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Review Article

Transfusion medicine and solid organ transplant – Update and review of some current issues

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ABSTRACT

Transfusion medicine holds a place of prime importance in organ transplant surgeries. There is a huge demand of organs worldwide with long waiting periods before the organ is available for transplant. Currently the dependency on ABO and HLA matching has decreased considerably with the use of modern immunosuppressant drugs and transplant techniques. The greatest advance in clinical implementation of ABO-incompatible transplants came about through desensitization and isoagglutinin elimination techniques with immunoadsorption and anti-CD20 antibodies becoming the norm, and splenectomy fading out. The implications and practices of transfusion medicine in organ transplant are also undergoing drastic changes. The practice of infusion of one unit of donor's blood preoperatively for immunomodulation is no longer practiced. Use of leuco-reduced products has shown decreasing trends of alloimmunization and graft rejection in cases of multiple surgeries related to organ transplants. Worldwide donor and recipient registry programmes are being setup and existing ones are being upgraded. Such a registry system has been opened in India for kidney transplant cases very recently. Due to such registry programmes the dependency on siblings and directed donations have decreased considerably. This review deals with some of the current issues contributing to the successful outcome of mismatched transplants and the changing concepts of transfusion medicine related to it.

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Introduction

The clinical application of our knowledge of immune barriers to transplantation has advanced allo-organ replacement therapy to the level of routine practice. The success of an organ transplant is the function of several variables. However, the major determinant of acceptance or non-acceptance (rejection) of an

otherwise technically perfect graft is the magnitude of the immunologically mediated responses against graft. Currently the dependency on ABO and HLA matching has decreased considerably with the use of modern immunosuppressant drugs and transplant techniques. The greatest advance in clinical implementation of ABO-incompatible transplants came about through desensitization and isoagglutinin

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elimination techniques with immunoadsorption and anti-CD20 antibodies becoming the norm, and splenectomy fading out.¹ The practice of infusion of one unit of donor's blood preoperatively is now no more practiced in developed centers. Use of leuco-reduced products has shown decreasing trends of alloimmunization and graft rejection in cases of multiple surgeries related to organ transplants. Worldwide donor and recipient registry programme are being setup and existing ones are being upgraded. Such a registry system has been opened in Mumbai, India for the kidney transplant cases very recently.²

By definition an **organ transplant** is the moving of a whole or partial organ from one body to another (or from a donor site on the patient's own body), for the purpose of replacing the recipient's damaged or failing organ with a working one from the donor site. Organ donors can be *living*, or *deceased* (previously referred to as *cadaveric*). Organ transplants can be categorized as "life-saving", while tissue transplants are "life-enhancing". Organs that can be transplanted are the heart, kidneys, liver, lungs, pancreas, and intestine. Tissues include bones, tendons, cornea, heart valves, veins, and skin. **Table 1** shows the United States data on solid organ transplants.

Solid organ transplantation: current status of perioperative transfusion

The number and choice of blood products transfused during an organ transplant surgery is highly variable and it depends on the center and the organ to be transplanted. There is a huge deficit of the published data with regard to transfusion and blood product use during the entire perioperative period of solid organ transplantation.³ Transplantation places a huge demand on the blood product pool and conversely, transfusion therapy is a major issue in any transplantation program. There are no fixed biochemical or patient-related factors which can clearly predict transfusion needs in any organ transplant surgery. **Table 2** provides usage of various blood components in solid organ transplants. Amongst the perioperative team of doctors; surgeons and anesthesiologists, plays the determining role in the utilization of blood products.⁴

Table 2 – Usage of blood components in various organ transplants.

	Red cells	FFP	Platelets
Renal	0–1	–	–
Liver (85%)	3	6–12	2
Liver (15%)	20	30	6
Heart	2–4	1–6	1
Heart after LVAD/ heart–lung	8	12	2
Pancreas	1–2	–	–

Role of transfusion in transplant

Blood products are used either for improving hemoglobin levels or facilitating coagulation or sometimes for both.⁵ **Table 3** provides mean component usage in non-hepatic organ transplants as studied by different workers. In addition, blood transfusion is also used specifically for its immunomodifying effect which can favorably alter the transplant outcome. Opelz et al found out that blood transfusion enhanced renal graft survival. They subsequently demonstrated that this response was transfusion dose-dependent and white cell-depleted red cells were less effective in promoting graft survival.⁶ Transfusion-associated immunosuppression has been well documented and favorably utilized in other conditions, such as in women with recurrent abortions who shared a HLA type with their husbands.⁷ Similar suppression of cytotoxic T-lymphocytes may play a role in graft survival. Other suggested mechanisms include the development of anti-idiotypic antibodies or pre-transplant selection. In pre-transplant selection, transfusion protocols eliminate sensitized patients from the transplant pool who are more likely to have graft failures. These results led to the consideration of blood transfusion as a strategy to improve graft survival in transplant recipients. With the rapid improvement in immunosuppression therapy, the additional effect of transfusion became marginal. The relevance of such protocols in clinical practice have diminished due to the improvement in HLA technology and remarkable advances in targeted and safe immunosuppression. More recent experience suggests no difference in graft survival between transfused and non-transfused organ recipients.⁸

Table 1 – US organ transplants, waiting lists and adult three year graft and patient survival rates.

Organ	2006 Transplants	2007 Waiting list	Graft survival rate (%)	Patient survival rate (%)
Kidney	17,090	73,233		
Deceased donor	10,659		79	88
Living donor	6431		88	95
Kidney and pancreas	924	2321	85 kidney 75 pancreas	91
Liver	6650	16,714	74	79
Heart	2192	2627	79	80
Lung	1405	2,335	64	66
Heart–lung	31	115	53	54
Pancreas	463	1644	63	91
Intestine	175	215	51	62

Table 3 – Mean blood component usage in non-hepatic organ transplantation.

Organ	RBC	Plasma	Platelets
<i>Cardiac</i>			
Primary	1	1–3	1–4
Repeated sternotomy	1–2	1–6	1–8
After support device (with aprotinin)	8	13	12
<i>Lung</i>			
Single	2	1	2
Double	6	4	6
<i>Pancreas</i>	2	0	0
<i>Kidney</i>	1	0	0

Immunohaematological basis of transplants

ABO grouping is still the primary test for organ donation and transplantation. The first and foremost step in graft rejection is the binding of anti-A and anti-B antibodies to the endothelial cells. This leads to initiation of cycle of complement fixation, vascular damage, and thrombosis that leads to ischemia and rejection. Avoidance of splenectomy and its accompanying life-long risk of blood born infections has been possible in selected cases of patients with A2 donors.² Livers do not require HLA matching or cross-matching. ABO-incompatible liver transplants are less susceptible to hyperacute rejection than are other organs but the risk of eventual rejection is still high.⁹ Non-hepatic transplant candidates are assessed for HLA antibodies. History of HLA exposure through pregnancy, transfusion, or prior transplant is studied.¹⁰ Recipient HLA antibodies against non-hepatic grafts lead to a much higher risk of acute and chronic rejection. Kidney and pancreas transplants, together or separate, must be HLA Class I (T lymphocyte) crossmatch-compatible. Organ Procurement and Transplant Network (OPTN) and United Network for Organ Sharing (UNOS) policy requires that heart and lung grafts also be prospectively HLA compatible if the recipient has HLA antibodies or has been exposed to non-self HLA. Primary cardiac transplants without prior cardiac surgery poses hardly any problems of alloimmunisation toward HLA or red cell antigens.⁹

Concept of passenger lymphocytes in organ transplants

The incidence of passenger lymphocyte syndrome is highest in the non-group O recipients when they are transplanted organs from group O donors. There is a restriction on the use of group O deceased-donor organs for non-group O patients in many countries.¹⁰ But the reverse situation has also been studied. The favorable outcome of A₂ to O group liver grafting, with a patient survival of 10/10 and graft survival of 8/10, makes it possible to consider this blood group combination in non-urgent liver transplants.⁶ In transplant recipients, receiving an ABO-unmatched organ, the patient develops IgG antibodies from lymphocytes transplanted along with the graft. Although in general, red cell antibodies do not pose major problems in cardiac transplant patients, these patients

have the highest risk for passenger lymphocyte syndrome (PLS) and post-transplant hemolysis occurs in 2–5%. The patient's direct antiglobulin test becomes reactive 1–2 weeks after transplantation. These antibodies produce sudden marked hemolysis and the antibodies typically persist for a few weeks.⁹ Passive hemolysis most frequently occurs after heart transplantation, followed by liver transplantation, kidney transplants and is rare after visceral transplants. In case of hemoglobin decrease after transplantation, hemolysis due to passive lymphocyte syndrome should be considered primarily.¹¹ Immunoglobulin allotyping proved that these antibodies are of donor origin and are not patient autoantibodies. This phenomenon emerged more after azathioprine was replaced by cyclosporine for immunosuppression. Cyclosporine is more permissive for secondary antibody responses. It has occurred with tacrolimus as well.⁹ Use of aprotinin in transplant patients significantly lower (60%) blood loss and PRBC transfusion volume when compared with control subjects.¹²

Antibody depletion practices in solid organ transplants

Antibodies formed in the recipients against the transplanted organ, play a major role in the graft rejection. Thus these antibodies should be removed from the recipients circulation as far as possible. Options for antibody depletion in sensitized patients include plasma exchange with or without antibody adsorption columns; intravenous immunoglobulin (IVIG); monoclonal antibodies, e.g. rituximab; and other immunosuppressive drugs.

Role of irradiation

Irradiation to prevent transfusion-associated graft versus-host disease (TA-GvHD) is not recommended on a routine basis for all cases.⁹

Role of leuco-reduction

Sensitization to HLA antigens can occur even after the use of leucocyte-reduced blood products. Thus the use of these leuco-reduced products must be restricted for prospective renal and heart transplant patients. Although exact role is unknown, it has been shown that leuco-reduction of red cell products are associated with less complications as compared to leucocyte containing transfusions. Cellular blood components used in the pre-, peri- and postoperative setting must be leucocyte reduced to reduce HLA immunization, CMV transmission and prevent post-perfusion complications after liver and cardiac surgery.

Assays of coagulation factors

The quantitative assay of coagulation parameters is determined by standard coagulation tests, such as PT, PTT, and

platelet count. These parameters do not help in the qualitative assessment of the clot formation and hence are non-reliable. For e.g., the diagnosis of fibrinolysis, a major cause of persistent coagulopathy unresponsive to conventional treatment in liver transplant patients, cannot be made by the usual coagulation tests, mandating the need for a Thromboelastogram (TEG). Transplantation of the heart, heart and lungs, and liver, in particular, place a significant burden on the patient's coagulation system. Cardiopulmonary bypass for heart transplant requires systemic anticoagulation and results in bypass-related platelet and coagulation dysfunction.⁵

Preoperative management of an organ transplant recipient

Preoperative management involves maintenance of hematologic parameters, nutrition and preoperative blood loss. Preoperative Hb levels, PT and INR (PT/INR) are good indicators of blood product utilization.⁵ Some therapies directly enhance the patient's red cell mass, which, in many ways, can be considered equivalent to autologous donation without the use of blood banking.¹³ By adequate stimulation of the erythropoietic machinery, patients can produce in excess of 1 g of hemoglobin (equivalent to one unit of red cells) per week. Subcutaneous rHuEPO given every 72 h is a convenient and cost-effective way to maintain effective stimulatory levels in blood and enhance reticulocyte responses even in the presence of malnutrition, liver disease, or portal hypertension.¹⁴ Enhanced rHuEPO driven erythropoiesis frequently results in functional iron deficiency therefore iron supplementation becomes mandatory in such cases. Furthermore, vitamin B12 and folate levels must also be monitored and supplemented as necessary during rHuEPO therapy.¹⁵ **Preoperative autologous donation (PAD)** is a technique wherein the patient's own blood is collected and stored preop. The prerequisites for this technique are Hb levels equal to or more than 11 g% and Hct of 33%. Platelet concentrates may be collected immediately preoperatively in the anesthetic room, using an apheresis machine, and infused during surgery.

Perioperative management of an organ transplant recipient

Acute Normovolemic Hemodilution (ANH) involves the collection of blood and its replacement with a colloid and/or crystalloid infusion followed by reinfusion of the collected blood at the end of the surgery. By inducing a moderate isovolemic anemia during surgery, the blood lost is diluted in concentration.¹⁶ ANH spares not only the red cell mass but platelets and clotting factors as well. ANH offers following advantages over preoperative autologous donation (PAD). ANH is a convenient and less expensive technique performed only once, on the day of surgery, whereas PAD can involve multiple clinical visits. PAD does not guarantee against the clerical errors or mishandling.¹⁷ **Intraoperative Cell Salvage (ICS)** is an effective tool in blood conservation. It allows the retrieval and reuse of blood lost in the operative field. Electron microscopy reveals only minor alterations in red cell

morphology with ICS as red cells maintain near normal survival and 2,3 diphosphoglycerate concentrations.¹⁸ Patient's hemoglobin should be maintained at levels just sufficient to provide adequate oxygenation to the tissues. Perioperative management goal should be always focused toward safe transfusion-free transplantation with zero tolerance for blood loss of any kind. Minor bleeding should not be always managed by simple packing only but more dependable measures such as argon beam electrocautery and suture ligation should also be resorted to whenever required. The role of the anesthesiologist in blood management is critical (ICS and ANH). A low CVP can markedly reduce blood loss during major surgeries. Avoidance of hypothermia can help to prevent temperature-related coagulopathy.

Postoperative management of an organ transplant recipient

Currently twin pronged approach is being followed in management of these patients which includes early recognition and prevention of blood loss. Any sudden drop in hematocrit or ongoing blood loss from drains should be monitored continuously and stopped immediately. Needless work-up, including laboratory testing, should not delay institution of appropriate interventions. Phlebotomy represents a major and under-appreciated source of blood loss, especially in the intensive care setting. Iatrogenic postoperative anemia can be significantly limited by restricting investigations to the absolutely essential, avoidance of blood draw from large bore or high-flow lines and minimizing the quantity of blood drawn by using pediatric collection tubes.¹⁹ rHuEPO can also be used postoperatively to improve red cell mass.²⁰ Additional goals that complement reducing blood loss and improving hemoglobin levels in the postoperative period include augmenting oxygen delivery and reducing oxygen consumption. Oxygen delivery can be improved by increasing the fractional inspired oxygen concentration via supplemental oxygen, use of mechanical ventilation or hyperbaric oxygen, maintaining adequate intravascular volume and optimizing cardiac performance. Measures to minimize O₂ consumption are appropriate cardiac and respiratory support, control of fevers and shivering, bed rest with sedation, or complete paralysis in selected instances⁵

Viral infections in transplant recipients

Most of the organ transplant patients are maintained on a long term immunosuppressive therapy postoperatively, in order to prevent transplant rejection. Thus this group of patients is highly vulnerable to viral infections, particular those that need life-long T-cell immunity. Most important from a clinical point of view as well as by virtue of their transmission by transfusions or the organ graft are the herpes viruses, CMV (cytomegalovirus) and EBV (Epstein–Barr virus). CMV infection in cardiac allografts may lead to development of atherosclerosis resulting in decreased graft survival.¹¹

Salient features of (i) kidney transplant (ii) liver transplant and (iii) cardiac transplant

(i) Kidney transplant

A successful transplantation, across a positive crossmatch barrier, is one of the most persistent long-standing problems in the field of kidney transplant medicine.²¹ Kidneys can also be stored longer than other organs, permitting transport to a matched recipient.⁹ Kidney, pancreas and BMT must be HLA matched at the HLA-A, -B, and -DR loci which improves the life of the transplant.²² The recent availability of specific anti-A or anti-B immunoadsorption columns (Glycosorb) and the use of anti-CD20 monoclonal antibody (rituximab) in different immunosuppressive regimens resulted in the introduction of ABO-incompatible renal transplantation as a routine procedure in different European countries, mainly in Sweden and Germany without splenectomy. The immunosuppressive regimen consisted of one dose of rituximab (375 mg/m²) given 2–4 weeks before immunoadsorption, followed by a conventional triple-drug immunosuppression consisting of tacrolimus, mycophenolate mofetil and prednisolone, starting 1 week before immunoadsorption. Preoperatively, anti-A or anti-B antibodies were removed using the Glycosorb ABO column, a low-molecular carbohydrate column with A or B blood group antigen linked to a sepharose matrix. Immunoadsorption with Glycosorb columns is very effective, and IgG and IgM isoagglutinin titers can be reduced by two to three titer steps with every immunoadsorption session.^{1,23,24} similar results have been found by American and Japanese workers too. With the growing immune-manipulation of the recipient, survival rates can be raised considerably, although they remain significantly inferior to those of ABO-compatible transplantation. Data from the Collaborative Transplant Study indicate a 1-year graft survival rate of approximately 50–60% following cadaveric ABO-incompatible kidney, liver or heart transplantation, compared with 70–80% for an ABO-compatible organ.²⁵

(ii) Liver transplant

Liver transplant procedures require maximum blood component support amongst all solid organ transplants. The liver being a highly vascular organ is prone to excessive bleeding more so in patients with portal hypertension due to ESLD. Intraoperative blood losses and transfusion requirements during adult transplantation remain difficult to predict and several studies have shown no firm conclusion in this regard. Liver transplantation is associated with considerable blood product requirement, yet bloodless transplantation has been achieved in Jehovah's Witness patients²⁶ Currently the five issues that are challenging the clinical practice of liver transplantation and relevant to gastroenterologists are living donor liver transplantation (LDLT), recurrent viral hepatitis, non-heart-beating donors, hepatocellular carcinoma, and ABO-incompatible liver transplantation. Living donor and non-heart-beating donor transplantations were initiated as a solution to increase the donor organ pool and it is expected that there will be an increase in the number of these

donors.²⁷ Data from the Collaborative Transplant Study indicate a 1-year graft survival rate of approximately 50–60% following cadaveric ABO-incompatible liver or heart transplantation, compared with 70–80% for an ABO-compatible organ. The results for infants and young children are much better than those of adults, particularly for liver and heart transplantations. Data suggest that B-cell tolerance can develop in the infant age group.²⁵ HLA matching is not required for liver transplants and so not done in centers worldwide.⁹ Preoperative plasmapheresis, immunoadsorption, or splenectomies are still being considered at some centers but some studies have shown excellent results even without these practices.²⁸ ATG interferes with T-cell dependent activation of alloreactive B-cells by removing CD4 + T helper cells. It has been shown to trigger apoptosis not only in T-cells but also in B-cells²⁹ and may thus be more effective than rituximab.³⁰ Important variables affecting transfusion requirements include the severity of disease (Child's classification), preoperative PT, history of abdominal operations, and factor V levels. Other factors identified as independent predictors of transfusion include the preoperative hematocrit value, use of the piggyback transplantation method, and operative time.

(iii) Cardiac transplant

Heart transplants are now the third most common organ transplant operation in the U.S. Primary cardiac transplant without prior cardiac surgery poses hardly any problems of alloimmunisation toward HLA or red cell antigens. After prior coronary artery bypass surgery, leucocyte antibodies have been found in 10–15% and red cell antibodies in 3–5% of patients. Heart transplantation requires similar transfusion support as coronary artery bypass surgery. In primary transplants, 0–2 units of red cells are required. Twice this amount is generally needed when there has been prior surgery. In particular, patients who have left ventricular assist devices (LVADs) implanted as a bridge to transplantation need multiple blood components and approximately 30% develop HLA antibodies, reducing the chance of a cross-match-negative graft. DR-shared heart transplants have a better outcome than DR-mismatched grafts.¹¹

Conflicts of interest

All authors have none to declare.

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