ORGAN TRANSPLANTATION AND ITS PHYSIOLOGICAL IMPLICATIONS – A Review

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ABSTRACT

Organ transplantation is the mechanism of transferring an organ (heart, lung, etc.) from one body to another or from one donor site on the patient's own body for the purpose of replacing the recipient's damaged or absent organ. The different types of transplantation considering the relationship between the donor and the recipient species are autotransplantation, xenotransplantation, iso-transplantation and allotransplantation. Allotransplantation is further divided into split and damino-transplant. Donors for organ transplantation are classified into living and deceased donors. Living donors remain alive and donate renewable or regenerative organs. Deceased or cadaveric donors are those that are cardiac dead or brain dead. Some of the organs that can be transplanted include intestine, eyes, thymus, heart, kidney, liver, and lung, out of which the last four are done worldwide. The transplantation of organs, mainly of allotransplantation and xenotransplantation types is accompanied by graft rejection. Other implications of organ transplantation include: immune system inefficiency, transplant rejection, chimerism and xenozoonosis. Graft rejection can be solved using immunosuppressive mechanism aided by immunosuppressant drugs. Immusuppression is also limited by some side effects and immune system inefficiency. Some of the strategies for overcoming rejection include the interruption of the complement cascade, use of transgeneic organs and induction of non-responsive haematopoietic-chimerism.

Keywords: Organ transplantation, Transgeneic organs, Allotransplantation, Autotransplantation, Xenotransplantation, Isotransplantation, Allografts, Haematopoietic-chimerism

Introduction

Organ transplantation is the transfer of an organ (heart, liver, etc.) 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 absent organ. The emerging field of Regenerative medicine is allowing scientists and engineers to create organs to be re-grown from the patient's own cells (stem cells, or cells extracted from the failing organs). Organs and/or tissues that are transplanted within the same person's body are called autografts. Transplants that are performed between two subjects of the same species are called allografts. Allografts can either be from a living or cadaveric source (Gutkind, 1990).

Organs that can be transplanted are the heart, kidneys, eyes, liver, lungs, pancreas, intestine and thymus. Tissues include bones, tendons (both referred to as musculoskeletal grafts), cornea, skin, heart valves and veins. Worldwide, the kidneys are the most commonly

transplanted organs, followed closely by the liver and then the heart. The cornea and musculoskeletal grafts are the most commonly transplanted tissues; these outnumber organ transplants by more than ten fold (Whetstine *et al.,* 2005).

Organ donors may be living, or brain dead. Tissue may be recovered from donors who are cardiac dead - up to 24 hours past the cessation of heartbeat. Unlike organs, most tissues (with the exception of corneas) can be preserved and stored for up to five years, meaning they can be "banked"(Whetstine *et al.,* 2005).

In some countries, tissue and organ transplants are regulated by some agencies which set strict regulations on the safety of the transplants, primarily aimed at the prevention of the spread of communicable disease. In the United States of America, tissue transplants are regulated by the United States Food and Drug Administration (USFDA). The regulations include criteria for donor screening and testing as well as strict regulations on the processing and distribution of tissue grafts (Sayeed, 2009).

Transplantation medicine is one of the most challenging and complex areas of modern medicine. Some of the key areas for medical management are the problems of transplant rejection, during which the body has an immune response to the transplanted organ, possibly leading to transplant failure and the need to immediately remove the organ from the recipient. When possible, transplant rejection can be reduced through serotyping to determine the most appropriate donor-recipient match and through the use of immunosuppressant drugs, which also have associated risk factors (MacCauley, 2004).

Overview of Transplantation: Despite efforts of international transplantation societies, it is not possible to access an accurate source on the number, rates and outcomes of all forms of transplantation globally, the best that can be achieved is estimations (OPTN, 2008).

In Nigeria, University of Maiduguri Teaching Hospital (UMTH), in collaboration with the Bayero University Teaching Hospital (BUTH), Kano and Obafemi Awolowo University Teaching Hospital (OAUTH), Ile-Ife, has successfully conducted the first kidney transplant on a 31 year old Suleiman Usman. The kidney was donated by his brother (Abubakar Usman) at the university's Kidney Centre.

South Africa has long employed transplantation to help protect life. Many transplantation centres and organ banks in South Africa contributes to successful organ transplantation and management in South Africa. For example, the Milpark Hospital Netcare has transplantation programmes for kidney, heart, lung and kidney/pancreas. Others include; Eye banks - Eyebank Foundation of South Africa (Cape Town) and Gauteng Cornea and Eye Bank (Johannesburg) (Morris, 2004).

In Latin America the donor rate is 40 – 100 per million per year, similar to that of developed countries. However, in Uruguay, Cuba and Chile, 90% of organs used for transplants came from cadaveric donors. Cadaveric donors represent 35% of donors in Saudi Arabia. There is continuous effort to increase the utilization of cadaveric donors in Asia. In India cadaveric donor prevalence of less than 1 donor per million population has been reported (OPTN, 2008). Organ transplantation in China has taken place since the 1960s and China has one of the largest transplant programmes in the world, peaking at over 13,000 transplants a year by 2004. Organ donation, however, is against Chinese tradition and culture, and involuntary organ donation is illegal under Chinese law (OPTN, 2008). China's transplant programme attracted the attention of international news media in the 1990s due to ethical concerns about the organs and tissues removed from the corpses of executed criminals being commercially traded for transplants (Huang *et al.,* 2008).

With regard to organ transplantation in Israel, there is a severe organ shortage due to religious objections by some rabbis who oppose all organ donations and others who advocate that a rabbi participate in all decision making regarding a particular donor. One third of all heart transplants performed on Israelis are done in the Peoples' Republic of China; others are done in Europe (UNOS, 2009). Transplantation rates also differ based on race, sex and income.

A study done with patients beginning long term dialysis showed that the socio-demographic barriers to renal transplantation present themselves even before patients are on the transplant list. For example, different groups express definite interest and complete pre-transplant workup at different rates. Previous efforts to create fair transplantation policies had focused on patients currently on the transplantation waiting list (Morris, 2004). In the light of the above background, this study undertook a comprehensive review of the principles, art and status of organ transplantation and its physiological implications.

MATERIALS AND METHODS

A comprehensive internet search of literature on organ transplantation was undertaken using Google Search. Literatures recovered were analyzed in pros and relevant cited tables and figures adopted.

RESULTS AND DISCUSSION

Types of Transplantation and Types of Organ Donors

Types of transplantation

Autograft and autotransplantation: Autotransplantation is the transplantation of organs/tissues or even protein from one part of the body to another in the same individual. It is the transplant of tissue to the same person. Sometimes this is done with surplus tissue, or tissue that can regenerate, or tissues more desperately needed elsewhere (examples include skin grafts, vein extraction for Coronary Artery Bypass Graft [CABG], etc.) (Gutkind, 1990). Sometimes an autograft is done to remove the tissue and then treat it or the person, before returning it; examples include stem cell autograft and storing blood in advance of surgery. In a rotationplasty a distal joint is use to replace a more proximal one, typically a foot and ankle joint is used to replace a knee joint. The patient's foot is severed and reversed, the knee removed, and the tibia joined with the femur. It is contrasted with xenotransplantation (from another species) and allotransplantation (from other individual of same species) (Hood *et al.,* 1987).

Autologous blood donation: In blood banking terminology, autologous blood donation refers to a blood donation marked for use by a donor typically for a scheduled surgery. Some advantages of autologous blood donation are; the blood type will always match, even with a rare blood type. When only autologous blood is used during surgery the risk of exposure to infectious diseases like HIV or Hepatitis from infected blood is eliminated. Lastly, the risk of allergic reaction is reduced (Hood *et al,* 1987).

Autotransplantation has disadvantages of high cost, due to individual processing, record keeping and management. In most cases, the blood is discarded if not in use instead of being added to the general supply. Autologous blood is not routinely tested for infectious diseases such as HIV antibodies. There is also a risk that in an emergency or if more blood is required than has been set aside in advance, a patient could still be exposed to donor blood instead of autologous blood. Autologous donation is not also suitable for patients who are medically unable to or not advised to give blood, such as cardiac patients, infants and small children (Hood *et al.,* 1987).

Bone autograft: In orthopeadic medicine, bone graft can be sourced from patients' own bone in order to fill space and produce an osteogenic response in a bone defect. However due to the donor- site morbidity associated with autograft, other methods such as bone allograft, morphogenetic proteins and other synthetic graft materials are often used as alternatives (Hood *et al.,* 1987). Autograft have long been considered the 'gold standard' in oral surgery and dentistry because it offered the best regeneration result. Later the introduction of morphogenic-enhanced bone graft substitute has shown similar success rates and quality on regeneration, however, there price is still very high.

Xenograft and xenotransplantation: Xenotransplantation is the transplant of living cells, tissues and organs from one species to another. Such cells, tissues and organs are called xenografts (Cooper and Lanza, 2000).

An example is porcine heart valve transplants, which are quite common and successful. Another example is attempted piscine-primate (fish to non-human primate) transplant of islet (i.e. pancreatic or insular tissue) tissue. The latter research study was intended to pave the way for potential human use, if successful. However, xenotransplantation is often an extremely dangerous type of transplant with few successful cases because of the increased risk of non-compatibility, rejection and disease carried in the tissue (Bols *et al.,* 2010).

A continuing concern is that many animals such as pigs have shorter lifespan than humans meaning that their tissues age at a quicker rate than human tissues. Disease transmission (xenozoonosis) and permanent alteration to the genetic code of animals are also causes for concern. There are few published cases of successful xenotrans-plantation (Bols *et al.,* 2010). Xenotransplants could save thousands of patients waiting for donated organs. The animal organ probably pig or baboon could be genetically altered with human genes to trick a patient's immune system into accepting it as part of its own body. Xenotransplants of ovarian tissue into immunodeficient nude mice is already used in research to sturdy the development of ovarian follicles (Lan *et al.,* 2008). Both host and graft vessels contribute to the revascularization of xenografted human ovarian tissue in mice. Chimpanzees were originally considered to be the best option since their organs are of similar size and they have good blood type compatibility with humans. Baboons are more readily available since chimpanzees are listed as endangered species. Problems include there smaller body size, infrequency of blood group 'O', there long gestation period, they typically produce few offspring and increased risk of disease transmission since they are so closely related to humans (Lan *et al.,* 2008). Pigs are currently thought to be the best because the risk of cross specie disease transmission is reduced because of their increased phylogenetic distance from humans. They are readily available, their organs are anatomically comparable in size and new infectious agents are less likely, since they have been in close contact with humans through domestication for many generations. Current experiments in xenotransplantation most often use pigs as the donor and baboons as human models (Cooper and Lanza, 2000).

Immunological barriers arise due to responses of the recipient's immune system. The response which is generally more extreme than in allotransplantation ultimately results in rejection of the xenograft and can in some cases result in immediate death of the recipient. Some of the rejection types are hyperacute, acute vascular rejection, cellular rejection and chronic rejection (Cooper and Lanza, 2000).

Allograft and allotransplantation: An allograft is a transplant of cell, organ or tissue between two genetically non-identical members of the same species. The transplant is called allograft or allogeneic transplant or homograft. Most human tissue and organ transplants are allografts. Due to the genetic difference between the organ and the recipient, the recipient's immune system will identify the organ as foreign and attempt to destroy it, causing transplant rejection (Hood *et al.,* 1987). Allografts include anterior cruciate ligament (ACL) repair, joint reconstruction in the knee or ankle, meniscal replacement, ridge augmentation in dental procedures, shoulder repair, spinal fusion, urological procedures, liver transplant, skin, transplant, intestinal transplant, coneal transplant, heart transplant, bone marrow transplant etc. Allograft may be used to replace damaged heart valves and skin however, they are frequently used in orthopeadic surgery to replace tendons or bones (Hood *et al.,* 1987).

i. Isograft: Isograft is the subset of allografts in which organs or tissues are transplanted from a donor to a genetically identical recipient (such as an identical twin). Isografts are differentiated from other types of transplants because while they are anatomically identical to allografts,

they do not trigger an immune response. In bone marrow transplantation, the term for a genetically identical graft is syngeneic whereas the equivalent of an autograft is termed autotransplantation. Transplant rejection between two such individuals virtually never occurs. As monozygotic twins have same histocompatibility complex, there is very rarely any rejection of transplanted tissue by the adapted immune system. There is virtually no graft-versus-host disease. This forms the basis for why the preferred choice of a physician considering an organ donor will be a monozygotic twin (Hood *et al.,* 1987).

ii. Split transplants: Sometimes a deceased-donor organ, usually a liver, may be divided between two recipients, especially an adult and a child. This is not usually a preferred option because the transplantation of a whole organ is usually more successful.

iii. Domino transplants: This operation is usually performed on patients with cystic fibrosis because both lungs need to be replaced and it is a technically easier operation to replace the heart and lungs at the same time (Ericzon *et al.,* 2008). As the recipient's native heart is usually healthy, it can be transplanted into someone else needing a heart transplant. That term is also used for a special form of liver transplant in which the recipient suffers from familial amyloidotic polyneuropathy, a disease where the liver slowly produces a protein that damages other organs. This patient's liver can be transplanted into an older patient who is likely to die from other causes before a problem arises (Ericzon *et al.,* 2008).

This term also refers to a series of living donor transplants in which one donor donates to the highest recipient on the waiting list and the transplant center utilizes that donation to facilitate multiple transplants. These other transplants are otherwise impossible due to blood type or antibody barriers to transplantation. The "Good Samaritan" kidney is transplanted into one of the other recipients, whose donor in turn donates his or her kidney to an unrelated recipient. Depending on the patients on the waiting list, this has sometimes been repeated for up to six pairs, with the final donor donating to the patient at the top of the list. This method allows all organ recipients to get a transplant even if their living donor is not a match to them (Ericzon *et al.,* 2008). This further benefits patients below any of these recipients on waiting lists, as they move closer to the top of the list for a deceased-donor organ.

Types of Organ Donor

Organ donors may be living, or brain dead. Brain dead means the donor must have received an injury (either traumatic or pathological) to the part of the brain that controls heartbeat and breathing (Whetstine *et al.,* 2005). Breathing is maintained via artificial sources, which, in turn, maintains heartbeat. Once brain death has been declared the person can be considered for organ donation. Criteria for brain death vary. Tissue may be recovered from donors who are cardiac dead. That is, their breathing and heartbeat has ceased (Whetstine *et al.,* 2005; Gruessner and Benedetti, 2008). They are referred to as cadaveric donors. In general, tissues may be recovered from donors up to 24 hours past the cessation of heartbeat. In contrast to organs, most tissues (with the exception of corneas) can be preserved and stored for up to five years, meaning they can be "banked." Also, more than 60 grafts may be obtained from a single tissue donor. Because of these factors, the ability to recover from a non-heart beating donor, the ability to bank tissues and the number of grafts available from each donor, tissue transplant is much more common than organ transplants.

Living: In living donors, the donor remains alive and donates a renewable tissue, cell, or fluid (e.g. blood, skin), or donates an organ or part of an organ in which the remaining organ can regenerate or take on the workload of the rest of the organ (primarily single kidney donation, partial donation of liver, small bowel). Regenerative medicine may one day allow for laboratory-grown organs, using patient's own cells (stem cells, or healthy cells extracted from the failing organs) (Gruessner and Benedetti, 2008).

Deceased: Deceased (formerly cadaveric) are donors who have been declared brain-dead and whose organs are kept viable by ventilators or other mechanical mechanisms until they can be excised for transplantation (Whetstine *et al.,* 2005). Apart from brain-stem dead donors, who have formed the majority of deceased donors for the last twenty years, there is increasing use of donation after cardiac death donors (formerly non-heart beating donors) to increase the pool of donors as demand for transplants continues to grow. These organs have inferior outcomes to organs from a brain-dead donor; however given the scarcity of suitable organs and the number of people who die waiting, any potentially suitable organ must be considered (Ross *et al.,* 1997a,b).

Reasons for Donation

i. Living related donors: Living related donors donate to family members or friends in whom they have an emotional investment. The risk of surgery is offset by the psychological benefit of not losing someone related to them or not seeing them suffer the ill effects of waiting on a list.

ii. Paired exchange: A paired-exchange is a technique of matching willing living donors to compatible recipients using serotyping (Ross *et al.,* 1997ab). For example a spouse may be willing to donate a kidney to their partner but cannot since there is no biological match. The willing spouse's kidney is donated to a matching recipient who also has an incompatible but willing spouse. The second donor must match the first recipient to complete the pair exchange (Figure 1).

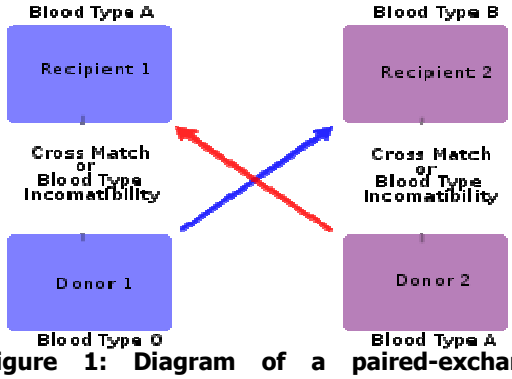

Figure 1: Diagram of a paired-exchange between otherwise incompatible pairs

Some people choose to do this out of a need to donate. Some donate to the next person on the list; others use some method of choosing a recipient based on criteria important to them. Web sites are being developed that facilitate such donation (Appel and Fox, 2005).

iv. Compensated donation: In compensated donation, donors get money or other compensation in exchange for their organs. This practice is common in some parts of the world, whether legal or not, and is the major factors driving medical tourism. In the United States, The National Organ Transplant Act of 1984 made organ sales illegal (Rothman, 2002). In the United Kingdom, the Human Organ Transplants Act 1989 first made organ sales illegal, and has been superseded by the Human Tissue Act 2004 (Rothman, 2002; Shimazono, 2007).

Compensation for donors also increases the risk of introducing diseased organ to recipients because these donors often yield from poorer population unable to receive health care regularly and organ dealers may evade disease screening processes. The majority of such deals include payment and no follow–up care for the donor (Ibrahim *et al.,* 2009).

Transplantable Organs

Tissues/organs that can be transplanted can be grouped into the following:

i. Thoracic organs: Heart (deceased-donor only), lung (deceased-donor and living-related lung transplantation) and heart /lung (deceased-donor and domino transplant).

ii. Abdominal organs: Kidney (deceased-donor and living-donor), liver (deceased-donor and living-donor), pancreas (deceased-donor only), intestine (deceased-donor and living-donor), stomach (deceased-donor only) and testis.

iii Tissues, cells, fluids: Hand (deceased-donor only), cornea (deceased-donor only), skin including face replant (autograft) and face transplant (extremely rare), islets of langerhans

(pancreas islet cells) (deceased-donor and living-donor), bone marrow/adult stem cell (living-donor and autograft), blood transfusion/blood parts transfusion (living-donor and autograft), blood vessels (autograft and deceased-donor), heart valve (deceased-donor, living-donor and xenograft [porcine/bovine]) and bone (deceased-donor and living-donor) (Gutkind, 1990; Morris, 2004; Wikipedia, 2011).

Transplant of Some Important Organs

Heart Transplantation: A heart transplant, or a cardiac transplantation, is a surgical transplant procedure performed on patients with end-stage heart failure or severe coronary artery disease. The most common procedure is to take a working heart from a recently deceased organ donor (cadaveric allograft) and implant it into the patient. The patient's own heart may either be removed (orthotopic procedure) or, less commonly, left in to support the donor heart (heterotopic procedure); both are controversial solutions to one of the most enduring human ailments. Post operation survival periods now average 15 years (Morris, 2005).

Worldwide, about 3,500 heart transplants is being performed every year; about 800,000 people have a Class IV heart defect and need a new organ (Gutkind, 1990; Bishay, 2011). This disparity has spurred considerable research into the use of non-human hearts since 1993. It is now possible to take a heart from another species (xenograft), or implant a man-made artificial one, although the outcome of these two procedures has been less successful in comparison to the far more commonly performed allografts. Engineers want to fix the remaining problems with the manufactured options in the next 15 years (Bishay, 2011).

i. Contraindications: Some patients are less suitable for a heart transplant, especially if they suffer from other circulatory conditions unrelated to the heart. The following conditions in a patient would increase the chances of complications occurring during the operation: Kidney, lung, or liver disease, Insulin-dependent diabetes with other organ dysfunction, life-threatening diseases unrelated to heart failure, Vascular disease of the neck and leg arteries, High pulmonary vascular resistance, Recent thromboembolism, Age over 60 years (some variation between centres) and alcohol, tobacco or drug abuse (Jeffery, 2003).

ii. Pre-operative procedure: Typical heart transplantation begins with a suitable donor heart being located from a recently deceased or brain dead donor, also called a beating heart cadaver. The transplant patient is contacted by a nurse coordinator and instructed to attend the hospital in order to be evaluated for the operation and given pre-surgical medication. At the same time, the heart is removed from the donor and inspected by a team of surgeons to see if it is in a suitable condition to be transplanted (Reid, 2005). This can often be a very distressing experience for an already emotionally unstable patient, and they will usually require emotional support before being sent home. The patient must also undergo many emotional, psychological, and physical tests to make sure that they are in good mental health and will make good use of their new heart. The patient is also given immunosuppressant medication so that their immune system will not reject the new heart (Bishay, 2011).

iii. Operative procedure: Once the donor heart has passed its inspection, the patient is taken into the operating room and given a general anesthetic. Either an orthotopic or a heterotopic procedure is followed, depending on the condition of the patient and the donor heart.

iv. Orthotopic procedure: The orthotopic procedure begins with the surgeons performing a median sternotomy to expose the mediastinum. The pericardium is opened, the great vessels are dissected and the patient is attached to cardiopulmonary bypass. The failing heart is removed by transecting the great vessels and a portion of the left atrium. The pulmonary veins are not transected; rather a circular portion of the left atrium containing the pulmonary veins is left in place (Reid, 2005).

Normally a donor's heart is injected with potassium chloride in order to stop it beating, before being removed from the donor's body and packed in ice in order to preserve it (Reid, 2005). The ice can usually keep the heart fresh for a maximum of four to six hours with proper preservation, depending on its starting condition. Rather than cooling the heart, this new procedure involves keeping it at body temperature and connecting it to a special machine called an Organ Care System that allows it to continue beating with warm, oxygenated blood flowing through it. This can maintain the heart in a suitable condition for much longer than the traditional method (Potechuk, 2006).

The donor heart is trimmed to fit onto the patient's remaining left atrium and the great vessels are sutured in place (Potechuk, 2006). The new heart is restarted, the patient is weaned from cardiopulmonary bypass and the chest cavity is closed (Figure 2) (Wikipedia, 2011).

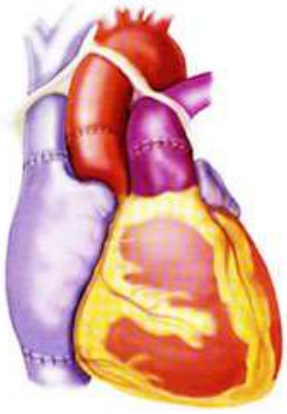

Figure 2: Procedure for heart transplant (orthotopic procedure). Source: Wikipedia (2011)

v. Heterotopic procedure: In the heterotopic procedure, the patient's own heart is not removed before implanting the donor heart. The new heart is positioned so that the chambers and blood vessels of both hearts can be connected to form what is effectively a 'double heart'. The procedure can give the patients original heart a chance to recover, and if the donor's heart happens to fail (e.g. through rejection), it may be removed, allowing the patient's original heart to start working again (Reid, 2005). Heterotopic procedures are only used in cases where the donor heart is not strong enough to function by itself (due to either the patient's body being considerably larger than the donor's, the donor having a weak heart, or the patient suffering from pulmonary hypertension) (Morris, 2004; Potechuk, 2006).

vi. Post-operative: Doctors typically like the new recipients to leave hospitals soon after surgery because of the risk of infection in a hospital (typically 1 – 2 weeks without any complications). Since the vagus nerve is severed during the operation, the new heart will beat at around 100 beats per minute unless nerve regrowth occurs (Gutkind, 1990).

The patient will be monitored to detect rejection of the heart by the body. This surveillance can be performed via frequent biopsy or a gene expression blood test known as AlloMap Molecular Expression Testing. Typically, biopsy is performed immediately post-transplant and then AlloMap blood testing is performed once the patient is stable. The transition from biopsy to AlloMap could occur as soon as 55 days post transplants (Morris, 2004).

vii. Prognosis: The prognosis for heart transplant patients following the orthotopic procedure have greatly increased over the past 20 years, and as of June 5, 2009, the survival rates were as follows (Figure 3).

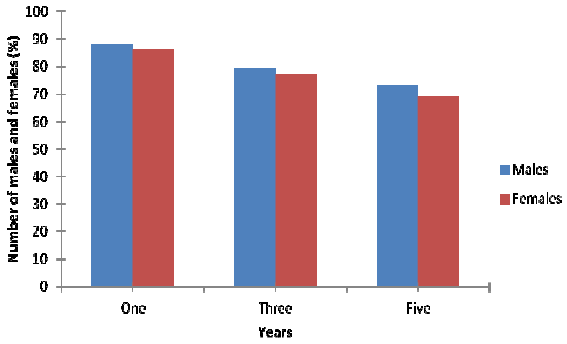

Figure 3: The prognosis for heart transplant patients following the orthotopic procedure over the past 20 years. Source: Bishay (2011)

In a November 2008 study conducted on behalf of the United States Federal Government by Dr. Eric Weiss of the Johns Hopkins University

School of Medicine, it was discovered that heart transplants — all other factors being accounted for — work better in same-sex transplants (male to male, female to female). However, due to the present acute shortage in donor hearts, this may not always be feasible (OPTN, 2008).

Lung Transplantation: Lung transplant or pulmonary transplantation is a surgical procedure in which a patient's deceased lungs are partially or totally replaced by lungs which come from a donor. While lung transplants carry certain associated risks, they can also extend life expectancy and enhance the quality of life for end-stage pulmonary patients (Gutkind, 1990).

i. Qualifying conditions: Lung transplantation is the therapeutic measure of last resort for patients with end-stage lung disease who have exhausted all other available treatments without improvement (Gutkind, 1990). A variety of conditions may make such surgery necessary. The most common reasons for lung transplantation in the United States as at the year 2005 indicated that chronic obstructive pulmonary disease ranged highest among patients (Table 1).

Table 1: The reasons for lung transplantation in the United States for the year, 2005

Reasons	Percentages
Chronic obstructive pulmonary disease	27
Idiopathic pulmonary fibrosis	16
Cystic Fibrosis	14
Idiopathic pulmonary hypertension	12
Alpha 1-antitrypsin deficiency	5
Replacing previously transplanted lungs that have since failed	2

Source: OPTN (2008)

Despite the severity of a patient's respiratory condition, certain pre-existing conditions may make a person a poor candidate for lung transplantation: concurrent chronic illness (e.g. congestive heart failure, kidney disease, liver disease), current infections, including HIV and hepatitis, although more and more often hepatitis C patients are both being transplanted and are also being used as donors if the recipient is Hepatitis C positive: current or recent cancer, current use of alcohol, tobacco, or illegal drugs, age, psychiatric conditions and history of noncompliance with medical instructions (Brando *et al.,* 1995).

ii. Transplant requirements: There are certain requirements for potential lung donors, due to the needs of the potential recipient. In the case of living donors, there is also consideration on the effect of the surgery on the donor's health and lung size match of the recipient. The donated lung or lungs must not only be large enough to adequately oxygenate the patient, but small enough to fit within the recipient's chest cavity. The age and blood type of both donor and recipient are often considered (Arcasoy and Kotloff, 1999).

While a transplant center is free to set its own criteria for transplant candidates, certain requirements are generally agreed upon: end-stage lung disease; has exhausted other available therapies without success; no other chronic medical conditions (e.g. heart, kidney, liver); no current infections or recent cancer (Arcasoy and Kotloff, 1999). There are certain cases where pre-existing infection is unavoidable, as with many patients with cystic fibrosis. In such cases, transplant centers, at their own discretion, may accept or reject patients with current infections of *B. cepacia*; no HIV or hepatitis; no alcohol, smoking, or drug abuse; within an acceptable weight range (marked undernourishment or obesity are both associated with increased mortality); age (single vs. double) and acceptable psychological profile (Brando *et al.,* 1995; Arcasoy and Kotloff, 1999).

iii. Types of lung transplant

a. Lobe: A lobe transplant is a surgery in which part of a living donor's lung is removed and used to replace part of recipient's diseased lung. This procedure usually involves the donation of lobes from two different people, thus replacing a single lung in the recipient. Donors who have been properly screened should be able to

maintain a normal quality of life despite the reduction in lung volume (Brando *et al.,* 1995).

b. Single-lung: Many patients can be helped by the transplantation of a single healthy lung. The donated lung typically comes from a donor who has been pronounced brain-dead.

c. Double-lung: Certain patients may require both lungs to be replaced. This is especially the case for people with cystic fibrosis, due to the bacterial colonisation commonly found within such patients' lungs; if only one lung were transplanted, bacteria in the native lung could potentially infect the newly transplanted organ (Brando *et al.,* 1995).

Heart-lung Transplantation: Some respiratory patients may also have severe cardiac disease which would necessitate a heart transplant. These patients can be treated by a surgery in which both lungs and the heart are replaced by organs from a donor or donors.

Procedure for lung transplant

i. Incision: While the patient is deeply asleep and pain-free (general anesthesia), an incision is made through the breast bone (sternum). One or two donor lungs are transplanted, depending on the disease process being treated.

ii. Procedure: Tubes are used to re-route the blood to a heart-lung bypass machine to keep the blood oxygenated and circulating during the surgery. The patient's lungs are removed and the donor lungs are stitched into place. Drainage tubes (chest tubes) are inserted to drain air, fluid and blood out of the chest for several days to allow the lungs to fully re-expand (Figure 4) (Brando *et al.,* 1995; Wikipedia, 2011).

iii. Post-operative care: The patient's lungs are removed and the donor lungs are stitched into place. Drainage tubes (chest tubes) are inserted to drain air, fluid, and blood out of the chest for several days to allow the lungs to fully reexpand. Patients will require immunosuppressive medications for the rest of their lives to prevent immune rejection of the transplanted lung. Lung transplantation results vary depending on the disease being treated and the experience of the center performing the surgery (Arcasoy and Kotloff, 1999).

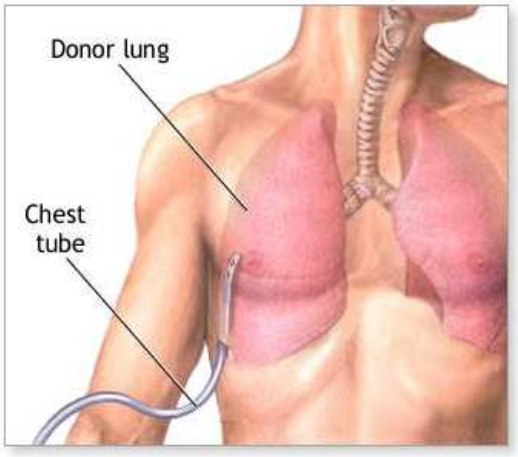

Figure 4: Drainage tubes are inserted to drain air, fluid and blood out of the chest. Source: Wikipedia (2011)

iv. Prognosis: The duration of lung transplant before showing rejection indicated that the percentage survival decreased with increasing years of post transplant (Table 2). The source data made no distinction between living and deceased donor organs, nor was any distinction made between lobar, single, and double lung transplants (OPTN, 2008).

Table 2: Average duration of lung transplant before showing rejection

Transplant	1 year survival	5 years survival	10 years survival
Lung transplant	83.6%	53.4%	28.4%
Heart-lung transplant	73.8%	46.5%	28.3%

Source: OPTN (2008)

Liver Transplantation: Liver transplantation or hepatic transplantation is the replacement of a diseased liver with a healthy liver allograft. The most commonly used technique is orthotopic transplantation, in which the native liver is removed and replaced by the donor organ in the same anatomic location as the original liver (Eghtesad *et al.,* 2005). Liver transplantation nowadays is a well-accepted treatment option for end-stage liver disease and acute liver failure. It is also one of the most

expensive treatments in modern medicine. Typically three surgeons and one anesthesiologist are involved, with up to four supporting nurses. The surgical procedure is very demanding and ranges from 4 to 18 hours depending on outcome. Numerous anastomoses and sutures, and many disconnections and reconnections of abdominal and hepatic tissue, must be made for the transplant to succeed, requiring an eligible recipient and a well-calibrated live or cadaveric donor match. By any standard, hepatic transplantation is a major surgical procedure with an appreciable degree of risk (Starzl *et al.,* 1963).

i. Indications: Liver transplantation is potentially applicable to any acute or chronic condition resulting in irreversible liver dysfunction, provided that the recipient does not have other conditions that will preclude a successful transplant (Adam *et al.,* 2003). Uncontrolled metastatic cancer outside liver, active drug or alcohol abuse and active septic infections are absolute contraindications. While infection with HIV was once considered an absolute contraindication, this has been changing recently. Advanced age and serious heart, pulmonary or other disease may also prevent transplantation (relative contra-indications) (Eghtesad *et al.,* 2005). Most liver transplants are performed for chronic liver diseases that lead to irreversible scarring of the liver, or cirrhosis of the liver. Another cause is cryptogenic liver disease (Adam *et al.,* 2003).

ii. Procedure: Before transplantation, liver-support therapy might be indicated (bridging-to-transplantation). Artificial liver support like liver dialysis or bioartificial liver support concepts are currently under preclinical and clinical evaluation (Eghtesad *et al.,* 2005). Virtually all liver transplants are done in an orthotopic fashion, that is, the native liver is removed and the new liver is placed in the same anatomic location. The transplant operation can be conceptualized as consisting of the hepatectomy (liver removal) phase, the anhepatic (no liver) phase, and the postimplantation phase (Eghtesad *et al.,* 2005). The operation is done through a large incision in the upper abdomen. The hepatectomy involves division of all ligamentous attachments to the liver, as well as the common bile duct, hepatic artery, hepatic vein and portal vein. Usually, the retrohepatic portion of the inferior vena cava is removed along with the liver, although an alternative technique preserves the recipient's vena cava (piggyback technique) (Starzl *et al.,* 1963).

Vohra (2006) suggested that the donor's blood in the liver will be replaced by an ice-cold organ storage solution, such as UW (Viaspan) until the allograft liver is implanted. Implantation involves anastomoses of the inferior vena cava, portal vein, and hepatic artery. After blood flow is restored to the new liver, the biliary (bile duct) anastomosis is constructed, either to the recipient's own bile duct or to the small intestine (Starzl *et al.,* 1963). The surgery usually takes between five and six hours, but may be longer or shorter due to the difficulty of the operation and the experience of the surgeon (Vohra, 2006).

Adam *et al.* (2003) reported that in majority of cases of liver transplants, the entire liver from a non-living donor is used for the transplant, particularly for adult recipients. A major advance in pediatric liver transplantation was the development of reduced size liver transplantation, in which a portion of an adult liver is used for an infant or small child. Further developments in this area included split liver transplantation, in which one liver is used for transplants for two recipients, and living donor liver transplantation, in which a portion of a healthy person's liver is removed and used as the allograft (Eghtesad *et al.,* 2005). Living donor liver transplantation for pediatric recipients involves removal of approximately 20% of the liver (Figure 5) (Adam *et al.,* 2003).

iii. Prognosis: Prognosis is quite good. However, those with certain illnesses may differ. There is no exact model to predict survival rates; however, those with transplant have a 58% chance of surviving 15 years. Failure of the new liver occurs in 10% to 15% of all cases. These percentages are contributed to by many complications. Early graft failure is probably due to preexisting disease of the donated organ.

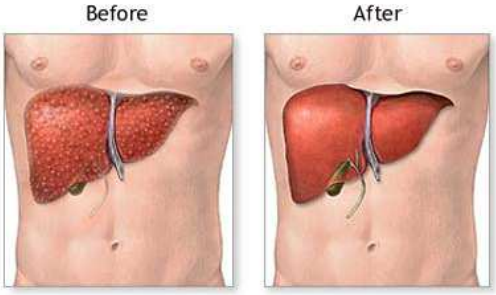

Figure 5: Images of liver before and after liver transplant. Source: Wikipedia (2011)

Others include technical flaws during surgery such as revascularization that may lead to a nonfunctioning graft (Umeshita *et al.,* 2003).

iv. Living donor transplantation: Living donor liver transplantation (LDLT) has emerged in recent decades as a critical surgical option for patients with end stage liver disease, such as cirrhosis and/or hepatocellular carcinoma often attributable to one or more of the following: long-term alcohol abuse, long-term untreated hepatitis C infection, long-term untreated hepatitis B infection. The concept of LDLT is based on (a) the remarkable regenerative capacities of the human liver and (b) the widespread shortage of cadaveric livers for patients awaiting transplant. In LDLT, a piece of healthy liver is surgically removed from a living person and transplanted into a recipient, immediately after the recipient's diseased liver has been entirely removed (Umeshita *et al.,* 2003).

Death after LDLT has been reported; 0% in Japan, 0.3% in USA and <1% in Europe, with risks likely to decrease further as surgeons gain more experience in this procedure (Adam *et al.,* 2003). In a typical adult recipient LDLT, 55 to 70% of the liver (the right lobe) is removed from a healthy living donor. The donor's liver will regenerate approaching 100% function within 4 – 6 weeks, and will almost reach full volumetric size with recapitulation of the normal structure soon thereafter. It may be possible to remove up to 70% of the liver from a healthy living donor without harm in most cases. The transplanted portion will reach full function and the appropriate size in the recipient as well, although it will take longer than for the donor (Starzl *et al.,* 1963).

Living donors are faced with risks and/or complications after the surgery. Blood clots and biliary problems have the possibility of arising in the donor post-op, but these issues are remedied fairly easily. Although death is a risk that a living donor must be willing to accept prior to the surgery, the mortality rate of living donors in the United States is low. The LDLT donor's immune system does diminish as a result of the liver regenerating, so certain foods which would normally cause an upset stomach could cause serious illness (Adam *et al.,* 2003).

a. Liver donor requirements: Any member of the family, parent, sibling, child, spouse or a volunteer can donate their liver. The criteria for a liver donation include: Being in good health, Having a blood type that matches or is compatible with the recipient's, having a charitable desire of donation without financial motivation, being between 18 and 60 years old, being of similar or bigger size than the recipient, before one becomes a living donor and the donor must undergo testing to ensure that the individual is physically fit. Sometimes CT scans or MRIs are done to image the liver. In most cases, the work up is done in 2 – 3 weeks (Eghtesad *et al.,* 2005; Fan, 2006).

Kidney Transplantation: Kidney transplantation or renal transplantation is the organ transplant of a kidney into a patient with end-stage renal disease. Kidney transplantation is typically classified as deceased-donor (formerly known as cadaveric) or living-donor transplantation depending on the source of the donor organ. Living-donor renal transplants are further characterized as genetically related (living-related) or non-related (living-unrelated) transplants, depending on whether a biological relationship exists between the donor and recipient (Potechuk, 2006).

i. Indications: The indication for kidney transplantation is end-stage renal disease (ESRD), regardless of the primary cause. This is defined as a glomerular filtration rate of <15ml/min/1.73 per square meter. Common diseases leading to ESRD include malignant hypertension, infections, diabetes mellitus and

focal segmental glomerulosclerosis. Genetic causes include polycystic kidney disease, a number of inborn errors of metabolism and autoimmune conditions such as lupus and Good pasture's syndrome (McDonald and Russ, 2002). Diabetes is the most common cause of kidney transplantation accounting for approximately 25% of cases in the United States. The majority of renal transplant recipients are on some form of peritoneal dialysis or similar process of haemofiltration at the time of transplantation (Wolfe *et al.,* 1999). However, individuals with chronic renal failure who have a living donor available may undergo preemptive trans-plantation before dialysis is needed.

ii. Living donors: More than one in three donations in the UK is now from a live donor and almost one in three in Israel. The percentage of transplants from living donors is increasing (Brooks and Nicholson, 2003). Potential donors are carefully evaluated on medical and psychological grounds. This ensures that the donor is fit for surgery and has no disease which brings undue risk or likelihood of a poor outcome for either the donor or recipient. The psychological assessment is to ensure the donor gives informed consent and is not coerced (Jordan *et al.,* 2004). There is good evidence that kidney donation is not associated with long-term harm to the donor. This has increased the rate of kidney donation and transplant over some other organs (Figure 6).

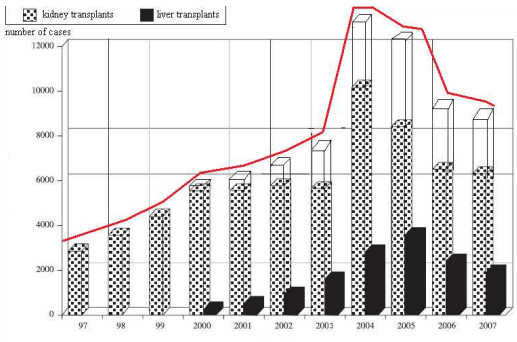

Figure 6: Kidney and liver transplant cases in China from 1997 to 2007 (with liver cases transposed on top of kidney cases). Source: Huang *et al.* (2008)

In some cases of male living donors a hydrocele may occur in the scrotum related to the side of the nephrectomy. As an example, a living donor who had a left side laproscopic nephrectomy, the left side of the scrotum can develop a hydrocele that envelopes the left testicle and enlarges the left side of the scrotum (Chin and Hazzan, 2007). Traditionally, the donor procedure has been through a single incision of 4 – 7 inches (10 – 18 cm), but live donation is being increasingly performed by laparoscopic surgery. This reduces pain and accelerates recovery for the donor. Operative time and complications decreased significantly after a surgeon performed 150 cases. Live donor kidney grafts tend to perform better than those from deceased donors (MacDonald and Russ, 2002; Chin and Hazzan, 2007). Since the increase in the use of laparoscopic surgery, the number of live donors has increased. Any advance which leads to a decrease in pain and scarring and swifter recovery has the potential to boost donor numbers (Table 3).

Table 3: Statistics of kidney transplant by country, year and donor type

Country	Year	Cadaveric donor	Living donor	Total
Canada	2000	724	388	1,112
France	2003	1,991	136	2,127
Italy	2003	1,489	135	1,624
Spain	2003	1,991	60	2,051
United Kingdom	2003	1,297	439	1,736
United States	2008	10,551	5,966	16,517
Pakistan	2008		1,854	1,932

Source: OPTN (2009)

iii. Deceased donors: Deceased donors can be divided in to two groups: Brain-dead (BD) donors and cardiac death (DCD) donors (Whetstine *et al.,* 2005). Although brain-dead (beating heart) donors are considered dead, the donor's heart continues to pump and maintain the circulation. This makes it possible for surgeons to start operating while the organs are still being perfused. During the operation, the aorta will be cannulated, after which the donor's blood will be replaced by an ice-cold storage solution, such as UW (Viaspan), HTK or Perfadex. Depending on which organs are transplanted, more than one solution may be used simultaneously. Due to the temperature of

the solution, and since large amounts of cold NaCl-solution are poured over the organs for a rapid cooling, the heart will stop pumping (Brooks and Nicholson, 2003). Donors after cardiac death are patients who do not meet the brain-dead criteria but, due to the small chance of recovery, have elected via a living will or through family to withdraw support. In this procedure, treatment is discontinued (mechanical ventilation is shut off). After a time of death has been pronounced, the patient is rushed to the operating room where the organs are recovered. Storage solution is flushed through the organs. Since the blood is no longer being circulated, coagulation must be prevented with large amounts of anti-coagulation agents such as heparin. Several ethical and procedural guidelines must be followed; most importantly, the organ recovery team should not participate in the patient's care in any manner until after death has been declared (Whetstine *et al.,* 2005; El-Agroudy *et al.,* 2007).

iv. Compatibility: If plasmapheresis or IVIG is not performed, the donor and recipient have to be ABO blood group compatible. Also, they should ideally share as many HLA and "minor antigens" as possible. This decreases the risk of transplant rejection and the need for another transplant. The risk of rejection may be further reduced if the recipient is not already sensitized to potential donor HLA antigens and if immunosuppressant levels are kept in an appropriate range (Frohn *et al.,* 1998; Gruessner and Benedetti, 2008). The level of sensitization to donor HLA antigens is determined by performing a panel reactive antibody test on the potential recipient. In the United States, up to 17% of all deceased donor kidney transplants have no HLA mismatch (MacDonald and Russ, 2002). However, HLA matching is a relatively minor predictor of transplant outcomes. In fact, living non-related donors are now almost as common as living genetically-related donors.

v. Procedure: The donor kidney must be transplanted within 24 – 28 hours of removal from the donor. The new kidney is placed low in the right or left groin area (Ibrahim *et al.,* 2009). In most cases the barely functioning existing kidneys are not removed, as this has been shown to increase the rates of surgical morbidities. Therefore, the kidney is usually placed in a location different from the original kidney, often in the iliac fossa, so it is often necessary to use a different blood supply. The renal artery of the kidney, previously branching from the abdominal aorta in the donor, is often connected to the external iliac artery in the recipient and the renal vein of the new kidney, previously draining to the inferior vena cava in the donor, is often connected to the external iliac vein in the recipient (Figure 7) (Brooks and Nicholson, 2003; Wikipedia, 2011).

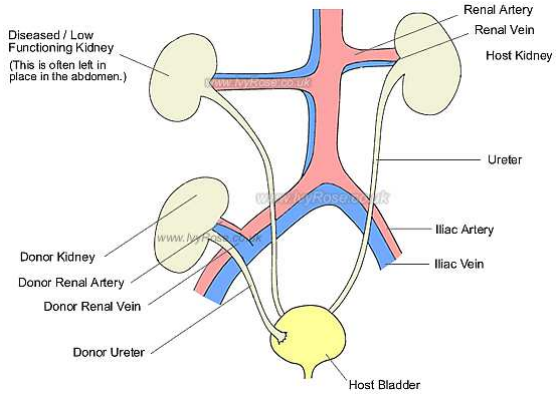

Figure 7: Procedure for kidney transplant; the donor kidney is typically placed inferior of the normal anatomical location. Source: Wikipedia (2011)

vi. Post operation: The transplant surgery takes about three hours. The donor kidney will be placed in the lower abdomen and its blood vessels connected to arteries and veins in the recipient's body. When this is complete, blood will be allowed to flow through the kidney again. The final step is connecting the ureter from the donor kidney to the bladder. In most cases, the kidney will soon start producing urine (Brooks and Nicholson, 2003).

Depending on its quality, the new kidney usually begins functioning immediately. Living donor kidneys normally require 3 – 5 days to reach normal functioning levels, while cadaveric donations stretch that interval to 7 – 15 days. Hospital stay is typically for 4 – 7 days. If complications arise, additional medications (diuretics) may be administered to help the

kidney produce urine (Brooks and Nicholson, 2003; Potechuk, 2006).

Kidney transplant recipients are discouraged from consuming grapefruit, pomegranate and green tea products. These food products are known to interact with the transplant medications, specifically tacrolimus, ciclosporin and sirolimus. The blood levels of these drugs may be lowered, potentially leading to a rejection episode (MacCauley, 2004).

vii. Prognosis: Kidney transplantation is a life-extending procedure. The typical patient will live 10 to 15 years longer with a kidney transplant than if kept on dialysis. The increase in longevity is greater for younger patients, but even 75-year-old recipients (the oldest group for which there is data) gain an average four more years of life. People generally have more energy, a less restricted diet, and fewer complications with a kidney transplant than if they stay on conventional dialysis (Wolfe *et al.,* 1999).

Some studies seem to suggest that the longer a patient is on dialysis before the transplant, the less time the kidney will last. It is not clear why this occurs, but it underscores the need for rapid referral to a transplant program. Ideally, a kidney transplant should be preemptive i.e. take place before the patient begins dialysis (Wolfe *et al.,* 1999).

Kidney-Pancreas Transplantation: Occasionally, the kidney is transplanted together with the pancreas. This is done in patients with diabetes mellitus type 1, in whom the diabetes is due to destruction of the beta cells of the pancreas and in whom the diabetes has caused renal failure (diabetic nephropathy) (IPTR, 2002). This is almost always a deceased donor transplant. Only a few living donor (partial) pancreas transplants have been done. For individuals with diabetes and renal failure, the advantages of earlier transplant from a living donor (if available) are far superior to the risks of continued dialysis until a combined kidney and pancreas are available from a deceased donor. A patient can either receive a living kidney followed by a donor pancreas at a later date (PAK, or pancreas-after-kidney) or a combined kidney-pancreas from a donor (SKP, simultaneous kidney-pancreas) (Potechuk, 2006). Transplanting just the islet cells from the pancreas is still in the experimental stage, but shows promise. This involves taking a deceased donor pancreas, breaking it down, and extracting the islet cells that make insulin. The cells are then injected through a catheter into the recipient and they generally lodge in the liver. The recipient still needs to take immunosuppressant to avoid rejection, but no surgery is required. Most people need two or three such injections, and many are not completely insulin-free (El-Agroudy *et al.,* 2007). Statistics from the International Pancreas Transplant Registry (IPTR) show the distribution among the procedures: simultaneous Kidney/Pancreas transplant (SKP) is followed by number performed by Pancreas after Kidney (PAK) transplants and finally, by Pancreas Transplant Alone (PTA) (Table 4) (IPTR, 2002).

Table 4: Distribution among Kidney / pancreas procedures

Types of transplant procedure	Number	Percentages
Pancreas transplants alone	777	6
Pancreas after kidney transplants	1,816	14
Simultaneous kidney/ pancreas transplants	10,412	78
Pancreas and another organ or type unknown	325	2
Total pancreas transplants	13,330	100

Source: IPTR (2002)

Pancreas Transplantation: A pancreas transplant is an organ transplant that involves implanting a healthy pancreas (one that can produce insulin) into a person who usually has diabetes. Because the pancreas is a vital organ, performing functions necessary in the digestion process, the recipient's native pancreas is left in place, and the donated pancreas is attached in a different location (Larsen, 2004). In the event of rejection of the new pancreas which would quickly cause life-threatening diabetes, the recipient could not survive without the native pancreas still in place. The healthy pancreas comes from a donor who has just died or it may be a partial pancreas from a living donor

(Fishman and Rubin, 1998). At present, pancreas transplants are usually performed in persons with insulin-dependent diabetes, who can develop severe complications. Patients with pancreatic cancer are not eligible for valuable pancreatic transplantations, since the condition has a very high mortality rate and the disease, being highly malignant, could and probably would soon return. There are three main types of pancreas transplantation according to Kelly *et al.* (1967).

i. Pancreas transplant: (alone) is for the patient with type 1 diabetes who usually has severe, frequent hypoglycemia, but adequate kidney function.

ii. Simultaneous pancreas-kidney transplant (**SPK**): when the pancreas and kidney are transplanted simultaneously from the same deceased donor.

iii. Pancreas-after-kidney transplant (**PAK**): when a cadaveric, or deceased, donor pancreas transplant is performed after a previous, and different, living or deceased donor kidney transplant.

Indications: In most cases, pancreas transplantation is performed on individuals with type 1 diabetes with end-stage renal disease. The majority of pancreas transplantations (>90%) are simultaneous pancreas-kidney transplantation (Gruesner and Sutherland, 2005). It may also be performed as part of kidney-pancreas transplantation. Standard practice is to replace the donor's blood in the pancreatic tissue with an ice-cold organ storage solution, such as UW (Viaspan) until the allograft pancreatic tissue is implanted (Larsen, 2004).

Prognosis: The prognosis after pancreas transplantation is very good. Over the recent years, long-term success has improved and risks have decreased. One year after transplantation more than 95% of all patients are still alive and 80 – 85% of all pancreases are still functional. After transplantation patients need lifelong immunosuppression. Immunosuppression increases the risk for a number of different kinds of infection and cancer (Fishman and Rubin, 1998).

Implications of Transplantation and Solutions

i. Reduction in immune system efficiency: Organ transplants are followed by medications which suppresses the immune system. This involves an act that reduces the activation or efficacy of the immune system. Some portion of the immune system itself has immune-suppressive effects on other parts of the immune system. An immunosuppression may occur as an adverse reaction to other conditions (MacCauley, 2004).

Deliberately induced immunosuppression (apart from many bacterial virulence factors induced ones) is generally done to prevent the body from rejecting an organ transplant, treating graft-versus-host disease after organ transplant. In the past, radiation therapy was used to decrease the strength of the immune system, but now immunosuppressant drugs are used to inhibit the reaction of the immune system (MacCauley, 2004). The immune system efficiency is reduced by the same mechanism of immunosuppression. Various immunosuppress-ants work differently according to their target sites. They are as follows: (a) Glucocorticoids **–** in pharmacologic (supraphysiologic) dose glucocorticoids are used to suppress various types of allergic inflammatory and autoimmune disorders. They are also administered as post transplantary immunosuppressant to prevent the acute transplant rejection and graft-versus-host disease. Glucocorticoids function through interaction with the glucocorticoid receptor: up-regulate the expression of anti-inflammatory proteins and down-regulate the expression of proinflammatory proteins. Glucocorticoids are also shown to play a role in the development and homeostasis of T lymphocytes. This has been shown in transgenic mice with either increased or decreased sensitivity of T cell lineage to glucocorticoids (Amstrong, 2002), (b) cystostatics – these inhibit cell division and proliferation of T-cells and b-cells, (c) drugs acting on immunophilins – they include

ciclosporin, tacrolimus and sirolimus. Ciclosporin inhibits lymphokine production and interleukin release, leading to a reduced function of effector T-cells. Tacrolimus is used primarily in liver and kidney transplants and sometimes in lung and heart transplantation. It binds to immunophilins (FKBPIA) followed by the binding of the complex to calcineurin and the inhibition of its phosphate activity (Liu *et al*., 1991). It prevents the cell from transitioning from Go to G1 phase of the cell cycle and (d) other drugs – These include interferons, opioids, TNF binding proteins and mycophenolate. The interferons are used to slow down the progression of multiple sclerosis (Liu *et al.,* 1991). Prolonged usage of opioids may cause immunosuppression of both innate and adaptive immunity. TNF – α (tumor necrosis factor -alpha) binding protein is a monoclonal antibody or circulating receptor such as infliximab that binds to TNF - α, preventing it from inducing the synthesis of IL – I and IL – 6 and the adhesion of lymphocyte – activating molecule. Mycophenolate acid acts as a non – competitive, selective and reversible inhibitor of inosine-5-monophosphate dehydro-genase (IMPDH) (Amstrong, 2002). The down-side is that with such a deactivated immune system, the body is very vulnerable to opportunistic infection, even those usually considered harmless (Amstrong, 2002). Also prolonged use of immunosuppressant increases the risks of cancer. Other side effects are caused by unintended drug interactions with the body. These side effects make immuno-supression difficult for the patient and significantly affect quality of life as immunosuppressant therapy is often life-long. Several severe side effects have been identified in association with oral and intravenous administration of most immunosuppressive drugs. Some of these include: (a) Nervous system – tremor, headache, paresthesia, dizziness, insomnia, seizure, coma, encephalopathy syndrome, confusion and neuropathy, (b) gastrointestinal – loss of appetite, diarrhea, constipation, nausea, vomiting and dyspepsia, (c) cardiovascular – chest pain, hypertension, (d) urogenital – creatinine is increased, urinary tract infection or kidney problems (tacrolimusnephrotoxicity in the case of tacrolimus), (e) metabolic and nutritional – hyperkalemia, hyperglycemia (new onset post- transplant diabetes mellitus), hyperlipidemia, hypophosphatemia, hypo-magnesemia, hypokalemia, edema, haemic and lymphatic – anaemia, leucopenia, (f) respiratory system – dyspnea, increased cough, (g) musculoskeletal – arthralgia and back pain, (h) skin – rashes and pruritus, and (i) miscellaneous - infections, peripheral edema, asthenia, abdominal pain and fever (Shishido *et al.,* 2001; Miwa *et al.,* 2006).

ii. Transplant rejection: Transplant rejection occurs when a transplanted organ or tissue is not accepted by the body of the transplant recipient. This is explained by the concept that the immune system of the recipient attacks the transplanted organ or tissue. This is expected to happen, because the immune system's purpose is to distinguish foreign material within the body and attempt to destroy it, just as it attempts to destroy infecting organisms such as bacteria and viruses. When possible, transplant rejection can be reduced through serotyping to determine the most appropriate donor-recipient match and through the use of immunosuppressant drugs.

iii. Types of rejection

a. Hyper-acute rejection: Hyperacute rejection is a complement-mediated response in recipients with pre-existing antibodies to the donor's (for example, ABO blood type antibodies) (LaTemple and Galili, 1998). Hyperacute rejection occurs within minutes after the transplant and must be immediately removed to prevent a severe systemic inflammatory response and rapid agglutination of the blood occurs (Frohn *et al.,* 1998). This is a particular risk in kidney transplants, and so a prospective cytotoxic cross match is performed prior to kidney transplantation to ensure that antibodies to the donor are not present. Hyperacute rejection is analogous to a blood transfusion reaction as it is a humoral-mediated immune response (Frohn *et al.,* 1998). For other organs, hyperacute rejection is prevented by transplanting only ABO-compatible grafts. Hyperacute rejection is not significant in liver

allografts and cellular transplants because these tissues have remarkable regenerative abilities. Hyperacute rejection is the outcome of xenotransplanted organ in non-immunosuppressed recipients (LaTemple and Galili, 1998).

b. Acute rejection: Acute rejection may begin as early as one week after transplantation (as opposed to hyperacute rejection, which is immediate). The risk of acute rejection is highest in the first three months after transplantation (LaTemple and Galili, 1998). However, acute rejection can also occur months to years after transplantation. A single episode of acute rejection is not a cause for concern if recognized and treated promptly, and rarely leads to organ failure. But recurrent episodes are associated with chronic rejection. Acute rejection occurs to some degree in all transplants (except those between identical twins) unless the immune response is altered through the use of immunosuppressive drugs. It is caused by mismatched HLA, which are present on all cells of the body (Frohn *et al.,* 1998). There are a large number of different alleles of each HLA, so a perfect match between all HLA in the donor tissue and the recipient's body is extremely rare.

c. Chronic rejection: The term "chronic rejection" was initially used to describe a long-term loss of function in transplanted organs, associated with fibrosis of the internal blood vessels of the transplanted tissue (Huang *et al.,* 2001). But this pathology is now termed chronic allograft vasculopathy. The term chronic rejection is reserved for cases of transplant rejection where the rejection is due to a poorly understood chronic inflammatory and immune response against the transplanted tissue (Huang *et al.,* 2001).

Chronic rejection after lung transplantation is the leading cause of long-term morbidity in lung transplant patients. The median survival of lung-transplant patients is approximately 4.7 years — about half that of other major transplanted organ recipients (LaTemple and Galili, 1998). Histopathologically, the condition is known as bronchiolitis obliterans. Clinically, patients present with progressive airflow obstruction often associated with dyspnea and coughing. Ultimately these patients succumb to pulmonary insufficiency or secondary infection (Huang *et al.,* 2001). Bronchiolitis obliterans syndrome (BOS) is used to describe patients with airflow obstruction that cannot be ascribed to any other specific cause.

d. Cellular rejection: Rejection of xenografts in hyperacute and acute vascular rejection is due to the response of the humoral immune system, since the response is elicited by the XNAs (Huang *et al.,* 2001). Cellular rejection is based on cellular immunity, and is mediated by (i) Natural killer cells, which accumulate in and damage the xenograft; and (ii) T-lymphocytes - which are activated by MHC molecules through both direct and indirect xeno-recognition (Candinas and Adams, 2000).

In direct xeno-recognition, antigen presenting cells from the xenograft present peptides to recipient $CD4^+$ T cells via xenogeneic MHC class II molecules, resulting in the production of interleukin 2 (IL-2). Indirect xeno-recognition involves the presentation of antigens from the xenograft by recipient antigen presenting cells to $CD4^+$ T cells. Antigens of phagocytosed graft cells can also be presented by the host's class I MHC molecules to $CD8^+$ T cells (Abbas and Litchman, 2005). The strength of cellular rejection in xenografts remains uncertain; however it is expected to be stronger than in allografts due to differences in peptides among different animals. This leads to more antigens potentially recognized as foreign, thus eliciting a greater indirect xenogenic response (Cooper and Lanza, 2000).

e. Rejection mechanisms: Rejection is an adaptive immune response and is mediated through both T cell mediated and humoral immune (antibodies) mechanisms. The number of mismatched alleles determines the speed and magnitude of the rejection response. Different mechanisms tend to act against different grafts (Table 5).

Figure 8 shows the stages of CD4 T-cell activation and cytokine production with identification of the sites of action of different

immunosuppressive agents. Antigen fragment-major histocompatibility complex (MHC) II molecule complexes are responsible for initiating the activation of CD4 T cells.

Table 5: Different mechanisms that act against different grafts

Organ/tissue	Mechanism
Blood	Antibodies (isohaemagglutinins)
Kidney	Antibodies, cell mediated immunity (CMI)
Heart	Antibodies, CMI
Skin	CMI
Bone marrow	CMI
Cornea	Usually accepted unless vascularised, CMI

Source: Cooper and Lanza (2000)

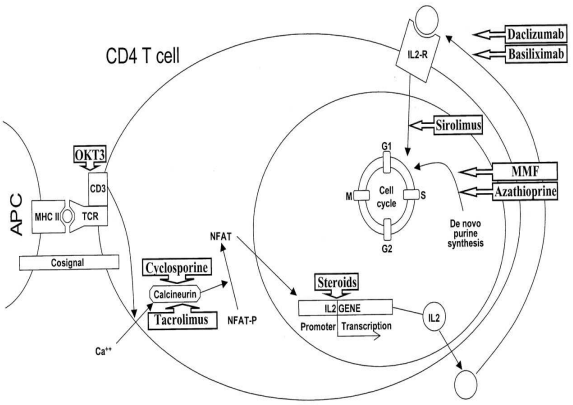

Figure 8: Immunologic response to allografts. Source: Mueller (2004)

These MHC-peptide complexes are recognized by the T-cell recognition complex (TCR), which consists of transmembrane proteins associated with the CD3 molecule (Mueller, 2004). Engagement of the TCR/CD3 complex and CD4 coreceptors in conjunction with a costimulatory signal initiates signal transduction with activation of second messengers. Downstream the cytoplasmic Ca^{2+} concentration increases through an influx of extracellular Ca^{2+}. The Ca^{2+} dependent enzymes, one of which is the calcineurine, are activated. Calcineurine removes phosphates from the nuclear factors (NFAT-P) allowing them to enter the nucleus. These nuclear factors specifically bind to an interleukin-2 (IL-2) promoter gene facilitating IL-2 gene transcription and interaction of IL-2 with its receptor (IL-2R) on the cell membrane (Mueller, 2004).

iv. Chimera: A chimera is a single organism (usually an animal) that is composed of two or more different populations of genetically distinct cells that originated from different zygotes involved in sexual reproduction (Ralston and Rossant, 2005). If the different cells have emerged from the same zygote, the organism is called a mosaic. Chimeras are formed from four parent cells (two fertilized eggs or early embryos fused together). Each population of cells keeps its own character and the resulting organism is a mixture of tissues. Chimeras are typically seen in animals; there are some reports on human and plant chimerism.

This condition is either inherited, or it is acquired through the infusion of allogeneic haematopoietic cells during transplantation or transfusion. In non-identical twins, chimerism occurs by means of blood-vessel anastomoses. The likelihood of offspring being a chimera is increased if it is created via in vitro fertilization. Chimeras can often breed, but the fertility and type of offspring depends on which cell line gave rise to the ovaries or testes; varying degrees of intersexuality may result if one set of cells is genetically female and another genetically male (Ralston and Rossant, 2005)

a. Tetragametic-chimerism: Tetragametic-chimerism is a form of congenital chimerism which occurs through the fertilization of two separate ova by two sperm, followed by the fusion of the two at the blastocyst or zygote stages (Tunaka *et al.,* 2001). This results in the development of an organism with intermingled cell lines. Put another way, the chimera is formed from the merging of two non-identical twins (although a similar merging presumably occurs with identical twins, but as their DNA is almost identical the presence would not be immediately detectable) in a very early (zygote or blastocyst) phase. As such, they can be male, female, or hermaphroditic (Yu *et al.,* 2002).

Affected person may be identified by the finding of two populations of red cells or, if the zygotes are of opposite sex, ambiguous genitalia and hermaphroditism alone or in combination such persons sometimes also have patchy skin, hair, or eye pigmentation (Yu *et al.,* 2002).

b. Micro-chimerism: Micro-chimerism is the presence of a small number of cells that are genetically distinct from those of the host individual. Apparently, this phenomenon is related to certain types of autoimmune disease however, the mechanisms responsible for this relationship are unclear (Yu *et al.,* 2002).

c. Germline-chimerism: Germline-chimerism occurs when the germ cells (for example, sperm and egg cells) of an organism are not genetically identical to its own. It has recently been discovered that marmosets can carry the reproductive cells of their (fraternal) twin siblings, because of placental fusion during development. (Marmosets almost always give birth to fraternal twins) (Tunaka *et al.,* 2001; Yu *et al.,* 2002).

v. Xenozoonosis: Xenozoonosis, also known as zoonosis or xenosis, is the transmission of infectious agents between species via a xenograft. Animal to human infection is normally rare, but has occurred in the past. An example of such is the avian influenza, when influenza A virus was passed from birds to humans (FDA, 2006). Xenotransplantation may increase the chance of disease transmission for 3 reasons: (i) Implantation breaches the physical barrier that normally helps to prevent disease transmission, (ii) The recipient of the transplant will be severely immunosuppressed; and (iii) Human complement regulators (CD46, CD55, and CD59) expressed in transgenic pigs have been shown to serve as virus receptors, and may also help to protect viruses from attack by the complement system (Takaeuchi and Weiss, 2000).

Examples of viruses carried by pigs include porcine herpesvirus, rotavirus, parvovirus, and circovirus. Porcine herpesviruses and rotaviruses can be eliminated from the donor pool by screening; however others (such as parvovirus and circovirus) may contaminate food and footwear then re-infect the herd. Thus, pigs to be used as organ donors will have to be housed under strict regulations and screened regularly for microbes and pathogens. Unknown viruses, as well as those which aren't harmful in the animal, may also pose risks (Takeuchi and Weiss 2000). Of particular concern are PERVS (porcine endogenous retroviruses), vertically transmitted microbes which are imbedded in swine genomes. The risks with xenosis are twofold as not only could the individual become infected, but a novel infection could initiate an epidemic in the human population.

Solution to rejection

i. Immunosuppressant: Immunosuppressive drugs or agents are those drugs/substances that inhibit or prevent activity of the immune system. They are usually used in immunosuppressive therapy in order to prevent the rejection of transplanted organs and tissues such as bone marrow, heart, kidney and liver (Kino *et al.,* 1987). They can also be used to treat auto-immune diseases or diseases that are most likely of auto-immune origin for example, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, system lupus erythematosis, focal segmental glomerulosclerosis, Crohn's disease, Belicet's disease, pemphigus and ulcerative colitis (Kornbluth and Sachar, 2004; Pravda, 2005; Summers *et al.,* 2005). In addition, they can be used to treat some other non-autoimmune inflammatory diseases such as long term allergic asthma control (Gillett and Chan, 2000).

The drugs are not without side effects and risks. The majority of them act non-selectively and as such, the immune system is less able to resist infections and the spread of malignant cells. There are also other side effects such as hypertension, dyslipidemia, hyper-glycemia, peptic ulcers, liver and kidney injury. The immunosuppressive drugs also interact with other medicines and by so doing, affect their metabolism and action. Actual or suspected immunosuppressive agents can be evaluated in terms of their effects on lymphocytes subpopulations in tissue during immuno-histochemistry (Table 6) (Gillet and Chan, 2000).

Table 6: Classification of immunosuppressive drugs

Types of Immunosuppressant	Effects	Drugs	References
Glucocorticoids	immunosuppressive mechanism, Anti inflammatory effect	Mycophenolate	Spencer *et al*. (1997) Gummert (1999)
Cytostatics	Alkylating agent And Antimetabolites	Methotrexate, Cytotoxic antibiotics Azathioprin and mercaptopurine	Gillet and Chan (2000)
Antibodies	Polyclonal antibodies Monoclonal antibodies	T-cell receptor-directed antibodies IL-2 receptor directed antibodies	Gillet and Chan (2000)
Drug acting on immunophilins	Anti inflammatory effect	Cyclosporine , Tacrolimus, Sirolimus	Gummert (1999)
Other drugs	Interferons, Opioids TNF binding proteins	Mycophenolate	Spencer *et al*. (1997) Gillet and Chan (2000)

ii. Overcoming rejection

a. Cellular rejection: A proposed strategy to avoid cellular rejection is to induce donor non-responsiveness using haematopoietic-chimerism. Donor stem cells are introduced into the bone marrow of the recipient, where they coexist with the recipient's stem cells. The bone marrow stem cells give rise to cells of all haematopoietic lineages, through the process of haematopoiesis.Lymphoid progenitor cells are created by this process and move to the thymus where negative selection eliminates T cells found to be reactive to self. The existence of donor stem cells in the recipient's bone marrow causes donor reactive T cells to be considered self and undergo apoptosis (LaTemple and Galili, 1998).

b. Hyperacute rejection: Since hyperacute rejection presents such a barrier to the success of xenografts several strategies to overcome it are under investigation:

Interruption of the complement cascade: The recipient's complement cascade can be inhibited through the use of cobra venom factor (which depletes C3), soluble complement receptor type 1, anti-C5 antibodies, or C1 inhibitor (C1-INH). Disadvantages of this approach include the toxicity of cobra venom factor, and most importantly these treatments would deprive the individual of a functional complement system (Huang *et al.,* 2001).

Transgeneic organs (Genetically engineered pigs): 1,3 galactosyltransferase gene knockouts - These pigs don't contain the gene which codes for the enzyme responsible for expression of the immunogeneic gal-α-1,3Gal moiety (the α-Gal epitope) (LaTemple and Galili, 1998).

Increased expression of H-transferase (α 1,2fucosyltransferase): an enzyme that competes with galactosyltransferase. Experiments have shown this reduces α-Gal expression by 70% (Sharma *et al.,* 1996).

Expression of human complement regulators (CD55, CD46 and CD59): to inhibit the complement cascade (Huang *et al.,* 2001).

Plasmaphoresis: on humans to remove 1,3galactosyltransferase, reduces the risk of activation of effector cells such as CTL (CD8 T cells), complement pathway activation and delayed type hypersensitivity (DTH).

c. Acute vascular rejection: Due to its complexity, wide arrays of approaches are necessary to prevent acute vascular rejection, following the use of immunosuppressive drugs. These include: (i) Administering a synthetic thrombin inhibitor to modulate thrombogenesis, (ii) depletion of anti-galactose antibodies (XNAs) by techniques such as immune-adsorption, to prevent endothelial cell activation, and (iii) inhibiting activation of macrophages (stimulated by $CD4^+$ T cells) and NK cells (stimulated by the release of Il-2). Thus, the role of MHC molecules and T cell responses in activation would have to be reassessed for each species combo (Candinas and Adams, 2000).

Conclusion: Transplantation has risen from research surgery to life-saving treatment. As the rising success rate of transplants and modern immunosuppression make transplants more common, the need for more organs has become critical. Advances in living-related donor transplants have made that increasingly more common. Additionally, there is substantive research into xenotransplantation, or transgenic organs; although these forms of transplant are not yet being used in humans, clinical trials involving the use of specific cell types have been conducted with promising results, such as using porcine islets of Langerhans to treat type 1 diabetes. However, there are still many problems that would need to be solved before they would be feasible options in patients requiring transplants. Examples include, conducting match tests, age consideration and patient's position in the waitlist.

The operative stage of organ transplantation is affected by some complications which may affect the patient's later health improvement. In lung transplantation, as with any surgical procedure, there are risks of bleeding and infection (Arcasoy and Kotloff, 1999). The newly transplanted lung itself may fail to properly heal and function. Because a large portion of the patient's body has been exposed to the outside air, sepsis is a possibility, so antibiotics will be given to try to prevent that. Other complications include Post-transplant lympho-proliferative disorder, a form of lymphoma due to the immune suppressants, and gastrointestinal inflammation and ulceration of the stomach and esophagus (Kornbluth and Sachar, 2004). Bronchiolitis obliterans syndrome (BOS) is used to describe patients with airflow obstruction that cannot be ascribed to any other specific cause. This diagnosis is confirmed by a persistent drop (three or more weeks) in forced expiratory volume (FEV_1) of at least 20%. Unfortunately, BOS is common in patients after lung transplant and presents in at least 50% of patients by 5 years and over 80% by ten years post-transplant (Arcasoy and Kotloff, 1999).

The progression of disease is unpredictable and heterogeneous. In some cases, patients may develop a sudden drop in lung function which then stabilizes for years. In other instances, the progression is rapid leading to death within a few months. Although the onset of chronic lung rejection is unknown, risk factors include prior acute cellular rejection episodes, gastro-esophageal reflux disease, infection (viral and bacterial), age of transplant recipient, HLA mismatching, lymphocytic bronchiolitis and graft dysfunction (e.g. airway ischemia) (Arcasoy and Kotloff, 1999).

Living donors of liver transplants are faced with risks and/or complications after the surgery. Blood clots and biliary problems have the possibility of arising in the donor post-op, but these issues are remedied fairly easily. Even though the procedure is very safe, all potential donors should know there is a 0.5 to 1.0 percent chance of death and death is a risk that a living donor must be willing to accept prior to the surgery. The LDLT donor's immune system does diminish as a result of the liver regenerating, so certain foods which would normally cause an upset stomach could cause serious illness (Chin and Hazzan, 2007). Other risks of donating a liver include bleeding, infection, painful incision, possibility of blood clots and a prolonged recovery (Chin and Hazzan, 2007). The vast majority of donors enjoy complete and full recovery within 2 – 3 months.

Kidney transplantation is associated with risks like transplant rejection (hyperacute, acute or chronic), Infections and sepsis due to the immunosuppressant drugs that are required

to decrease risk of rejection (Ibrahim *et al.,* 2009). Post-transplant lympho-proliferative disorder (a form of lymphoma due to the immune suppressants) and Imbalances in electrolytes including calcium and phosphate which can lead to bone problems amongst other things. Other side effects of medications including gastrointestinal inflammation and ulceration of the stomach and esophagus, hirsutism (excessive hair growth in a male-pattern distribution), hair loss, obesity, acne, diabetes mellitus type 2, hypercholesterolemia, and others (Chin and Hazzan, 2007; Ibrahim *et al.,* 2009).

Some complications noticed immediately after pancreas transplantation includes thrombosis, pancreatitis, infection, bleeding and rejection. Rejection may occur immediately or at any time during the patient's life. Organ rejection is a serious condition and ought to be treated immediately. In order to prevent it, patients must take a regimen of immunosuppressive drugs (Spencer *et al.,* 1997; Fishman and Rubin, 1998).

A patient's age and health condition before transplantation affect the risk of complications. Different transplant centers have different success at managing complications and therefore, complication rates are different from center to center. The average lifetime for a donated kidney is ten to fifteen years. When a transplant fails, a patient may opt for a second transplant, and may have to return to dialysis for some intermediary time (Ibrahim *et al.,* 2009). However, the process of organ transplantation like allo-transplantation and xeno-transplantation is always accompanied with rejection. The quest to reduce menace of rejection has led to immunosuppressive mechanism aided by the production of immunosuppressive drugs like azathioprine and tacrolimus. The process of immunosuppression is not without side-effects and reduction of immune system efficacy and strict restrictions. There are no adequate and well-controlled studies in pregnant women. Limited immunologic and other abnormalities have occurred in a few infants born of renal allograft recipients on azathioprine. In a detailed case report, documented lymphopenia, diminished IgG and IgM levels, CMV infection, and a decreased thymic shadow were noted in an infant born to a mother receiving 150 mg azathioprine and 30 mg prednisone daily throughout pregnancy (Frohn *et al.,* 1998).

Recently, researchers have been looking into means of reducing the general burden of immunosuppression. Common approaches include avoidance of steroids, reduced exposure to calcineurin inhibitors, and other means of weaning drugs based on patient outcome and function. While short-term outcomes appear promising, long-term outcomes are still unknown, and in general, reduced immunosuppression increases the risk of rejection and decreases the risk of infection. Recent technological advancements have led to genetic expression testing in the form of a blood test. These tests, such as Allo-Map Molecular Expression Testing have a high negative predictive value help manage the ACR rejection in transplant patients. These genetic expression tests are specific to the transplanted organ type (Cooper and Lanza*,* 2000).

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