

# Effect of Blood Transfusion on Subsequent Organ Transplantation

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## 1. Introduction

In the current era, tissue and organ transplantation is an established specialty for treatment of multiple disorders. However, the chief immunological problem of organ transplantation is the risk of occurrence of acute or chronic rejection, initiated by host lymphocytes in response to graft alloantigens. Though the success of transplantation is attributed to the modern methods of immunosuppression, the role of pre-transplant blood transfusions cannot be ignored.

Since the beginning of clinical 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 again returning to abstinence (*Carpenter, 1990*). Pre-exposure to alloantigens has been discovered to have a dual effect: it is detrimental in some cases, while in others, it prolongs the graft survival.

Therefore, in this chapter, we would explore the mechanisms involved in both the detrimental and the beneficial effects of blood transfusion on graft survival and provide an overview of the current recommended practice.

## 2. Basics of HLA and graft rejection

2.1 *Human leukocyte antigens (HLA)* are a set of human major histocompatibility complex derived glycoproteins. These are expressed on cell surfaces and allow for discrimination of self from non-self. HLA have been classified into two major groups, Class I (HLA-A, HLA-B, and HLA-C) and Class II (HLA-DP, HLA-DQ, and HLA-DR). Recognition of the alloantigens (antigens displayed by the transplanted organ) is the prime event initiating the immune response against an allograft (*Gabardi, 2010*).

2.2 *Hyperacute rejection* is an immediate immune response in the recipient against an allograft, due to preformed recipient antibodies directed against the donor's HLA.

2.3 *Acute rejection* is a cell mediated process that usually occurs within 5 to 90 days after a transplant. Rarely, it can occur after this time.

2.4 *Humoral rejection* is characterized by B lymphocytes injuring the allograft through immunoglobulin and complement activities.

2.5 *Chronic rejection*: Although poorly understood, immunologic processes of chronic rejection may result from cell-mediated, humoral, or drug-induced allograft damage.

### 3. History of blood transfusion effect in clinical transplantation

Most patients with end-stage renal disease awaiting renal transplantation, sustained by dialysis machines, became profoundly anaemic and benefitted symptomatically from blood transfusions. Many required large numbers of blood transfusions, frequently exceeding 20 units over a period of months. Some even required as many as 50-100 units. Even those, who had some residual production of erythropoietin (EPO) by the remnant renal tissue, benefitted by transfusion of 2-5 units per year. Thus, the first phase in clinical transplantation was the high-volume use of blood to keep the patient's red cell mass in the 20-25% range (Carpenter, 1990).

In the second phase in the 1970s, efforts were made to avoid blood exposure. This trend began with the realization that blood exposure could be highly immunogenic leading to production of anti-HLA antibodies, which precluded transplantation at the time of cross-match (Opelz, 1973). This concept was originally described in the mouse by Medawar (Medawar, 1946). Subsequently, Hattler et al demonstrated that a single transfusion of whole blood can provoke sufficient immune response to induce accelerated rejection of a skin graft from the blood donor (Hattler, 1966). This policy of with-holding pre-transplant transfusions was reinforced by growing concerns about the serious long-term consequences of transfusion-induced hepatitis in the immunosuppressed graft recipient (Parfrey, 1984).

However, within a few years, it was reported that non-transfused patients receiving cadaveric donor grafts were at higher risk for graft rejection, having a 20-30% lower one-year graft survival rate (Matas 1975, Opelz 1978). In the pre-cyclosporine era, failure to transfuse a potential kidney recipient was the most important predictor of a poor outcome. It was shown that patients who had never received transfusions were not the optimal recipient population (Opelz 1974). Patients who had received blood transfusions prior to transplantation appeared to accept a significantly higher proportion of kidney transplants successfully (Opelz 1976, Polesky 1976). A similar trend in recipients of heart allografts was also noted (Caves 1973).

Thus, kidney transplant candidates received elective immunomodulatory red cell transfusions to improve graft survival. Survival of kidney graft from living related donors was enhanced by the pre-transplant conditioning of the recipient with several transfusions. However, the volume and timing of blood transfusion which was beneficial, was not established. This led to many attempts to define the optimal dose and timing for the transfusion effect. Opelz et al found a distinct dose effect, with the one-year survival rates being directly proportional to the numbers of units of blood transfused prior to transplantation (Opelz 1978). Some improvement was seen with a single transfusion, and survival rates increased with up to 10-20 units of blood. However, more recent studies have shown more than 5 transfusions to worsen graft survival (Chavers 1997) and patient survival (Tang 2008).

Though the duration of the favourable effect of blood transfusion was unknown, it was found that preoperative blood transfusion at the time of surgery was usually not effective, while blood received within a year or two had a beneficial effect (*Opelz 1981a*). Thus, it was recommended that blood should be given at least 3 to 6 months prior to transplant (*Radley 1986*).

It was also not clear which component of the transfused blood was responsible for the beneficial effect. Allogeneic blood containing leukocytes was shown to have an adverse effect in patients with aplastic anaemia undergoing bone marrow transplantation and in renal transplant patients. It was assumed that sensitisation to transplantation antigens could potentially be prevented by leukodepleting blood components that are to be used in pretransplantation transfusions. Thus, leukocyte poor red cells and frozen deglycerolized red cells were assumed to have low incidence of HLA immunization (*Sanfilippo 1985, Polesky 1977*).

The incidence of alloimmunization was also low when stored units, rather fresh units of blood were used for transfusion (*Light 1982*). One study suggested that the agglomeration method for blood preservation resulted in a product which was less immunogenic in terms of producing antibodies, while retaining its ability to improve graft results (*Fuller 1978*). Thus, preparations of frozen blood deglycerolized by agglomeration were found to be beneficial and relatively free of the hazards inherent in conventional blood support. While saline-washed, "leukocyte-poor" blood cells may be an alternative to frozen blood for reducing the rate of patient sensitization (*Miller 1975*), prolonged use of this apparently leads to a much higher sensitization incidence (*Suarez-Ch 1972*).

Thus, numerous studies indicated that blood transfusions may actually be beneficial in prolonging the survival of renal allografts (*Festenstein 1976, Opelz 1976, Polesky 1976*). As a result of these data, most transfusion services followed a deliberate transfusion policy of administering 2-5 units of blood to all new dialysis patients while awaiting transplantation. These were usually given in the form of whole blood, however red blood cells, deglycerolized RBC's and buffy coats were also used as effective alternatives to whole blood.

With the introduction of cyclosporine in 1980s, graft and patient survival improved. Since then, the question of the beneficial role of blood transfusions has been subject to ongoing re-evaluation. There has been an overall decline in the transfusion effect and an increase in the HLA matching effect, which is more clearly recognized now because of improved typing capabilities. The HLA effect is additive to that of cyclosporine, which itself produces a 15% increase in one year survival rates (*Opelz 1985*).

In addition, blood transfusion involves a risk of blood-borne infections, including HIV. Also, there has been an emergence of new factors in blood banking (e.g. use of EPO for supporting red cell production). These formed clear incentives to move away from use of pre-transplantation blood transfusions. This led to the fourth phase of transfusion policy, a return to the withholding of blood as possibly unnecessary, at least for the improvement of graft survival.

Some recent studies show that transfusion may cause severe acute rejection (*Waanders 2008*). Few programmes now use elective pre-transplant transfusions to improve graft survival. Patients with end stage liver diseases are being treated by drug octreotide, variceal banding,

sclerotherapy, transjugular intrahepatic portosystemic shunt placements to relieve the effects of portal hypertension in order to have less gastrointestinal bleeding and to avoid transfusion (*Calcutti 2002*).

However, observations on patients having rejection episodes indicate that a beneficial blood transfusion effect still exists. Recent evidence suggests 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. In a single centre study of a no-transfusion policy, the non-transfused group had more early rejection episodes (*Lundgren 1986*). Another study on the relation of rejection activity to previous blood transfusions showed that 63% of the 231 non-transfused recipients had rejection episodes during the first 60 days after transplantation, while 48% of the transfused patients had rejection (*Toyotome 1987*). Additionally, it was found that if a rejection episode occurred, the one-year survival was 49% in those with no transfusions, and 70% in the transfused patients. Hence, the original deficit of 20% poorer survival in the absence of prior transfusions may still be discerned in those patients destined to reject.

Furthermore, though the change in the transfusion effect during the early 1980s (before the introduction of cyclosporine) is most marked by a disappearance of the graded response to increasing numbers of blood units, the deleterious effect of receiving no transfusions remains, with a 10% lower one-year survival rate (*Terasaki 1986*).

Unfortunately, there are no reliable predictive tests to know who would need to have transfusions prior to transplantation.

#### **4. Possible mechanism of beneficial effects of pre-transplant transfusion**

The exact mechanism by which blood transfusion enhances transplant survival remains unknown. However, several possible mechanisms have been postulated. These are as follows:

4.1 Pre-transplant blood transfusions may cause early immunization of some recipients to selected HLA antigens. This enables the pre-transplantation crossmatch to detect those cases where rejection of donor organ would be most likely to occur. Preformed HLA antibodies (presenting as incompatible crossmatch) are a major contraindication to transplantation. About 30% of cases who receive pre-transplant transfusions become highly immunized to HLA. This response may be beneficial by preventing an unsuccessful transplant.

4.2 The beneficial effect of transfusion may also be related to the immunosuppression induced by transfusion. This may occur through enhancement of suppressor T cell activity or induction of immune tolerance by some unknown mechanism.

#### **5. Responses to allogenic blood transfusion and HLA sensitization**

There are several individual differences in the effects of allogenic blood exposure. Some of these are discussed here:

5.1 Most patients do not develop anti-HLA antibodies following transfusion. Overall, 30% of transfused individuals develop antibodies (with the rate being higher in previously pregnant females and lower in males) (*Opelz 1981b*). In non transfused multiparous females,

about 10% develop such antibodies (the response being transient usually). Multiparous women challenged with blood transfusions show an increase in the responder rate to 30-40% (Opelz 1981b).

5.2 Some responders have a highly selective immune response directed to one to four HLA antigens, while others show sensitivity to better than 95% of a reference panel (Carpenter 1990).

Thus, even though a genetic control over responsiveness is evident, the responder status cannot be predicted from an individual's HLA phenotype.

The responder status to blood transfusions becomes evident very early after the initiation of blood transfusions. In the earlier days of frequent transfusions, many patients remained negative on antibody screens after more than 50 blood transfusions, and very few non-responders were found to convert after about six months.

The degree of sensitization is expressed as panel-reactive antibody (PRA). PRA testing evaluates who is most at risk of hyperacute or humoral rejection (Cecka 2010). A PRA of 80% reflects that the patient is crossmatch incompatible with 80% of donors. In general, patients with a PRA of more than 10% or more than 80% are considered sensitized or highly sensitized, respectively. However, different centres can use markedly different PRA cut-offs for determining sensitized and highly sensitized patients (Cecka 2010). On a typical waiting list for cadaveric renal transplantation, more than 50% of patients have antibodies to more than half of the reference panel, and 20% have antibodies to 90-100% (Carpenter 1990).

There are three types of assays used to determine PRA. The oldest is the Complement Dependent Cytotoxicity (CDC) test (Cecka 2010, Hajeer 2006). In this test, patient serum is tested against donor lymphocytes (B and T cells). Patients' antibodies will coat antigen expressing lymphocytes and upon administration of complement to the serum, lymphocytes are killed and detected by cell stain. The second type of assay is the Enzyme-Linked Immunoabsorbant Assay (ELISA), a solid phase assay which is more sensitive than the CDC. The third assay is the flow cytometry test. Also, there is the house method where locally acquired whole lymphocytes are used and a microbead method which uses purified HLA antigen coated microbeads. Commercial kits include the Flow PRA and Luminex tests. The CDC is thought to be inferior to the HLA Class I and II ELISA and microbead flow cytometry tests which are similar to each other (Cecka 2010, Hajeer 2006, Worthington 2001).

Though the superiority of one approach over another is debatable, it is important since PRA may be altered in response to stimuli. PRA response may be altered by the use of medications (rituximab, immune globulin, statins, cyclophosphamide/prednisolone with plasmapheresis) or certain Angiotensin Converting Enzyme genotypes (Vieira 2004, Vo 2008, Muhmoud 2007, Nurhan-Ozdemir 2004, Akcay 2004).

As previously stated, patients with antibodies to a given donor are not suitable for that transplant. Thus, blood transfusions provide a process of negative selection such that transplants destined to early failure are avoided. However, immunosuppressive agents such as cyclosporine, anti-lymphocyte globulins (ALG), etc, may suppress the responses previously subject to negative selection by transfusion, and thus lead to a decline in the transfusion effect. Other factors, such as prompt diagnosis and treatment of early rejections and HLA matching, may also play a role in this decline observed in the transfusion effect.

Iwaki et al demonstrated a benefit from transfusions in HLA-DR mismatched cases. This benefit was not observed when there were no mismatches. In cases with no mismatches, one-year survival was reported as 80% in both transfused and non-transfused recipients, while transfusions added an 8-10% benefit in the one- and two-DR mismatched groups (Iwaki 1990).

## 6. Nonspecific Immune suppression after transfusion

Allogeneic blood transfusions produce generalized immunosuppression in the recipient. This is due to a variety of changes in the immunological functions, such as decreased function of natural killer cells, macrophage migration to sites of injury, lymphocyte proliferation, and cutaneous delayed hypersensitivity. Donor leukocytes in allogeneic blood may play a role in suppressing cellular immune function.

Serial measurements of cell-mediated responses in previously non-transfused end-stage renal disease patients showed marked reductions in response to mitogens and recall antigens (e.g. PPD, tetanus, mumps, vaccinia) after a single blood transfusion. This effect lasted for over two weeks (Fischer 1980). More profound and lasting depression was seen after a second transfusion given after 4 weeks.

Reports have also suggested that allogeneic blood transfusions increase the incidence of postoperative infection and the tumour recurrence rate (Schriemer 1988, Wu 1988). Such postoperative morbidities have been attributed to the immunomodulatory effects of blood transfusion. However, this association is unproven, and there is currently insufficient evidence to recommend the routine use of leukodepleted blood components for surgical patients to prevent either postoperative infection or tumour recurrence.

## 7. Antigen specific immune-suppression

The final objective in transplantation is the induction of specific unresponsiveness, or tolerance, so that patients do not need to take anti-rejection medications indefinitely. This unresponsiveness is specific for donor antigens; i.e. the recipients produce perfectly normal responses to cells bearing other HLA antigens.

Patients, who have received pre-transplant transfusions, have marked reductions in cells capable of killing donor cells (Herzog 1987). However, full activation by polyclonal mitogens will restore the expected cytotoxic T cells precursor frequency to the normal level (Dallman 1989). Thus, the possibility of clonal deletion is unlikely. Though the full T-cell repertoire is present, the individual is functionally unresponsive in the absence of stimuli which bypass inhibitory immunoregulatory influences.

When living donor kidney graft recipients are prepared by single-donor blood transfusions from the potential kidney donor, this is known as "donor-specific transfusions" (DST). Such blood transfusions (which share an HLA haplotype, or at least one DR antigen with the transfused recipient) do not produce an increase in cytotoxic T cells precursor frequency or cell mediated immunity. If such recipients do not develop a positive cross-match, they are still reported to have superior graft survival, close to that of an HLA identical donor (Salvatierra 1980).

## 8. Effect of in-utero (feto-maternal) transfusion in adult renal transplant

Many people behave as if they were clonally deleted for the HLA antigens of their mothers which they did not inherit. This was first observed in an analysis of end-stage renal disease patients having very high PRA, but consistently having no antibodies against a small number of HLA antigens (*Claas 1988*). This unresponsiveness to antibody response in some sensitized patients was found to be due to a failure to respond to non-inherited maternal HLA antigens. These findings are important as this may be applicable to selection of donors for transplant recipients.

## 9. Conditioning with blood transfusions for tolerance induction

There have been studies reporting selection of single blood donors from an unrelated population matched for one DR antigen only and not for a whole HLA haplotype (*Lagaaij 1989*). In recipients, anti-HLA antibodies were less frequent as result of one DR matched versus no DR matched transfusions. Such transfusions may induce production of anti-idiotypic antibodies which can prevent the response of T cells specific to the immunizing HLA antigens (*Phelan 1989, Kawamura 1989*).

Studies of renal and heart transplant recipients have shown a reduced rejection frequency and better graft survival when the only blood received prior to transplantation was 1-3 units from donors matched for one DR antigen with the recipient (*Lagaaij 1989*). Anti-HLA antibody production was also diminished in the one DR transfused group. This immunization effect could be due to suppression via some antigen-specific immunoregulatory pathway.

An alternative possibility could be that provision of self DR on transfused cells induces a different sort of systemic response similar to the autologous mixed lymphocyte response (AMLR) (*Sakane 1979*). However, 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.

## 10. Conclusions and future research

Additional adequately powered multi-institutional studies should be conducted, because individual centre practices are variable. These studies should have adequate reporting of demographics and either use statistical means to account for confounders or use randomization. Patients receiving or being randomized to no transfusions should be screened to assure that this not only includes transfusions within the dialysis or transplant centre, but other transfusions as well.

The impact of different immunosuppressive regimens on outcomes in patients receiving transfusions should be studied to identify those regimens which can suppress the advantageous or detrimental effects of transfusion on outcomes. This should be specifically evaluated to determine whether transplants need to be encouraged, avoided, or matched with certain regimens.

Unlike the prior reports, where pre-transplant transfusions seemed to worsen renal allograft outcomes, transfusions generally have a beneficial to neutral effect on transplant outcomes.

There is not much support for the belief that transfusions increase the risk of graft rejection. There is evidence that patients receiving pre-transplant transfusions have increased levels of sensitization as assessed by PRA. With regard to rejection, the data are more ambiguous with some analyses showing benefit, some showing a neutral effect, and other analyses showing harm, although the number of studies evaluating more recent time periods is quite limited.

Thus, future application of deliberate HLA antigen exposure in conjunction with novel immunological manipulations may provide a more effective avenue to tolerance induction. However, the literature base is weak and future research is needed to assess the impact of transfusions on allograft and patient survival outcomes in renal transplant recipients.

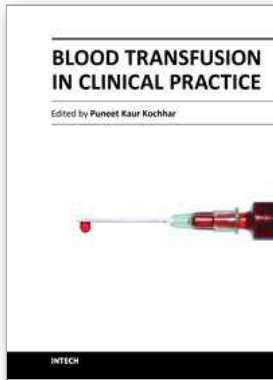
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