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Blood Transfusion Effects in Kidney Transplantation

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Within the three decades since the beginnings of the field of clinical renal transplantation there have been four phases in blood transfusion policies, swinging from liberal transfusions to avoidance of transfusions, followed by a repeat cycle of deliberate transfusions and at present turning back to abstinence again. Because of improving skills at the prevention and treatment of rejections, the beneficial effects of random transfusions in the transplant population as a whole is marginal. This comes at a time when community fears of blood-borne infections and the prospects of supporting red cell production by the use of EPO have emerged as new factors in blood banking. Observations on patients at risk for graft loss, namely those having rejection episodes, indicate that a beneficial blood transfusion effect still exists, however. Future application of deliberate HLA antigen exposure in conjunction with novel immunological manipulations may provide a more effective avenue to tolerance induction. The use of blood transfusions matched for one HLA-DR antigen with the recipient has produced major benefits in preliminary trials and represents one starting point in this direction.

Kidney transplantation has evolved to become an effective treatment for patients with end-stage renal disease. Intertwined with the history of this field over the past three decades has been the effect of prior allogeneic blood exposure upon graft survival. For many years it was customary to remove both diseased kidneys from the potential recipient to make it easier to manage hypertension, and to lessen the likelihood of recurrence of the original glomerulonephritic disease. Patients awaiting transplantation, sustained by dialysis machines, became profoundly anemic, with hematocrits close to 15 percent. Many required large numbers of blood transfusions over a period of months, as many as 50-100 units in extreme cases, but frequently exceeding 20 units. With the advent of more effective approaches to blood pressure control, and with the realization that removal of diseased kidneys plays no role in prevention of recurrent disease, native kidneys are generally left in place, except in instances of deep-seated infection in the organs. Even so, many patients benefit symptomatically from blood transfusions in the range of two to five units per year, with the variation probably dependent upon the residual production of EPO by the remnant renal tissue.

CHANGING PRACTICES IN THE PRE-TRANSPLANT USE OF BLOOD TRANSFUSIONS: AN OVERVIEW

The practice of blood transfusion over three decades has twice swung back and forth from one extreme to the other. The *first phase* was the high-volume use of blood as

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Abbreviations: ALG: anti-lymphocyte globulins AMLR: autologous mixed lymphocyte response CML: cell-mediated lympholysis CTLp: cytotoxic T cells DST: donor-specific transfusion(s) MLR: mixed lymphocyte response PRA: panel-reactive antibody

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described above in attempts to keep a patient's red cell mass in the 20–25 percent range. With the realization that blood exposure could be highly immunogenic in many patients, leading to production of anti-HLA antibodies, which at time of cross-match precluded transplantation [1], efforts were made in the 1970s in the *second phase* to avoid blood exposure, a policy that was reinforced by growing concerns about the serious long-term consequences of transfusion-induced hepatitis in the immunosuppressed graft recipient [2]. Indeed, the incidence of hepatitis in the dialysis population itself was a major concern, and the long-term consequences of hepatic failure were accelerated in the immunosuppressed graft recipient. Within a few years, reports appeared suggesting that non-transfused patients receiving cadaveric donor grafts were, in fact, at highest risk for graft rejection, having a 20–30 percent lower one-year graft survival rate [3,4]. The subsequent registry tabulation of thousands of cases showed that, in the pre-cyclosporine era, the failure to transfuse a potential kidney recipient was the single most powerful factor in prediction of a poor outcome. Naturally, this finding led to many attempts to define the dose and timing optima for the transfusion effect. In the first thorough analysis by Opelz et al. there was a distinct dose effect, with a gradation of one-year survival rates according to the numbers of blood units received prior to transplantation [4]. There was some improvement from a single transfusion, with increasing survival rates up to an optimum of 10–20 blood units. It was, furthermore, shown that the type of blood (fresh, frozen, washed packed red blood cells) made no difference, and it was the leucocyte component which mattered. Administration of blood in the perioperative period alone was without effect [5]. In one study, there was indication that the agglomeration method for blood preservation resulted in a product which was much less immunogenic in terms of producing antibodies, while retaining its ability to improve graft results [6]. The question of how long the favorable effect lasts (e.g., what if one had five transfusions many years ago, but none since the onset of end-stage renal disease), was difficult to answer, since few cases had such a history. It seemed clear, however, that blood received within a year or two had a beneficial effect. As a result of these data, most centers in *phase three* followed a deliberate transfusion policy of administering at least two to five units while awaiting transplantation. One problem at the time of these surveys, and continuing today, is the reliability of medical records and of the patient's memory in regard to blood transfusion, especially prior to the initiation of regular dialysis treatments.

As we entered the 1980s, and cyclosporine was introduced, graft and patient survival improved, and the question of the beneficial role of blood transfusions and also of HLA matching has been subject to ongoing re-evaluation. In large registry data, there has been an overall decline in the transfusion effect and an increase in the HLA matching effect. The latter is more clearly recognized now because of improved typing capabilities; indeed, the HLA effect is additive to that of cyclosporine, which itself produces a 15 percent increase in one year survival rates [7]. It is also clear, however, that there had been a progressive improvement, year by year, in graft results, even before the introduction of cyclosporine [8]. In centers that report 90 percent one-year cadaveric graft survivals, it is not possible to discern either an HLA or a transfusion effect, probably as a result of heavy immunosuppression in the early post-transplant period. The change in the transfusion effect during the early 1980s, which started before the introduction of cyclosporine, is most marked by a disappearance of the graded response to increasing numbers of blood units. Only the deleterious effect of receiving no

transfusions remains, with a 10 percent lower one-year survival rate, and this result has been seen whether cyclosporine or traditional azathioprine was used for immunosuppression [9]. Subsequent data bases show an almost trivial detriment to the non-transfused patient group, indicating that the transfusion effect has virtually disappeared in the transplanted population as a whole [10]. There is no simple explanation for this trend, yet because of these data we are now entering the *fourth phase* of transfusion policy, a return to the withholding of blood as possibly unnecessary, at least for the improvement of graft survival. With the recent concerns regarding transmission of viral diseases, including HIV, and with the coming on line of EPO therapy to maintain an adequate red cell mass, it is plain that there are clear incentives to move away from use of pre-transplantation blood transfusions. There are, however, intriguing indications that blood transfusions may play a very important role in particular patients. The remainder of this paper will discuss recent evidence that the blood transfusion effect remains in certain circumstances, when one considers effects of HLA antigens, rejection episodes, and possibly the prospects of tolerance induction. Unless otherwise mentioned, the data come from kidney transplantation, as extensive studies with other organs are unavailable.

THE SPECTRUM OF SENSITIZATION TO HLA AND EFFECTS OF MATCHING

The preceding overview reflects the behavior of the end-stage renal disease population as a whole. With closer analysis of the effects of blood transfusions, one realizes that there are crucial individual differences in the effects of allogeneic blood exposure. First, most patients do not develop anti-HLA antibodies, as measured by the usual cross-match technique of complement-mediated cytotoxicity, following transfusion. Overall, 30 percent of transfused individuals do develop antibodies, with a higher rate in previously pregnant females and a lower one in males [11]. In normal multiparous females, not transfused, about 10 percent make such antibodies, and this response is usually transient for a few weeks after term. These individuals provide the major source of anti-HLA typing sera. As noted, multiparous women challenged with blood transfusions will show an increase in the responder rate to 30–40 percent [11]. Among all responders, male or female, some have a highly selective immune response directed to one to four HLA antigens, while others show sensitivity to better than 95 percent of a reference panel. Clearly, there is genetic control over responsiveness, but this control has not been associated with the putative immune response genes of HLA class II. In other words, one cannot predict responder status from an individual's HLA phenotype. Responders and non-responders to blood transfusions declare themselves fairly early after the initiation of a series of blood transfusions, with very few non-responders converting after the first six months on dialysis. Indeed, there were many patients in the early era of frequent transfusion who remained negative on antibody screens after 50 or more transfusions. Inspection of waiting lists for cadaveric kidney transplantation gives the impression that the responder rate of highly sensitized patients is very much higher than an overall 30 percent. On a typical list, over 50 percent of patients will have antibodies to more than half of the reference panel, and 20 percent or so will have antibodies to 90–100 percent. The degree of sensitization is commonly expressed as "PRA," panel-reactive antibody. Patients with antibodies accumulate over time because they frequently have positive cross-matches with potential donors. In addition, many are awaiting second transplants, and this group has a much higher likelihood of

having anti-HLA antibodies induced by rejection of the first graft. Since patients with antibodies to a given donor are ruled out for that transplant, it is possible that a major effect of blood transfusions is to reveal the strong immune response preferences, at least in terms of antibody formation, of responder patients. Blood transfusions, in this view, provide a process of negative selection, with the result that transplants destined to early failure are avoided. This mechanism most certainly played a role in the pre-cyclosporine era, especially when there still existed an increasing benefit with higher numbers of transfusions. These blood exposures were in essence providing surrogates for first transplants. The contributions of cyclosporine and other more potent therapies, such as anti-lymphocyte globulins (ALG), to the decline in the transfusion effect may be to suppress those responses previously subject to negative selection by transfusion. As mentioned, however, the transfusion effect was already declining before the introduction of cyclosporine, and it is likely that other factors, such as prompt attention to the diagnosis and treatment of early rejections, may play a role. HLA matching can also play a role. A recent analysis indicates a benefit from transfusions in HLA-DR mismatched cases, but not when there were no mismatches. The latter situation alone produced the same 80 percent one-year survival in both transfused and non-transfused recipients, while transfusions add an 8–10 percent benefit in the one- and two-DR mismatched groups [12].

TRANSFUSIONS AND REJECTIONS

Although it may now be difficult to see a transfusion effect in the entire group of renal transplant recipients, close attention to rejection events provides evidence that transfusions do have effect in those destined to have rejection activity. In a single-center study of the controlled reinstatement of a no-transfusion policy, there was no difference in graft survival comparing transfused and non-transfused patients; however, the non-transfused group had more early rejection episodes [13]. A nine-center study on the relation of rejection activity to previous blood transfusions in 567 first cadaver kidney grafts showed that 63 percent of the 231 non-transfused recipients had rejection episodes during the first 60 days after transplantation, while 48 percent of the transfused patients had rejection [14]. Most striking, however, was the comparison of one-year graft survivals in those who had rejection and those who did not, in relation to blood transfusion history. Those with no rejections all had high rates of survival (84–88 percent at one year), whether they had received 0, 1–10, or >10 transfusions. If a rejection episode occurred, the results were 49 percent one-year survival for no transfusions, and 70 percent for the transfused patients (Table 1). Hence, the original deficit of 20 percent poorer survival in the absence of prior transfusions may still be discerned in those patients destined to reject. Unfortunately, there are no reliable predictive tests so that one can know who would need to have transfusions prior to transplantation.

TRANSFUSIONS AND NONSPECIFIC SUPPRESSION OF CELL-MEDIATED IMMUNITY

There is evidence to support the notion that there is an active mechanism to down-regulate cellular immunity following transfusion. Serial measurements of cell-mediated responses in previously non-transfused end-stage renal disease patients have shown marked reductions in response to mitogens and recall antigens (PPD, tetanus, mumps, vaccinia) after a single blood transfusion, and lasting for over two weeks [15].

TABLE 1
Rejections and the Transfusion Effect in First Cadaveric Kidney
Grafts—One-Year Graft Survivals
(from [14])

Rejection (First 60 Days)	Numbers of Transfusions		
	0	1-10	>25
Yes	49% (n = 145)	69% (n = 135)	71% (n = 25)
No	84% (n = 86)	88% (n = 146)	87% (n = 30)

A second transfusion at four weeks produced a more profound and lasting depression. There were, however, no significant depressions in the allogeneic HLA-directed mixed lymphocyte response (MLR). Similar results have been repeated in other populations, and there are indications that blood transfusions in patients with cancer may hasten the recurrence of malignancy [16], as well as increasing the risk for infections [17].

ANTIGEN-SPECIFIC UNRESPONSIVENESS

The ultimate goal in transplantation is the induction of specific unresponsiveness, or tolerance, so that patients need not take anti-rejection medications indefinitely, and, more important, that both the initial and long-term graft survival rates are limited only by other life-threatening diseases. In this regard, there is considerable interest in understanding the altered state of immunity in long-term stable patients maintained on minimal drug doses. In general, the proliferative response of T cells *in vitro* to HLA class II incompatible stimulator cells (MLR) is not depressed in such patients, but the capability of such cultures to develop cytotoxic T cells (cell-mediated lympholysis, CML) generally directed to HLA class I antigens, is absent in 70 percent of such stable patients six months after transplantation and beyond [18,19]. This unresponsiveness is specific for donor antigens; i.e., patients make perfectly normal responses to cells bearing other HLA antigens. When the precursor frequency of cytotoxic T cells (CTLp) is estimated by the technique of limiting dilution, such subjects are shown to have marked reductions in cells capable of killing donor cells [20]. The possibility of clonal deletion seems unlikely, however, since full activation by polyclonal mitogens will restore the expected CTLp to the normal level of about 1:2,000 [21]. Therefore, the full T-cell repertoire is present, but, in the absence of stimuli which bypass inhibitory immunoregulatory influences, the individual is functionally unresponsive. To date, there is no evidence that blood transfusions lead quickly and directly to unresponsiveness in CML, and except for the correlation of low CML and good graft function, there is no direct evidence that this phenomenon is the principal reason for graft success. It is of interest, however, to note that blood transfusions which do not produce an increase in CTLp and CML activity are those which share an HLA haplotype, or at least one DR antigen with the transfused recipient [22]. This situation occurs when living donor kidney graft recipients are prepared by single-donor blood transfusions from the potential kidney donor, so-called donor-specific transfusions (DST). Such recipients, if they do not develop a positive cross-match, are reported to have superior graft survival, close to that of an HLA identical donor [23]. The frequency of positive cross-matches in DST recipients was in the 30 percent range, as one would predict, until concurrent administration of azathioprine or cyclosporine was

shown to reduce this hazard to 10 percent or less [24,25]. Other studies in such familial haplotype identical combinations have also pointed to another possible mechanism for benefits of transfusion: the induction of anti-idiotypic antibodies having the potential of inhibiting the recognition of subsequent specific antigen by either antibodies or T-cell receptors [26,27].

TOLERANCE INDUCED IN UTERO

There is yet another factor to be considered in the response to blood transfusions and organ grafts, and that is the new evidence that many humans behave as if they were clonally deleted for those HLA antigens of their mothers which they did not inherit. The presumed mechanism would be similar to that of in utero or neonatal tolerance induced experimentally. The observation was first made by the van Rood group in Leiden in an analysis of those end-stage renal disease patients having very high PRA, but consistently having no antibodies against a small number of HLA antigens [28]. Such a small "hole" in the repertoire of antibody response in half of such sensitized patients is found to be a failure to respond to non-inherited maternal HLA antigens. This phenomenon has been extended to cell-mediated immunity in the CML assay, in preliminary studies from the same group. Although not directly related to effects of blood transfusions, these findings, if confirmed, need to be taken into account when interpreting states of specific unresponsiveness and may even be applicable to selection of donors for transplant recipients.

TOWARD MORE SELECTIVE IMMUNOSUPPRESSION

What of the future? Will it be possible to utilize antigen exposure to blood products as part of a conditioning regimen for tolerance induction? Most fascinating in this regard are the studies from Leiden on the selection of single blood donors from the unrelated population to be matched, not for a whole HLA haplotype, but for one DR antigen only [29]. It has already been mentioned that such transfusions do not increase sensitivity as measured by CML [22], and that they may induce production of anti-idiotypic antibodies which can prevent the response of T cells specific to the immunizing HLA antigens [26,27]. Furthermore, anti-HLA antibodies were less frequent as result of one DR matched versus no DR matched transfusions (Table 2). Retrospective studies of kidney recipients, and prospective studies of kidney and heart recipients have shown a reduced rejection frequency and superior graft survival when the only blood received prior to transplantation was one to three units from donors matched for one DR antigen with the recipient [29]. Matching for one DR antigen between the recipient and graft donor provided minimal benefit compared to having the one DR match between the recipient and the blood donor. The five-year kidney survival in patients receiving no or one pre-transplant transfusion is shown in Table 2. There is a significant improvement in results in the one DR group. Comparable results were reported in the numbers of rejections and graft losses in 20 singly transfused heart graft recipients, half of whom received a one DR matched blood transfusion (7/10 without rejection versus 1/10 in the unmatched transfusion group) ($p = 0.003$) [29]. Anti-HLA antibody production was also diminished in the one DR transfused group.

Although the mechanisms for the benefits of one DR matched blood transfusions from a single donor are not understood, this approach seems promising. The beneficial effect, though dependent upon a class II match, includes down-regulation to HLA class I antigens of the blood donor, as shown by the reduction in antibodies to HLA, and the

TABLE 2
Effect of One and Two HLA-DR Antigen Mismatched Blood
Transfusions on Anti-HLA Responses and Kidney Graft Survival
(from [29])

HLA-DR Matches	Number of Transfusions		Five-Year Graft Survival
	1 ^a	3 ^a	(one transfusion)
1 DR	6/28 ^b	2/16	81% (n = 32)
0 DR	18/30	12/16	57% (n = 30) (p = 0.02) 45% (n = 45) ^c (p = 0.001)

^ap = 0.02 (one transfusion); p = 0.0007 (three transfusions)

^bNumber making antibodies/total

^cNo transfusion controls

effect carries over to the organ graft regardless of the HLA antigens present on the new tissue. In some fashion, the known role of self HLA molecules to present antigenic peptides to T cells is likely to be a key part of the beneficial effect. It seems unlikely, however, that the effect is entirely immunologically specific, as the non-matched haplotype will have only one of the ten major DR antigens possible on the subsequent graft. On the other hand, DR as defined serologically may not be as important as some more widely shared "public" epitope. Since the improvement observed with a single blood donor is of the order of having 25 percent fewer graft losses, some of the effect could indeed represent chance DR sharing between blood donor and subsequent kidney donor, and be the result of immunization in the context of a self class II DR antigen to a foreign DR peptide; i.e., the phenomenon may be mediated by primed T cells restricted to self DR plus peptides coming from the subsequent graft [30]. In this view, the hypothetical active immunization effect would be one of suppression via some antigen-specific immunoregulatory pathway.

Alternatively, it is possible that provision of "self" DR on intravenously administered cells induces a different sort of systemic response similar to the so-called autologous mixed lymphocyte response (AMLR) which occurs when autologous T cells are cultured *in vitro* with greater numbers of autologous B cells than are normally present in blood [31]. The AMLR involves a limited subset of T cells and results in development of a nonspecific suppressor system capable of inhibiting activation of B and T cells [32], so that the specificity would be to self in the priming event, and not to the second immunization by the graft, which is modified by nonspecific suppression. In any event, additional confirmatory studies are needed, along with careful study of possibly different effects when alloantigens are presented in the context of self versus non-self class II HLA. So far, it does not seem that the immediate effect of a single one DR matched blood transfusion is one of induction of CML unresponsiveness, and data are lacking on the development or functional significance of anti-idiotypic responses following transfusions based upon HLA-DR matched blood transfusions.

One should be reminded that these as yet vaguely appreciated events occur in the setting of immunosuppressive therapies which are likely to be essential for their expression. By the same token, in considering the future of deliberate pre-transplant blood transfusions, it is conceivable that heavy loads of standard immunosuppressive agents could be counterproductive to the induction of active states of unresponsiveness.

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