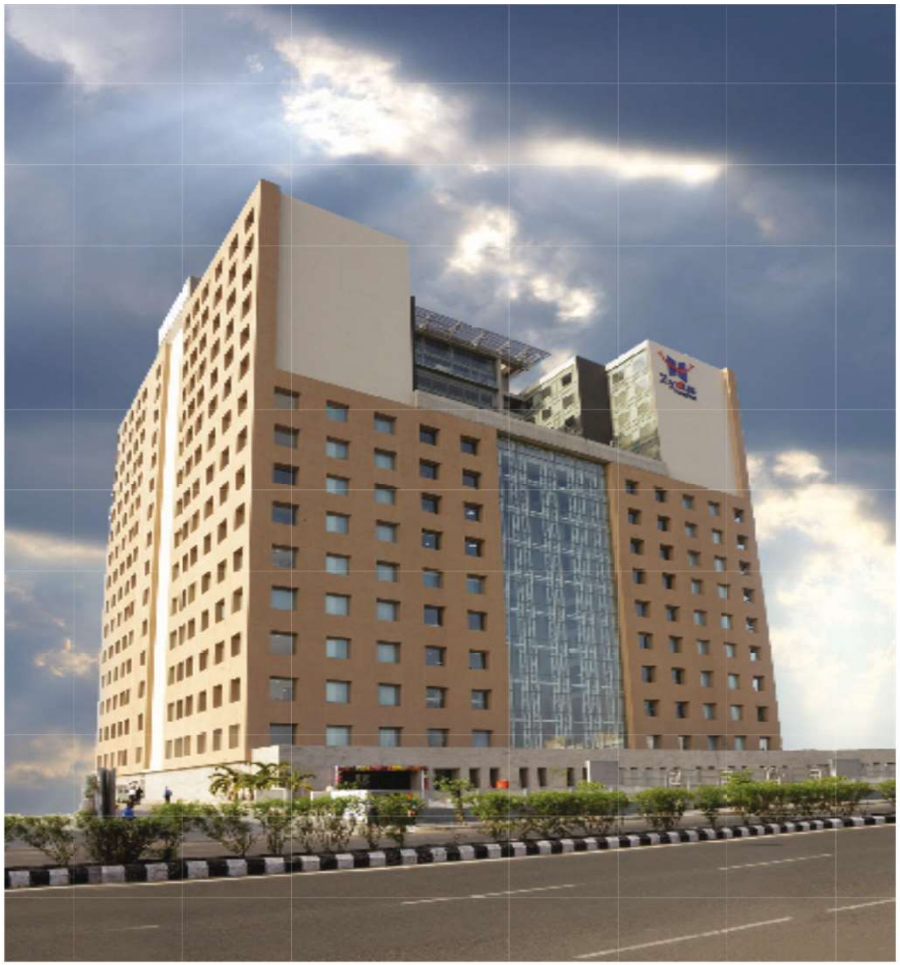

TRANSFUSION SUPPORT IN TRANSPLANT PATIENTS

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Organ Transplant

- 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 donation can be categorized as living, or deceased (previously referred to as cadaveric) as per the source. 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.

Transplantation of human organs act

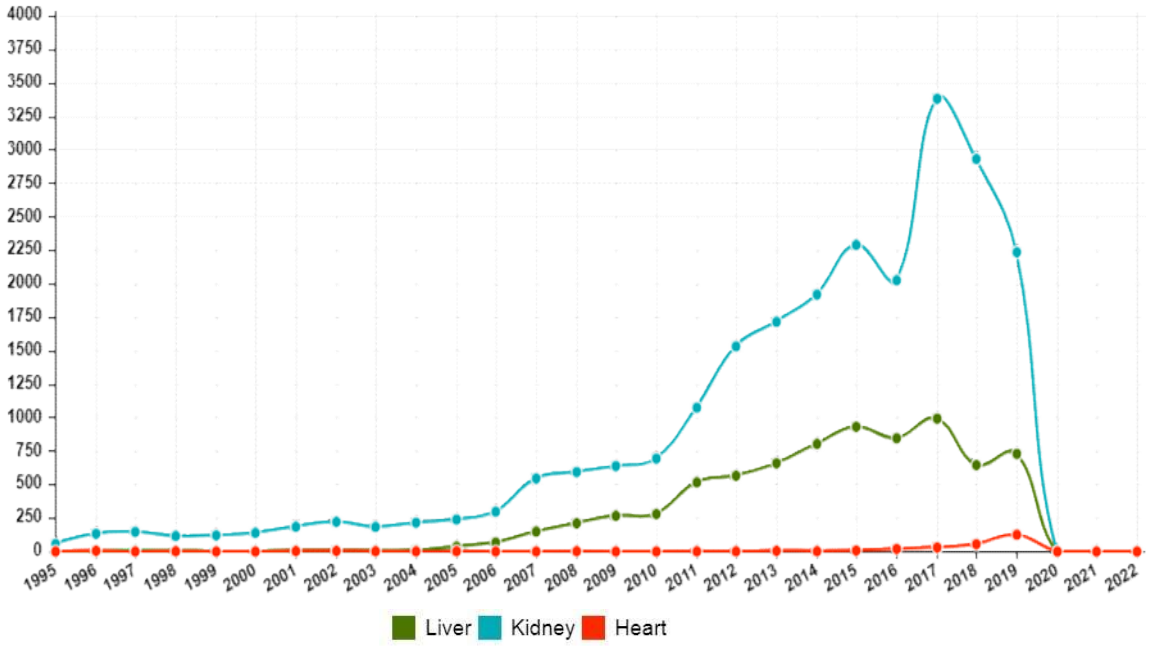
Transplantation of Human Organs and Tissues Rules (THOT), 2014

The Transplantation of Human Organs and Tissues Rules (THOT), 2014 has many provisions to remove the impediments to organ donation while curbing misuse/misinterpretation of the rules. The following are a few

1. The medical practitioner who will be part of the organ transplantation team for carrying out transplantation operation shall not be a member of the Authorisation Committee constituted under the Act.
2. When the proposed donor or recipient or both are not Indian nationals or citizens whether near relatives or otherwise, the Authorisation Committee shall consider all such requests and the transplantation shall not be permitted if the recipient is a foreign national and donor is an Indian national unless they are near relatives.
3. When the proposed donor and the recipient are not near relatives, the Authorisation Committee shall evaluate that there is no commercial transaction between the recipient and the donor and that no payment has been made to the donor or promised to be made to the donor or any other person
4. Cases of swap donation referred to under subsection shall be approved by Authorisation Committee of hospital or district or State in which transplantation is proposed to be done and the donation of organs shall be permissible only from near relatives of the swap recipients.

- Organ donation and transplants in India are regulated under Transplantation of human organs act, 1994 with main purpose to regulate the removal, storage and transplantation of human organs for therapeutic purposes and to prevent commercial dealings in human organs.
- The Act contains detailed provisions relating to the authority for removal of human organs, preservation of human organs, regulation of hospitals conducting the removal, storage or transplantation of human organs, functions of appropriate authority, registration of hospitals and punishment/penalties for offences relating to aforesaid matters.

Organ transplant scenario in India



- NOTTO/SOTTO
- apex centre for All India activities of coordination and networking for procurement and distribution of Organs and Tissues and registry of Organs and Tissues Donation and Transplantation in the country

Ref.: notto.gov.in

Role of BTS

- Successful transplant program requires an interdisciplinary team that has well define policies, procedures and communication pathways.
- The blood transfusion service provides appropriate compatibility testing and transfusion support before during and after transplantation.
- Transplantation places a huge demand on the blood product pool and conversely, transfusion therapy is a major issue in any transplantation program.
- Transfusion services not only quantitatively in terms of blood product support but also due to unique requirements for specialized blood components, the complex serological problems, immunological effects of transfusion on both allograft & recipients

Role of BTS (Cont.)

- Services that may be required by a transplant programme include
  - provision of leucodepleted blood components
  - blood irradiation
  - massive transfusion support
  - ABO subgroup typing and isoagglutinin titres
  - Antibody screening and identification and
  - advance immunohematology testing
  - Therapeutic apheresis
- Transfusion services should understand and address such expectations of the transplant team.

Mean Blood usage in organ transplant

- Liver transplant requires more blood transfusion support including components

- Heart or lung transplant RBC transfusions averaged around 3 units, but COVID-19 lung transplants needed a median 8 units (75th percentile 15) due to dense adhesions. (**Blood banking in solid organ transplantation** Ramsey - Annals of Blood – 2022)

- Bone marrow transplant has different challenges from blood transfusion perspective.

	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	–	–

Transfusion medicine and solid organ transplant – Update and review of some current issues Sarkar et al. - Medical Journal Armed Forces India - 2013

Selection of blood components

- Selection of blood components is very important in managing the blood requirement of the transplant patients.
- All types of the blood components shall be available in the blood centre before planning an organ transplantation surgery.
- The selected blood components shall be compatible by crossmatch on AHG phase.
- If possible, selecting the phenotype matched PRBCs help to reduce the further risk of alloimunization and prevent DHTR in already alloimunized recipients
- Role of Leucodepletion and Irradiation

Leucodepletion

- leukocyte content in a blood component unit should be less than 5×10^6/unit after leukoreduction (3 log reduction 99.9%) with a minimum of 85 percent red cell recovery in 95 percent of the units tested, as per the standards of the AABB
- Methods-Saline washed/Buffy coat/leucocyte filters
- Timing-Pre-storage vs. post-storage leucofiltration
- Proven benefits-
  - Reduced frequency and severity of FNHTRs
  - Reduced risk of CMV transmission
  - Reduced risk of HLA-alloimmunization and platelet refractoriness

Irradiated blood components

- X-ray or gamma irradiation inactivates T lymphocytes in cellular blood components (PRBC/Platelets/Granulocytes) at a given dose
- Helps to prevent TA-GVHD
- Guidelines for Irradiation of blood components
  - AABB standards 25 Gy to the central area of the component with no portion receiving <15 Gy- no upper limit
  - UK guidelines- minimum of 25 Gy is recommended, but with the dose to any bag in the container not exceeding 50 Gy
  - India-D & C act- recommends 25 Gy
- Date of expiry- 28 days or the original expiry whichever is earlier
- Quality assurance- Radiation monitoring by Dosimetry, Radiation label (RAD TAG/RAD SURE)

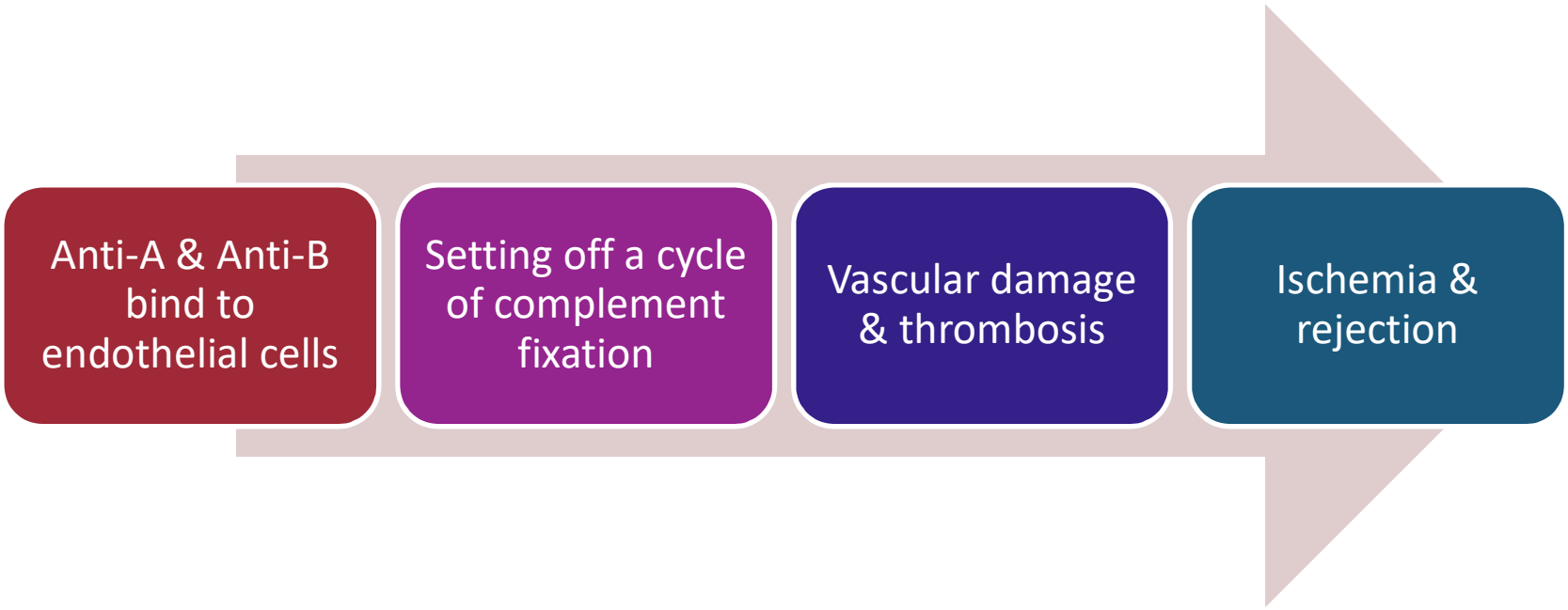
Blood investigations

- Blood group-ABO & Rh, Isoagglutinin titres
- Red cell antibody screening
- HLA typing
- Screening for HLA antibodies
- Coagulation profile-PT/INR, APTT, fibrinogen
- Thromboelastograph

ABO blood group and titres

- ABO and Rh blood grouping is the primary but important test required in the work up of organ transplant.
- Subgroups of ABO blood group system also play a key important role in the transplant outcome and management. Blood centre shall specifically adopt the systems which help to identification of ABO blood groups including presence of isoagglutinins, especially in case of subgroups.
- A2 is the second most common subgroup (20%) and possesses only one fifth the number of A antigen sites as A1. A2 does not agglutinate with lectin Dolichus Biflorus. 8% of A2 and 22-35% of A2B individuals possess alloanti-A1 in their sera. ***(AABB technical manual)***
- ABOi renal transplant- A preoperative IgG anti-A1 titer of <8, but some have used <16 or <32. ***(Hourmant M et al. Ne-w rules of ABO-compatibility in kidney transplantation. Transfus Clin Biol 2019)***

Effect of ABO antibodies on graft



Isoagglutinin titre

- Titration is semi-quantitative technique of measuring the concentration of an antibody in a serum.
- Performed using Double dilution technique (Serial dilution).
- Titer is simply the inverse of dilution at which the end point agglutination (1+) is achieved macrocopically.
- Various methods- Tube/Column/SPRCA, Manual vs. Automation

- Variation in results-
  - Different method(TT, Gel test, solid phase)
  - Coombs reagent 1drop or 2 drops
  - Serum or plasma, target cell(Donor or pool)
  - Freezing and thawing
  - End point +,+/-
  - Subjective reading
  - AntiA/B titer IgM 32 IgG 256 fold variation

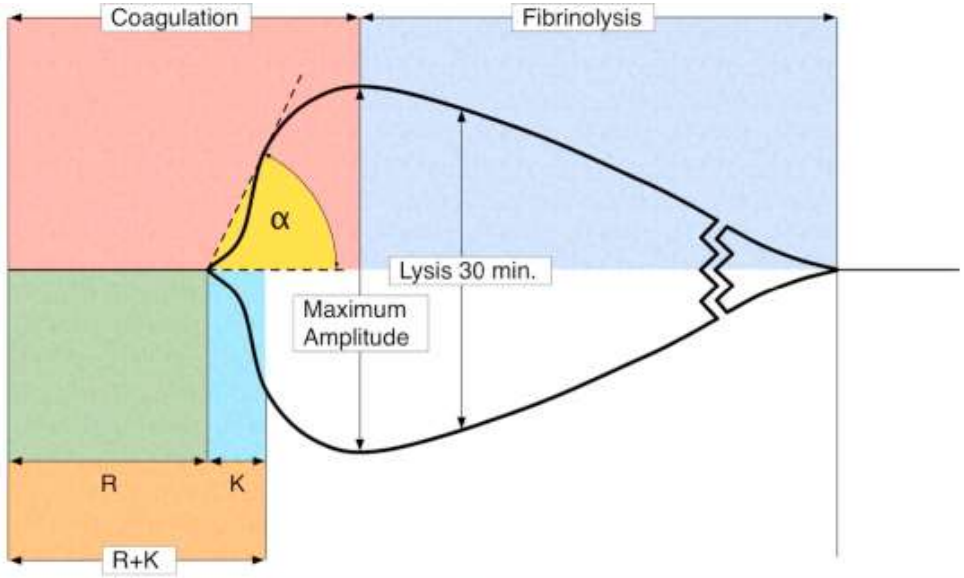
HLA antigens and antibodies

- After ABO compatibility, HLA compatibility is also important for most organs….Except liver….?
- Renal and cardiac organ recipients require HLA antibody tests
- HLA typing- Class 1 (A, B, C) and class 2 (DP, DQ, DR)
- Typing methods- SSO /SSP/ NGS
- HLA crossmatch- Donor lymphocytes are tested with recipient serum for compatibility
- Donor specific HLA antibodies and Panel reactive antibodies
- Antibody depletion methods

Coagulation tests

- Transplantation of the heart, lungs, and liver, in particular, place a significant burden on the patient's coagulation system.
- Coagulation tests help to determine the usage of blood components.
- Standard quantitative coagulation tests include platelet count, PT, APTT, fibrinogen assay. Usefulness of these quantitative parameters in the qualitative assessment of the clot formation and lysis is not much clear.
- Whole blood based Visco-elastic testing representing the global hemostasis environment is available in form of Thromboelastography (TEG) or Rotational Thromboelastometry(ROTEM). These tests help to assess various parameters of clot formation including rate of clot formation, strength of clot, clot lysis etc.

Thromboelastograph



Abnormal TEG parameter	Potential Treatment
Prolonged r or k time	Fresh Frozen Plasma
Reduced angle (α)	Cryoprecipitate
Reduced maximum amplitude (MA)	Platelets
Increased percent lysis 30 minutes after MA (LY30)	Aminocaproic Acid

Role of TEG in organ transplant

- 28 patients were included in the analysis with a median MELD (Model for End-Stage Liver Disease) score of 17; 36% received a massive transfusion. The TEG variables associated with MT (defined as ≥10 RBC units/24hr) were a low MA ($p<0.001$) and low angle ($p=0.014$). **MA had the highest area under the curve (0.861) followed by INR (0.803). A MA of less than 47mm has a sensitivity of 90% and specificity of 72% to predict a massive transfusion**. (**Preoperative thrombelastography maximum amplitude predicts massive transfusion in liver transplantation** Lawson et al. - Journal of Surgical Research - 2017)

Role of TEG in organ transplant

- Of patients undergoing liver transplantation, 47% (*n* = 170) were hypocoagulable and 53% (*n* = 194) were nonhypocoagulable preoperatively. **Hypocoagulable patients had higher transfusion requirements compared to nonhypocoagulable patients**, requiring more units of packed red blood cells (7 vs 4, *P* < .01), fresh frozen plasma (14 vs 8, *P* < .01), cryoprecipitate (2 vs 1, *P* < .01), platelets (3 vs 2, *P* < .01), and cell saver (3 vs 2 L, *P* < .01). Additionally, **these patients were more likely to receive platelets and cryoprecipitate in the first 24 hours** following liver transplantation (both *P* < .05).
- (**Perioperative thrombelastography serves as an important assessment tool of transfusion requirements during liver transplantation** Graff et al. - Surgery Open Science – 2020)

ALTERNATIVES OF BLOOD TRANSFUSION

- **Preoperative autologous donation (PAD)** is a technique wherein the patient's own blood is collected and stored preoperatively. The prerequisites for this technique are Hb levels equal to or more than 11 g% and Hct of 33%.

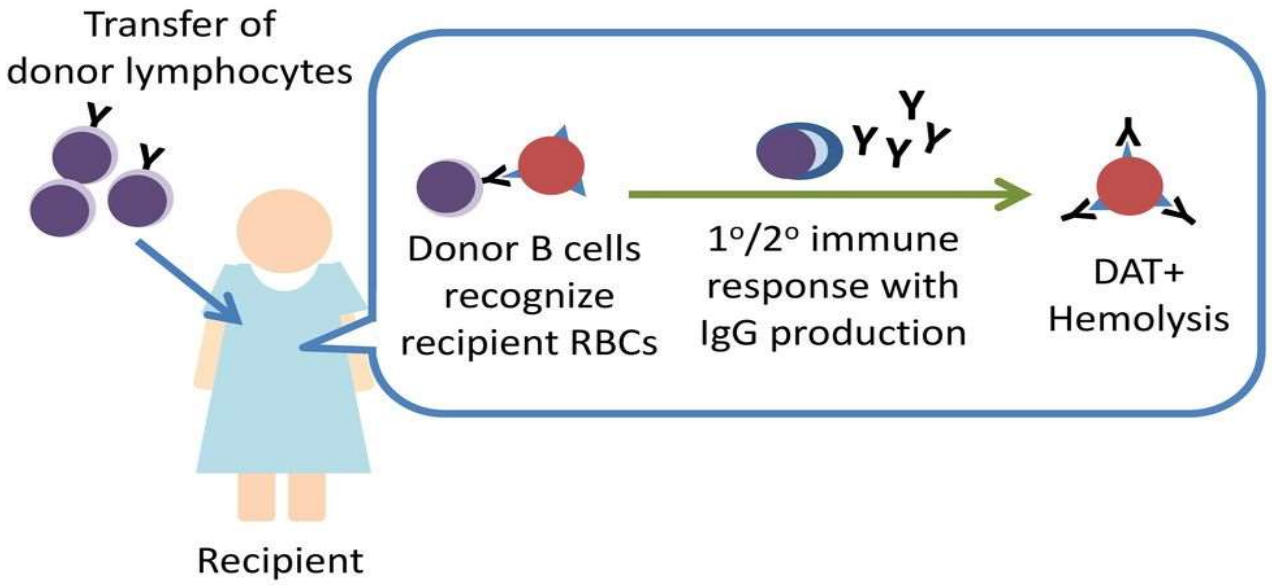
- **Acute Normovolemic Hemodilution (ANH)** involves the collection of blood and its replacement with a colloid and/or crystalloid infusion followed by reinfusion of the collected blood at the end of the surgery.

- **Intraoperative Cell Salvage (ICS)** is an effective tool in blood conservation. It allows the retrieval and reuse of blood lost in the operative field. Perioperative management goal should be always focused toward safe transfusion-free transplantation with zero tolerance for blood loss of any kind. However, these measures have limited usefulness where multiple transfusions are required.

PASSENGER LYMPHOCYTE SYNDROME

- Passenger lymphocyte syndrome is a complication of both solid-organ and stem cell transplant.
- Caused by antibodies produced by donor B lymphocytes, causing a primary or secondary immune response to recipient erythrocytes.
- Most commonly, it is in minor ABO mismatches, such as with a group B liver transplanted into a group AB recipient.
- Although less common, there have also been reported cases with other blood group system mismatches, such as Rh, Kidd, and Lewis antigens.
- Antibodies do not appear until 7 to 14 days postoperatively and can be found for 14 to 21 days after transplant.
- Treatment- supportive care and blood transfusions -(from donor blood group)
- Therapeutic plasma exchange and use of monoclonal antibodies like rituximab may help to remove antibodies from the circulation.

Passenger Lymphocyte Syndrome (PLS)



PASSENGER LYMPHOCYTE SYNDROME

Risk Factors

- Blood group O to A transfer
- Possible sensitizing events: Pregnancy, Blood trnasfusion
- Cyclosporine- more permissive to secondary immune response
- Infection in immediate posttransplantation period

- Mild, self-limiting hemolytic anemia.
- Decrease in Hb without any identified source of bleeding
- Laboratory findings are suggestive of hemolytic anemia including decreased hemoglobin and haptoglobin, elevated reticulocyte count and indirect bilirubin.
- DAT – Positive
- Adsorption-elution
- Rx-Supportive care and Blood transfusion (of Donor blood group)

ANTIBODY REDUCTION

- 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.
- 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.
- Preoperative use of immunoadsorption columns like Glycosorb may help to reduce Anti-A and Anti-B blood group antibody titers in ABO incompatible transplants.

Therapeutic Apheresis

- the effectiveness of therapeutic plasma exchange in 37 patients who experienced allograft rejection in solid organ transplant between 2013-2016. Eight transplanted patients (heart, lung) had more than one set for separate rejection episodes and all liver transplant recipients received photo-pheresis after the therapeutic plasma exchange. All patients had IVIG as an adjunct, and only six patients received Rituximab, Eculi-zumab or Bortezomib.
- **The use of therapeutic plasma exchange for the treatment of antibody mediated rejection in solid organ transplant is safe and effective when used along with other treatment modalities**.

(Alhamar M, Uzuni A, and Lopez-Plaza I. The Role of Therapeutic Plasma Exchange for the Treatment of Allograft Rejection in Solid Organ Transplant: A Single Center Experience. Vox Sanguinis 2019)

Indications for therapeutic apheresis in organ transplants: ASFA guidelines

Organ	Indication	Procedures	Cat	Grade
Kidney ABO-c	Desensitization LD	TPE/IA	I	1B
	Antibody mediated rejection	TPE/IA	I	1B
	Desensitization DD	TPE/IA	III	2C
Kidney ABO-i	Desensitization LD	TPE/IA	I	1B
	Antibody mediated rejection	TPE/IA	II	1B
Liver ABO-i	Desensitization LD	TPE	I	1C
	Desensitization DD	TPE	III	2C
	Desensitization	ECP	III	2C
Liver	Acute rejection	ECP	III	2B
	Immune suppression withdrawal	ECP	III	2B
	Antibody mediated rejection	TPE	III	2C
Heart	Rejection prophylaxis	ECP	II	2A
	Cellular/recurrent rejection	ECP	II	1B
	Desensitization	TPE	II	1C
	Antibody mediated rejection	TPE	III	2C

Other adverse transfusion reactions

- 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 like herpes viruses, CMV (cytomegalovirus) and EBV (Epsteine Barr virus)
- Bacterial infections
- TRALI
- TACO

Bone Marrow transplant- special considerations

- Autologus/Allogeneic
- High resolution HLA typing of donor and patient
- Donor specific HLA antibodies in patient
- Platelet engraftment is defined as a platelet count of at least 20,000/uL for three consecutive days without any platelet transfusions
- Neutrophil engraftment is the presence of an absolute neutrophil count of greater than 500(/uL) for three consecutive days
- Granulocyte transfusion: absolute neutrophil count < 500/µL with either a bacterial infection not responsive to antimicrobial therapy or an invasive fungal and/or yeast infection
- Leucodepleted and Irradiated blood components- SDP availability on shelf
- Choice of blood components and processing of product is important in ABO-incompatible bone marrow transplants

ABOi BMT- Processing of the product

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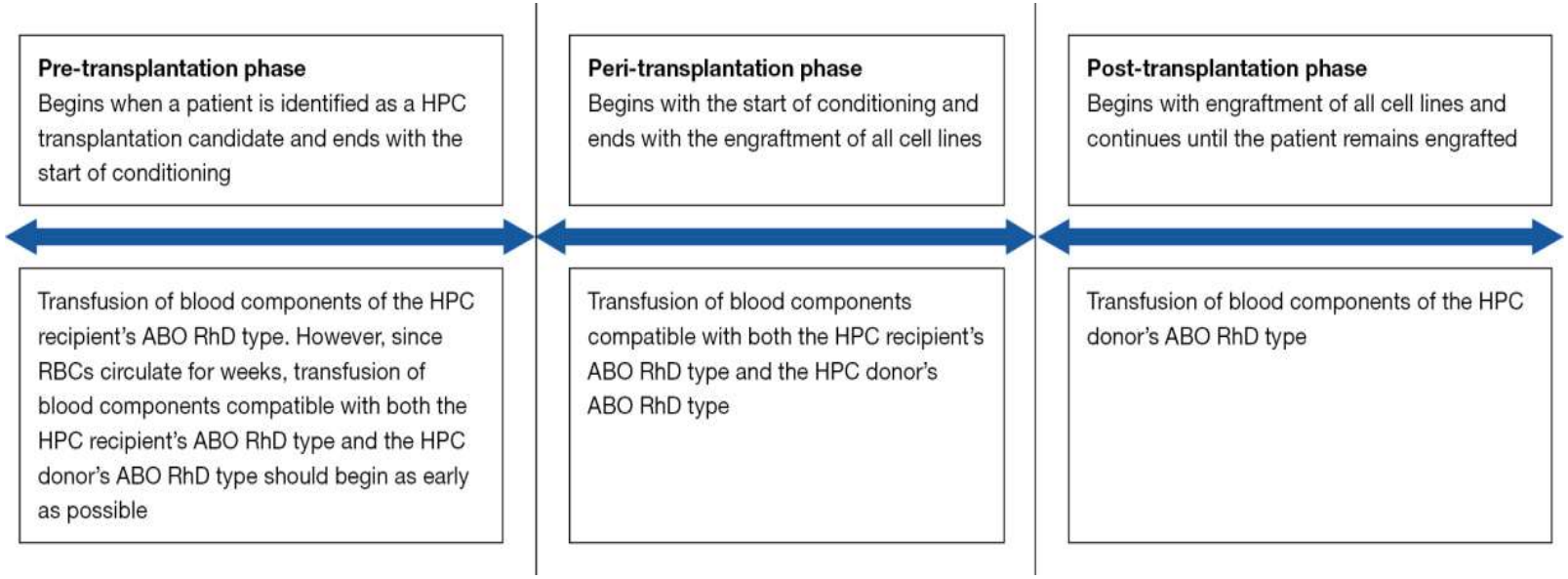
9.1 **Plasma depletion** is performed in recipients of minor ABO-mismatch allograft, children with a small blood volume or patients with coexisting renal or cardiac comorbidities. In the setting of minor ABO-mismatch allograft, plasma depletion is done when donor anti-recepient isoagglutinin titers are higher than or equal to 1:256 with a target of decreasing it to less than or equal to 1:128.

9.2 **Red cell depletion:** In major ABO-incompatible transplants with recipient anti-donor isoagglutinin titer >= 1:32, the red cell contamination in PBSC graft should be kept <20 ml and RBC depletion of BM grafts should be considered using sedimenting agents like hydroxyl ethylstarch (HES), centrifugation, or cell separator (automation) to prevent hemolytic transfusion reaction. Red cell depletion is also performed in patients with renal dysfunction, to help reduce lysed red cell fragments and free hemoglobin.

National guidelines for hematopoietic transplantation, ICMR, MOHFW, Govt of India, 2021

ABOi BMT-considering a transfusion



Immunoserologic and hemotherapy considerations in patients undergoing hematopoietic progenitor cell transplantation
Hassan & Andrzejewski Jr - Annals of Blood - 2022

ABOi BMT- selection of blood group for transfusion

	HPC donor	HPC recipient	Transfusion RBCs	Transfusion platelets/plasma
Major	A	O	O	A, AB
	B	O	O	B, AB
	AB	O	O	AB
	AB	A	A, O	AB
	AB	B	B, O	AB
Minor	O	A	O	A, AB
	O	B	O	B, AB
	O	AB	O	AB
	A	AB	A, O	AB
	B	AB	B, O	AB
Bidirectional	A	B	O	AB
	B	A	O	AB

Our centre experience (Year 2022)

- Transplants at Zydus Hospital, Ahmedabad
  - Liver transplant surgeries- 49
  - BMT-34 (Autologus 19, Allogeneic 15)
  - Heart -1
  - Renal -50+
- Availability of Leucodepleted and Irradiated blood components
- Inhouse peripheral blood stem cell collection, therapeutic apheresis
- Intraoperative TEG- guide for blood transfusion

Average Blood usage (Liver Tx)					
	PRBC	**FFP**	**PC**	**CRYO**	**SDP**
Peri-op	17.7	13.6	9.9	25.1	2.3
Intra-op	11.4	7.2	2.9	18.2	1.8

Average Blood usage (BMT)		
PRBC	**SDP**	**PC**
7.0	5.3	2.4

Summary

- Transfusion medicine plays a key important role behind the successful transplant program
- Availability of leucodepleted, irradiated cellular blood components can assure the minimum post transfusion complications
- Visco-elastic testing like TEG can help to understand the coagulation status and rationalization of blood component usage
- Use of plasma exchanges can help to reduce the circulating antibodies like HLA antibodies or Anti-A ,Anti-B blood group antibodies in ABO-incompatible organ transplant

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