Transplantation

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HISTORY OF TRANSPLANTATION

The first successful organ transplants were performed in the 1950s and 1960s. Here is a brief timeline of some of the first successful transplant procedures:

Kidney transplant: The first successful kidney transplant was performed in 1954 by Dr. Joseph E. Murray and his team at the Peter Bent Brigham Hospital in Boston, Massachusetts. The donor was a healthy twin and the recipient was his identical twin brother.

Liver transplant: The first successful liver transplant was performed in 1963 by Dr. Thomas E. Starzl at the University of Colorado. The donor was a cadaver and the recipient was a two-year-old boy with biliary atresia.

Pancreas transplant: The first successful pancreas transplant was performed in 1966 by Dr. Richard Lillehei and Dr. William Kelly at the University of Minnesota. The donor was a cadaver and the recipient was a young man with type 1 diabetes.

Small bowel transplant: The first successful small bowel transplant was performed in 1963 by Dr. David Hume and Dr. J. Hartwell Harrison at the Johns Hopkins Hospital in Baltimore, Maryland. The donor was a cadaver and the recipient was a two-year-old boy with short gut syndrome.

Heart transplant: The first successful heart transplant was performed in 1967 by Dr. Christiaan Barnard at Groote Schuur Hospital in Cape Town, South Africa. The donor was a 25-year-old woman who had been declared brain dead following a car accident, and the recipient was a 54-year-old man with coronary artery disease.

Heart-lung transplant: The first successful heart-lung transplant was performed in 1981 by Dr. Bruce Reitz and his team at Stanford University School of Medicine in California. The donor was a 20-year-old woman who had been declared brain dead following a car accident, and the recipient was a 29-year-old woman with Eisenmenger syndrome.SD

It's important to note that these transplant procedures have evolved significantly since they were first performed and have become much more common and successful in recent years, thanks to advances in medical technology and techniques.

CLASSIFICATION

According The relation between donor and recipient:

Autografts: Tissue is transferred from one area of the body to another in the same individual (Skin graft).

Isograftts: Tissues are transferred between genetically identical individuals (Monozygotic twins).

Allografts: Tissues are transferred between genetically dissimilar individuals of the same species (live or Cadaver renal transplant).
Xenografts: Tissues are transferred between different species. (Temporary porcine skin grafts in wide human burn victims).
Site of the transplant

- Orthotopic: The organ is situated in the place where organ had, e.g., heart and liver transplant.
- Heterotopic: The new organ is placed in a different site from the native organ e.g., renal transplantation –the kidney is placed in the iliac fossa.
- Paratopic: The transplantation when the donor organ is placed alongside the native organ, e.g., Pancreatic transplantation where the donor organ is placed in the lesser sac alongside the native panaceas.

The donated tissue or organ can be obtained from:

- Live related donors.
- Live unrelated donors.
- Cadaveric donors.

LIVE RELATED DONORS

- Organ is transferred from living donors:
  - Paired organs (kidneys, lung).
  - Part of single organ (segment of pancreas, lobe or segment of the liver, lobe of the lung).
- Tissue matching should be done by histocompatibility matching which results into one of the followings:
  - Perfect match: (2 Haplotype match) All antigens match. Chance of this occurring is 25%.
  - Half match: (1 Haplotype match) Half antigen match. Chance of this occurring is 50%.
  - No match: No antigen match. Chance of this occurring is 25%.

LIVE UNRELATED DONORS

- It had been found that transplantation from non-blood relatives can be as successful as those from blood relatives.
- At the present time anyone with close personal relationship, husbands, wives, very close friends may be considered as possible donors.
- Live unrelated donation is strictly controlled by Unrelated Live Transplant Regulatory Authority (ULTRA).
- The procedure which is used for (LUD) are the same for live related donors.

- It is important to ensure that no financial or other pressure is being put on the live donor to donate.
- Full medical examination should be done
- Explanation of the risks.
- Independent assessment by independent assessor that is neither responsible for the recipient nor a member of transplantation team to:
  - For the donor
    - Make sure that the donor understands the situation he is involved in.
    - To be sure about the reasons for wanting to donate.
    - To be sure that the donor is not under any form of pressure
  - For the recipient.
    - Doing interview for the recipient
- A report will be sent for the (ULTRA) so they can check that there is no possible exploitation of the donor
- (ULTRA) need to be aware of the followings:
  - The donor has not paid to donate & not subjected for pressure.
  - That the doctor who ask approval from (ULTRA) is acting on the behalf of the donor.
  - Assess or meet both recipient and donor and inform them about:
    - Donor understands the nature and risks involved in donating an organ.
    - Consent has been fully and freely given.
    - The donor is entitled to withdraw consent at any time before the operation.

CADAVER DONORS

- Specific criteria:
  - Selection of liver and heart, heart lung donors depend on size match with the recipient.
  - No attempt is made to attempt match other than blood group compatibility with these organs.
  - HLA typing and cross matching are not currently undertaken.
- General criteria for cadaver donors:
  - Brain death with intact circulation

  Cause of the death:
  1. Cerebral trauma.
  2. Cerebral hemorrhage.
  3. Suicide.
  4. Primary cerebral tumor (histologically proven).
  5. Cardiac arrest with brain death.
- Exclusion criteria:

- Malignancy.
- HIV infection.
- Hepatitis B infection.
- Hepatitis C infection.
- Creutzfeldt-Jakob disease (CJD)

organ	Specific criteria
kidney	2-75 years with normal renal function
Heart	0-55 years with no cardiac disease
Heart/lung	0-55 ,non smoker, no pulmonary disease including pulmonary edema, acceptable blood gas level.
Liver	0-65 ,no liver disease or drug addiction.
Pancreas	12-55 years , no history of diabetes , normal blood sugar.
corneas	No age limit ,up to 24 hours after circulatory arrest ,no history of corneal disease, no history of untreated viral infection at time of death , no history of neurological disease of unknown etiology(e.g. multiple sclerosis, Alzheimer disease or creutzfeld –Jacob syndrome),few other contraindications (malignancy is not necessarily a contraindication)
Heart valves	0-65 years ,no history of valve disease , can be removed up to 72 hours after circulatory arrest.
Bone	18-60 years , no relevant medical history
Skin	0-70 years

WARM AND COLD ISCHEMIC TIME

Organ	warm	Cold
kidney	30 min	Up to 48 hr
Heart	0	Up to 4 hr
Heart/lung	0	Up to 4 hr
Lung	0	Up to 4 hr
Liver	0	Up to 18 hr
Small bowel	0	As soon as possible
pancreas	0	Up to 12 hr

TISSUE MATCHING

- ABO compatibility
  - this must be present.
  - Group O is a universal.
- Human leukocyte antigen (HLA) matching:
  - HLA-A, B, C, D are on the short arm of chromosome 6, attempts are made to match these antigens. They are important in live related donor transplantation, a perfect match giving a 1-year survival in excess of 95%.
  - In cadaver transplantation the results are variable.
    - In this context DR locus matching is important.
    - A perfect match on the DR locus is associated with improved graft survival in cadaver transplant.
- cytotoxic cross match
  - it must be negative.
  - The recipient`s blood is tested for cytotoxic antibodies against antigens on donor T lymphocytes (Donor lymphocytes & Recipient serum are mixed in vitro).
  - If such antibodies are present they would attach to and destroy the transplanted kidney, and therefore the donor is unacceptable.

PRE-OPERATIVE PREPARATIONS

- The procedure and its complications should be explained to the patient with the next kin present.
- Live related kidney donor should have full medical and psychiatric assessment prior to donation.
- Blood group and tissue typing.
- Cross match between Donor lymphocytes & Recipient serum. Positive test should preclude the transplantation).
- Blood tests
  - Hb, FBC, ESR, Urea, Creatinine, LFTs, Glucose
  - Hepatitis B&C, HIV screening.
- CXR &ECG.
- If all tests are satisfactory:
  - Do arteriography to assess that both kidneys are normal and at least one of them has single artery which is necessary for anastomosis to recipient artery.
  - Kidneys with multiple arteries could be taken from cadaver with a patch of aorta for anastomosis (Not in living)
  - Excretory phase of angiogram (IVU) will check for any abnormality in excretory system.

REJECTION

Types of rejection:

- Hyper acute rejection.
- Accelerated acute rejection.
- Acute rejection.
- Chronic rejection.

Hyper acute rejection

- Occur due to ABO incompatibility or preformed cytotoxic antibodies against donor T lymphocytes.
- It occurs at the operating table and in the case of renal transplantation the kidney is seen to be flaccid, cyanotic, and eventually thrombosis of blood vessels occurs.
- Nephrectomy is required, often at the time of transplantation or within 24 hours.

Accelerated acute rejection

- Rapid onset within a week of transplantation.
- The success rate is poor.

Acute rejection

- Is the most common form of rejection.
- It occurs within 3 months of transplantation.
- The kidney is infiltrated with T lymphocytes.
- This may be treated with methylprednisolone, ALG, ATG or monoclonal antibodies OKT3

Chronic rejection

- This is heralded by slow decline of renal function.
- Vascular intimal thickening occurs.
- The condition is untreatable.

IMMUNOSUPPRESSION

- All transplanted patients require immunosuppression for life.
- Large doses are given in the perioperative period but these are gradually scaled down to a maintenance dose over few months post-transplant.
- Drugs include corticosteroids, anti-proliferative drugs e.g., Azathioprine (Imuran®) and mycophenolate mofetil (Collect®), calcineurin antagonist, e.g., cyclosporine (Sand immune®) and tacrolimus (Program®).

- Rejection episodes are treated with pulsed doses of methyl- Prednisolone (Medrol®), ALG (Antilymphocyte globulin), ATG (ant thymocyte globulin) or monoclonal antibodies.
- ALG, ATG or monoclonal antibodies may also be used prophylactically in high risk or highly sensitized patients.

Corticosteroids

- usually used along with Cyclosporine or Azathioprine.
- It has multi anti-inflammatory effects as well as immunosuppressive effect.
- Immunosuppressive effect is mainly due to:
  - Inhibition of cytokine production.
  - It has nonspecific effect on cell-mediated and humoral immunity.
- It is commonly used during transplantation and continued for at least the first few weeks.
- The dose is then gradually decreased or withdrawn to reduce the incidence of side effects.
- Pulse doses of Prednisolone are effective treatment for acute rejection episodes.
- Side effects of steroids: include Cushing syndrome, hypertension, peptic ulceration, poor wound healing, osteoporosis, myopathies, cataract, stunted growth, pancreatitis, avascular necrosis of bone, hyperglycemia.

Antiproliferative drugs

Azathioprine

- Antiproliferative drugs includes Azathioprine which is the first widely used immunosuppressive drug and the newer Mycophenolate Mofetil.
- Azathioprine is metabolized into 6-mercaptopurine by the liver this in turn inhibits DNA and RNA synthesis by interfering with purine metabolism which inhibit proliferation of lymphocytes in response to antigenic stimulation and impair antibody production.
- Side effects of Azathioprine include:
  - GI tract: nausea, vomiting.
  - Blood: agranulocytosis, leukopenia.
  - Liver: Impair liver function.
  - Skin: skin rashes.
  - Immunosuppression: can result in skin and lymphoid tumors

Mycophenolate mofetil

- Mycophenolate Mofetil is newer and more widely used nowadays.

- It inhibits T and B cells by inhibiting an enzyme in the pathway of purine synthesis.
- It prevents smooth muscle proliferation which might have additional benefits for acute and chronic rejection.
- Its use is associated with lower incidence of acute rejection episodes but long-term results are unknown.
- The main side effect:
  - Hematological effects.
  - Gastrointestinal effects particularly abdominal pain, diarrhea, GI hemorrhage.

Calcineurin antagonists

Cyclosporine

- Calcineurin antagonists include cyclosporin and tacrolimus
- Cyclosporine is a fungal metabolite that prevents the proliferation and clonal expansion of T lymphocytes by inhibition of interleukin -2.
- It significantly improves the result of transplantation since 1983.
- The dose is titrated to a blood level.
- Side effects include Nephrotoxicity, hypertension, hirsutism, tremor, gingival hyperplasia, hepatotoxicity.

Tacrolimus

- Has similar mechanism of action of cyclosporine but is considered more powerful.
- It is widely used in liver transplantation. In which greater water solubility and less dependence on bile salt absorption result in improved bioavailability.
- The side effects are similar to those of cyclosporine but with lower incidence of hirsutism, hypertension, and gingival hyperplasia.

Antilymphocyte Globulin (ALG) & Antithymocyte Globulin (ATG)

- They are prepared by immunized animals with lymphocytes.
- Thymocytes are used to produce (ATG).
- Antibodies are collected and purified.
- The dose is monitored by lymphocyte count in peripheral blood.
- Complications include: Anaphylaxis, high incidence of viral infection especially cytomegalovirus.
- Both are used to treat acute rejection or used prophylactically in highly sensitized patients.

Monoclonal antibodies

- There are large numbers of monoclonal antibodies directed against T lymphocytes and antigen-presenting cells.
- OK3 is the most commonly used against T3(CD3) antigen.
- It is used as prophylaxis against rejection or for treatment of acute rejection especially when the patient is resistant to steroid.
- It is associated with pulmonary edema if the patient has fluid overloaded.
- There is higher incidence of herpes virus re-activation, opportunistic infections (cytomegalovirus, fungi) and Epstein-Bar associated lymph proliferative disorders and B-cell lymphoma

KIDNEY (RENAL) TRANSPLANTATION

- Recipient: Patients with End-Stage kidney
  - Diabetic nephropathy, membranoproliferative glomerulonephritis.
  - If the disease which causes renal failure is malignant as in Wilm`s tumor or renal cell carcinoma, a period of time should be allowed for recurrence to occur if it does not occur within this period of time then the patient is reassessed for transplantation.
- Donor:
  - HLA typing is essential.
  - Cross matching should be negative.
  - Kidney can be safely kept for 36 hours and occasionally 48 hours.
- Operation:
  - Heterotopic, (right or left iliac fossae).
  - The renal vein is anastomosed with external iliac vein, while the renal artery is anastomosed end-to-end to the internal iliac artery or end-to-side to the external iliac artery.
  - The ureter is implanted to the bladder.
  - 70% of kidneys function immediately, 30% show delayed function due to ATN and require dialysis until kidney begins to function.

Kidney (Renal) transplantation

- Complications:
  - ATN
  - Rejection.
  - Renal infarction (thrombosis of R artery or vein)
  - Renal artery stenosis.
  - Urinary fistula.
  - Ureteric obstruction.

- Ø Lymphocele (collection of lymph around the kidney which may compress the Ureter causing Ureteric obstruction).

q Results:
- Ø 80-90% 1 year graft survival.
- Ø 75% 5-year graft survival.

Kidney (Renal) transplantation

q Diagnosis of rejection:
- Ø Clinical: general malaise, increased weight, decreased urine output.
- Ø Laboratory: Increased serum creatinine, decreased creatinine clearance.
- Ø Radioisotope scan: DTPA show reduced perfusion.
- Ø Wide bore (Trucut®) needle biopsy.
- Ø Fine needle aspiration cytology (FNAC) (in experienced hands)

LIVER TRANSPLANTATION

q Recipient:
- Ø patients with primary biliary cirrhosis, sclerosing cholangitis, chronic hepatitis, alcoholic cirrhosis, metabolic diseases, biliary atresia in children.
- Ø Fulminant hepatic failure following hepatitis or drug overdose may be treated by hepatic transplantation.
- Ø Hepatic resection where possible is preferred for malignant conditions owing to the high rate of recurrence post -transplant.

q Donor:
- Ø Blood group match, No HLA or cytotoxic cross match currently undertaken.
- Ø Size compatibility is required.
- Ø Preservation can be taken for up to 20 hours using university of Wisconsin solution.
- Ø Liver reduction techniques have been developed base on segmental anatomy of liver such parts of adult livers may be used in pediatric.
- Ø Living related donor liver transplantation can be used usually using left lateral segment.

q Operation
- Ø Is orthotopic operation.
- Ø The liver of the recipient is removed.
- Ø The donor vena cava is anastomosed to the recipient vena cava above and below the liver.
- Ø The portal veins are anastomosed end to end.
- Ø The donor hepatic artery on a patch of aorta is anastomosed to common hepatic artery.
- Ø End to end biliary tract anastomoses across a T tube is carried out.

- Complications
  - Early: acute rejection, vascular thrombosis, hemorrhage, biliary leak, and sepsis.
  - Late: biliary infections, chronic rejection (vanishing bile duct syndrome), recurrent disease.
- Results
  - 1-year graft survival depends upon underlying liver disease.
  - For chronic liver disease the 1-year graft survival is in excess of 80% but for fulminant hepatic failure is around 50%.
  - 5-year graft survival is around 70%in chronic liver disease but only around (45-50%) for fulminant liver disease.
  - Some individuals live for >25 years after liver transplant.
  - Late loss of graft is less common than other forms of solid organ transplantation.
  - About 20% of liver transplants at 5 years post-transplant appear to accept their graft without the need of continuing immunosuppression but still there is no criteria for defining such group.

HEART / LUNG TRANSPLANT

- Recipient:
  - End stage heart disease with survival 1 year unlikely (viral myocarditis, cardiomyopathies, severe ischemic heart disease).
  - Heart lung transplants are done for cardiac problems associated with pulmonary vascular hypertension.
  - The 4 possible lung transplant operation are heart /lung, double lung, sequential single lung or single lung transplantation.
  - The procedure which is used depends on the lung condition.
  - The commonest causes for heart/lung transplantation are cystic fibrosis, bronchiectasis, primary pulmonary hypertension, emphysema, idiopathic pulmonary fibrosis.
- Donor:
  - Blood group match, no HLA Or cytotoxic cross match.
  - Size compatibility is important.
  - Safe time limit for cold ischemia for the heart is 4-6 hours, the lung is less tolerant than the heart.
  - The lung is usually ventilated with 80%oxygen and kept semi- inflated during storage.
- Operation

Heart or Heart / lung

- heart: is an orthotopic operation as the recipient heart is remove.
- The recipient left atrium is anastomosed to the donor left atrium and the recipient right atrium to the donor right atrium (or the SVC and IVC are anastomosed to the corresponding vessels), the aorta and pulmonary arteries are anastomosed to the corresponding vessels end to end.
- The operation is carried out on cardiopulmonary bypass machine.

Lung

- The technique depends on whether is double lung transplant, sequential single or single lung transplantation.
- A single lung transplant offers the advantage of maximum use of donor organs and relative technical simplicity.
- Cardiopulmonary bypass is not required.
- The only disadvantage of single lung transplant is that there is only limited amount of lung tissue and complications may result from the remaining diseased lung, the operation is unsuitable for infective lung conditions such as bronchiectasis and cystic fibrosis.

- Diagnosis of rejection
  - Heart: cardiac arrhythmias, regular endomyocardial biopsies via forceps inserted in the external jugular veins and guided to the endocardium under radiographic control.

PANCREATIC TRANSPLANTATION

- Recipient:
  - Juvenile onset diabetes who has concomitant renal failure &require renal transplantation as well the aim is to prevent micro angiopathies of diabetes.
  - The kidney and pancreas are usually transplanted simultaneously from the same donor.
  - One organ is transplanted in the right iliac fossa and the other in the left iliac fossa.
  - Pancreatic transplantation alone is used in attempt to prevent the complication of diabetes mellitus is in an increasing use.
- Donor:
  - Blood group matching
  - No history of diabetes, no family hx of diabetes, normal; blood sugar.
- Operation
  - This is usually heterotopic transplant being placed either in the right or left iliac fossae
  - The majority of pancreatic transplant are whole pancreatic transplant with bladder exocrine drainage.

- Ø The pancreas is harvested with duodenal segment the duodenum is anastomosed to the bladder.
- Ø The vascular anastomoses are based on the splenic artery and portal vein which are anastomosed to the iliac vessels.

- q Diagnosis of rejection
  - Ø By radioisotope scan, reduction of urinary amylase where the pancreas is drained into the bladder, & biopsy

SMALL BOWEL TRANSPLANTATION

- q Is a complicated procedure due to both technical and graft versus host rejection.

FOLLOW UP OF TRANSPLANT PATIENTS

- q Every transplant patient should be long-term followed up by transplant unit.
- q Patients remain on immunosuppression for life and complications may develop.
- q Surveillance for development of malignancy is important.
- q Other important factors include prompt treatment of infection, advice on vaccination (live vaccines should never be given to immunosuppressed patients).
- q Avoidance of contact with infectious disease.
- q Travel abroad with care.
- q Pregnancy should be discussed with the transplant unit.