk of being highly sensitized at the time of transplantation was higher for men than for women [26], in contrast to the earlier data from Opelz et al. [29]. A 3-year cumulative incidence of transfusion in waitlisted patients was most common among patients who were highly sensitized at the time of transplantation [34].

There has also been much debate about whether leucocyte depletion will reduce the adverse consequences of red cell transfusion [35–40]. Despite the uncertainties, many European countries have already adopted universal leuco-reduction in blood products, and in the USA ~75% of blood is currently leucocyte depleted. A number of studies have reported that leuco-reduction in blood products is ineffective in decreasing sensitization in previously transplanted and in potential kidney transplant candidates [41–43]. A possible explanation for this is that the number of HLA molecules contributed by red cells is comparable with that of leucocytes [44].

**IS HLA SENSITIZATION ‘BAD’ FOR THE PATIENT?**

There are two major considerations in relation to this question. The first is whether a patient who is highly sensitized is likely to wait longer for a kidney transplant, or even be denied ever getting one. The evidence in support of this seems fairly clear. In 2005, non-sensitized patients in the USA (those with a 0% PRA at the time of listing) had the shortest waiting times, with a median of 2.5 years, while those with a PRA of 1–19% and 20–79% had median waiting times of 2.9 and 4.3 years, respectively [26]. Highly sensitized patients, i.e. those with a PRA of >80%,
wait the longest, with median waiting times still to be determined for all those patients listed in 2005 (USRDS Report 2010) [26]. There is clearly also difficulty in finding suitable donors for highly sensitized candidates with the percentage of patients with PRA >80% increasing from 7.5% at listing to 13.3% 5 years after listing (USRDS Report 2010) [26]. Clearly, more sensitized patients have to remain on dialysis, and it goes without saying that this associates with a lower survival [45, 46]. Even when transplanted, the presence of pre-formed HLA antibodies is associated with an increased risk of early and late graft loss, and a more recent study suggested that the presence of donor-specific HLA antibodies was associated with a higher incidence of antibody-mediated rejection and inferior graft survival [47]. Although there have been major improvements in novel immunosuppression protocols to allow the successful transplantation of sensitized patients, as well as the introduction of paired kidney exchange schemes, clearly neither of these strategies compares with the ease and success of transplanting compatible kidneys without pre-formed HLA antibodies.

TRIGGER HAEMOGLOBIN FOR RECOMMENDING BLOOD TRANSFUSION

Observational data show a clear relationship between the baseline haemoglobin concentration and the likelihood of the patient being transfused. The ‘break-point’ seems to be somewhere in the region of 9–10 g/dL [48, 49], and a similar break-point was found in an analysis of the Trial to Reduce cardiovascular Events with Aranesp Therapy (TREAT) study [6] conducted for the FDA Cardiovascular and Renal Drugs Advisory Committee meeting on 18 October 2010 (Figure 3). This does not mean that nephrologists are, or should be, transfusing patients when their haemoglobin falls to 9–10 g/dL. This simply means that the likelihood of the patient requiring a blood transfusion increases once the patient’s haemoglobin is 9–10 g/dL. Similar conclusions were reached in a retrospective cohort study of 1837 non-dialysis CKD patients, in which it was suggested that ESA initiation at a haemoglobin of 10.0–11.0 g/dL compared with 8.0–9.9 g/dL was associated with a reduced risk of blood transfusion and initial hospitalization [50]. It is clear, however, that the relationship between Hb level and likelihood of transfusions is confounded by the fact that lower baseline Hb levels are found in sicker patients.

The trigger haemoglobin for prescribing a blood transfusion in CKD patients is poorly researched. In other clinical disciplines, more robust scientific data are available. For example, in the critical care setting, a well-conducted prospective randomized controlled trial from Canada compared a trigger haemoglobin for transfusion of 7 g/dL (restrictive) with 10 g/dL (liberal) [51]. Contrary to expectation at the time, the restrictive strategy of red cell transfusion was as least as effective, and possibly superior to a liberal transfusion strategy in critically ill patients. In fact, for patients who are less acutely ill (APACHE II score of ≤20), the mortality rate was significantly lower with the restrictive transfusion strategy (8.7 versus 16.1%; P = 0.03). While this study cannot be directly extrapolated into patients with CKD, nonetheless, it has unquestionably influenced guidelines for transfusion in otherwise stable anaemic patients [52]. It has also provoked much interest in developing strategies to reduce blood transfusions in specific instances where this is possible; such strategies include the use of anti-fibrinolytic agents, haemostatic agents, haemoglobin substitutes, cell salvage techniques, fibrin sealants and desmopressin [53].

For patients who are actively bleeding, clearly blood transfusions are life-saving and without debate. For chronic anaemia, however, careful consideration now needs to be given as to whether there is a good rationale for recommending red cell transfusions. The age of the patient, degree of symptomatology and the presence or absence of cardiac disease may all impact on that decision. The use of ESA therapy and intravenous iron supplementation still have a major role in minimizing the use of red cell transfusions in CKD and the latest KDIGO Anaemia guideline suggests intervention with ESA therapy when the haemoglobin falls to 9–10 g/dL [54]. Much

**Figure 3:** Post hoc analysis of the TREAT study assessing the rate of red cell transfusion according to baseline haemoglobin.
of the rationale for this came from the TREAT study data [6], which indicated a near-doubling of the transfusion rate in the placebo-treated patients who were only rescued with darbepoetin alfa when their haemoglobin fell <9 g/dL compared with patients targeting a haemoglobin of 13 g/dL (24.5 versus 14.8%; P < 0.001, Figure 4). Similar data had previously been published from the US Normal Hematocrit Study, in which 129 patients (21%) received transfusions in the group randomized to a haematocrit of 42% (haemoglobin of 14 g/dL) compared with 192 patients (31%) randomized to a haematocrit of 30% (haemoglobin of 10 g/dL) [3].

CONCLUSIONS

Despite advances in technologies and treatments over the last 20 years, there is still a clear need to minimize the use of blood transfusion in patients with CKD where possible. The availability of improved viral detection methodology (which has reduced the likelihood of viral transmission), and the use of modern-day immunosuppression and antibody-removal technologies (which might lessen the adverse consequences of HLA sensitization), have gone someway towards reducing the adverse consequences of blood transfusions in our patient population, but by no means have eliminated them. Even if one accepts that the risks of transmissible infections and serious transfusions reactions are rare, they still exist, and transfusions also have immunosuppressive effects, which may amplify or compound the immune dysfunction already prevalent in CKD patients. Blood transfusions are also a scarce and not limitless resource. Finally, the effects of blood transfusion on subsequent transplantation remains pertinent even in 2013; the body of evidence suggests that blood transfusions still increase the risk of HLA sensitization, which increases time on the waiting list, increases graft rejection and worsens graft survival. These latter considerations, of course, apply only to patients who are potential transplant candidates, which these days represent less than a half of the dialysis population. ESA therapy has unquestionably reduced the requirements for blood transfusion in CKD and, despite some recent safety concerns, still has a critical role in limiting the use of blood transfusions.
34. Sanfilippo FP, Bollinger RR, MacQueen JM et al. A randomized study comparing leukocyte-depleted versus packed red cell transfusions in prospective cadaver renal allograft recipients. Transfusion 1985; 25: 116–119


**BLOG COMMENTARY**

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This is a comprehensive review by Mac Dougall and Obrador who revisit ESA treatment as well as trigger and target haemoglobin (Hb) levels in 2013. The authors highlight the fact that both trigger as well as target Hb levels have been lowered in the management of the anemia of CKD based on the growing literature highlighting risks associated with ESA treatment.

The authors address the emerging consequent trend of increasing blood transfusions in CKD and review the implications related to infections transmissions as well as HLA sensitisation of kidney patients.

The NDTERA-EDTAOLA readers may be interested to learn more from the authors of this very interesting article about:

1. Whether the risks of transfusion associated infections will be much higher in emerging economies where the cost of ESAs may be prohibitive and the quality of virological screening of blood transfusions less stringent when compared to higher economies.

2. Also the question of whether those whose trigger Hb is lower and those who are resistant to ESAs and require blood transfusions to deal with severe anemia and associated symptomatologies are, as mentioned by the authors, higher risk patients with shorter life expectations where priority is short term management of the anemia rather than overarching concerns about long term and chronic potential risks of blood transfusions. Many of such patients would be too ill to be considered candidates for renal transplantation. Many have terminal illnesses making the small risk of acquiring a transfusion related infection less of concern.

3. Finally, the question has to be viewed in the context of countries where ESAs are not refunded by healthcare providers. In such instances, CKD patients paying for expensive ESAs may opt for more affordable blood transfusions rather than chronic treatment with unaffordable ESAs. Such ESRD patients live in economies where dialysis itself is a short term option as often it is also not covered or refunded by healthcare providers. In such a case, ESA is a luxury many cant afford. Blood transfusions may make their terminal care more affordable and their anemia related symptoms manageable.

ESAs for all may not be the answer for managing the anemia of CKD. Blood transfusion may have a place. The question is to find the appropriate place of each in the global management of those suffering from anemia and CKD.

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