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Review of Natural History, Benefits and Risk Factors Pediatric Liver Transplantation

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Abstract

Liver or hepatic transplantation (LT) is the replacement of a diseased liver with part or whole healthy liver from another person (allograft). Human liver transplants were first performed by Thomas Starzl in the United States and Roy Calne in Cambridge, England in 1963 and 1967, respectively. Liver transplantation is a viable treatment option for end-stage liver disease and acute liver failure. Pediatric patients account for about 12.5% of liver transplant recipients. 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. Cirrhosis, or liver injury, is a common reason why adults need liver transplants and children with bile duct disease issues are often the candidates. Survival statistics depend greatly on the age of donor, age of recipient, skill of the transplant center, compliance of the recipient, whether the organ came from a living or cadaveric donor and overall health of the recipient. Survival rates improve almost yearly, due to improved techniques and medications.

Key Words: Liver transplantation; Hepatic transplantation; Pediatric transplantation; Survival rates.

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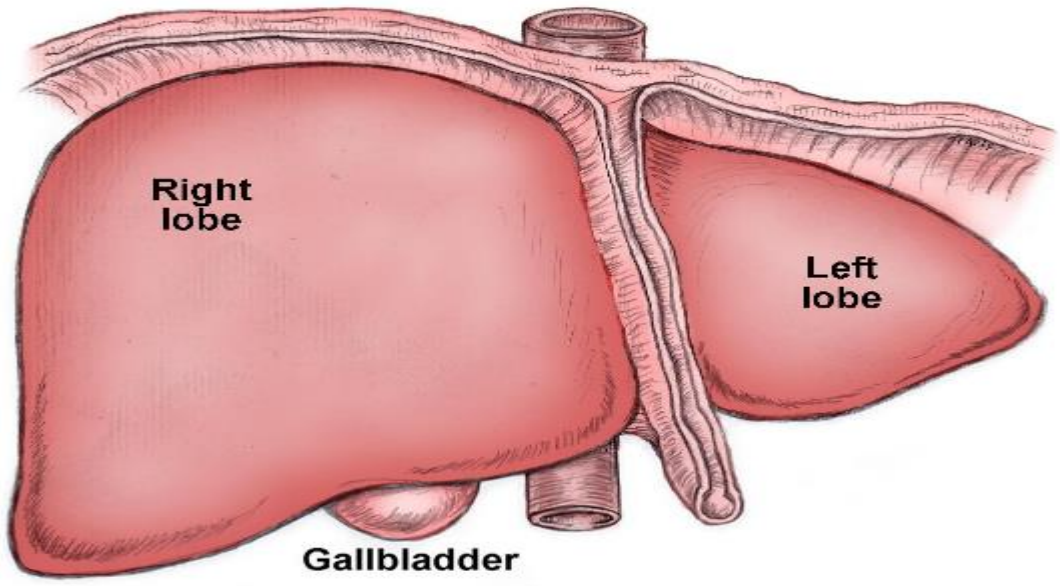
1-INTRODUCTION

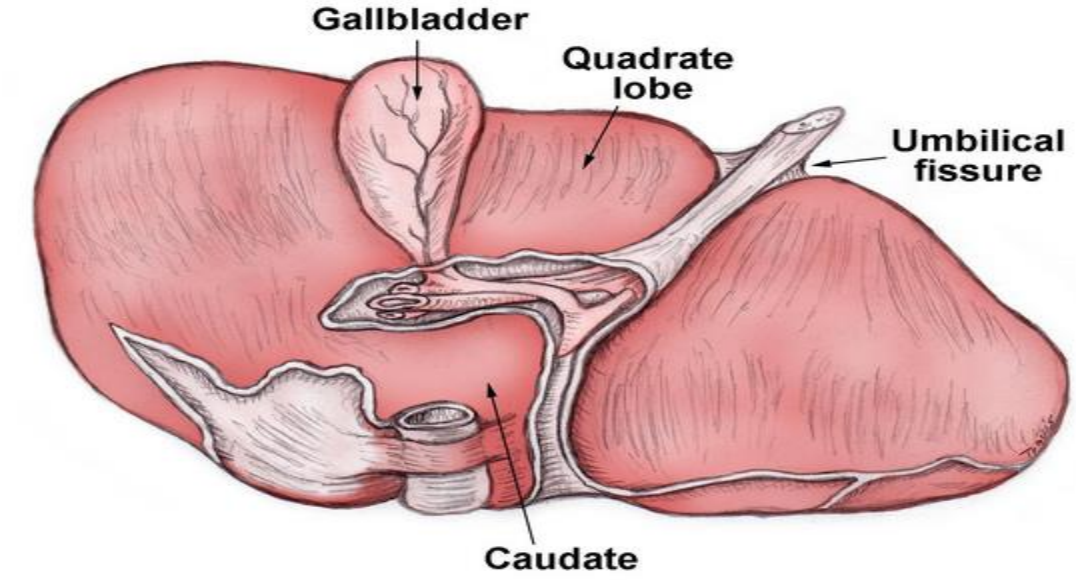
1-1. Liver anatomy

The liver is located in the right upper portion of the abdominal cavity, just beneath the diaphragm, and is protected by the rib cage. It sits on top of the stomach, right kidney, and intestines. It is supplied with blood by the portal vein, which drains the splenic, intestinal, and colonic areas and is a rich source of nutrients and substances absorbed from the gut. It is also supplied by the hepatic artery (a branch of the celiac artery), which provides most of the liver's oxygenated blood. The liver consists of 2 main lobes, which are made up of thousands of lobules. These lobules are connected to small ducts that connect with larger ducts, ultimately to form the common hepatic duct. The common hepatic duct transports the bile produced by the liver cells to the gallbladder and duodenum (1).

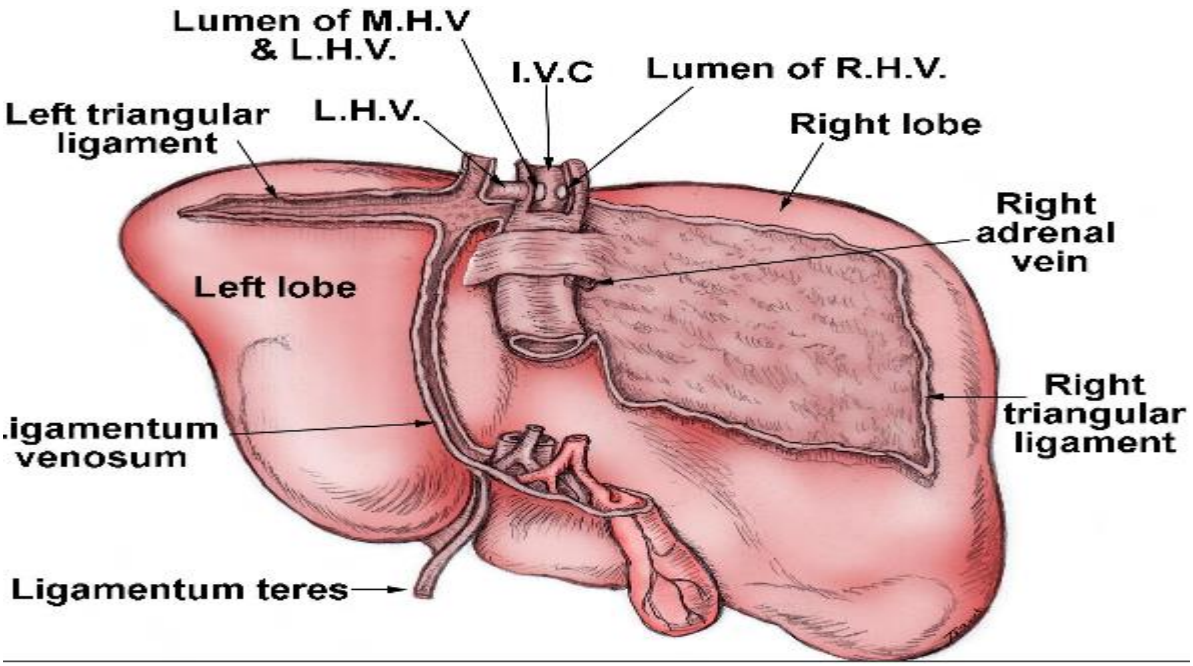
The liver has a wide range of functions, including detoxification of various metabolites, protein synthesis, and the production of biochemicals necessary for digestion (2, 3). The liver's highly specialized tissue consisting of mostly hepatocytes regulates a wide variety of high-volume biochemical reactions, including the synthesis and breakdown of small and complex molecules, many of which are necessary for normal vital functions. There is currently no way to compensate for the absence of liver function in the long term, although liver dialysis techniques can be used in the short term. Liver transplantation is the only option for complete liver failure (See the images below) (3-5).



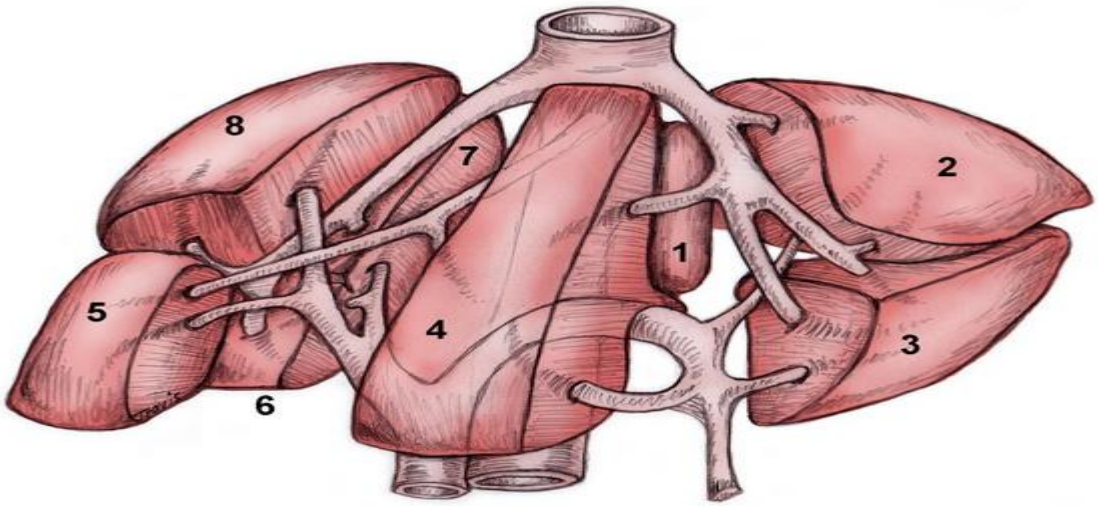
Anterior view of the liver. A large right and a smaller left lobe make up the liver. The gallbladder can sometimes be seen lying underneath the liver. The round ligament (ligamentum teres) of liver (obliterated umbilical vein) separates the right lobe from the left lobe of the liver. The diaphragm lies superior to the 2 lobes of the liver.



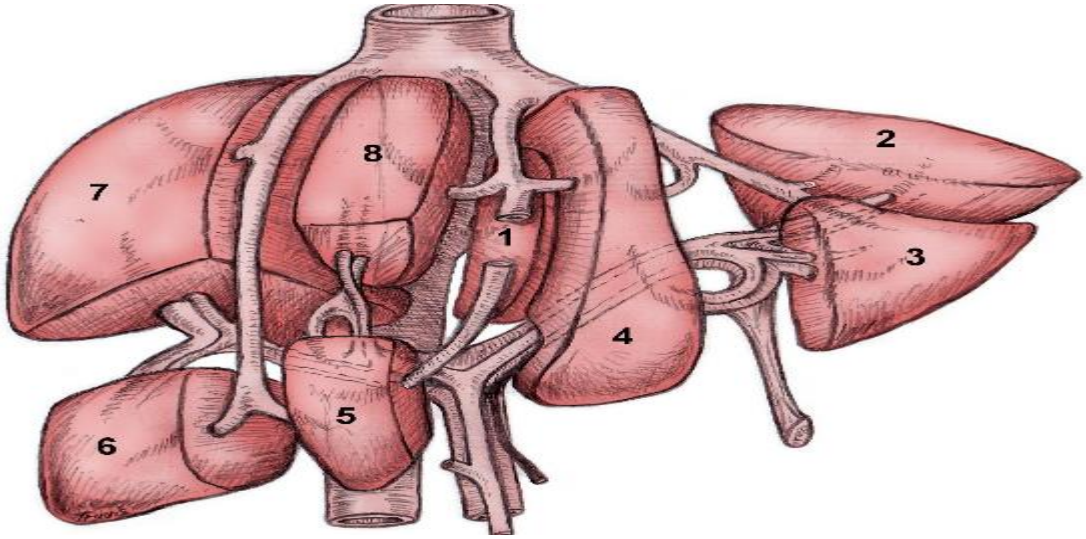
Visceral surface of liver. The portion of the right lobe located anterior to the fissure is called the quadrate lobe.



Posterior side view of the liver. The inferior vena cava (IVC) is seen in the deep groove. It is protected on the right side by a layer of fibrous tissue. Various ligaments serve to attach the liver to the nearby anatomical regions such as the diaphragm. (RHV = right hepatic vein, LHV = left hepatic vein, MHV = middle hepatic vein).



Liver segments according to functional division, seen in the normal anatomical position within the abdomen.



Liver segments according to functional division, seen outside the normal anatomical position.

1-1. Liver regeneration

The liver is the only human internal organ capable of natural regeneration of lost tissue; as little as 25% of a liver can regenerate into a whole liver. This is, however, not true regeneration but rather compensatory growth in mammals. The lobes that are removed do not regrow and the growth of the liver is a restoration of function, not original form. This contrasts with true regeneration where both original function and form are restored. In some other species, such as fish, the liver undergoes true regeneration by restoring both shape and size of the organ. In liver, large areas of the tissues are formed but for the formation of new cells there must be sufficient amount of material so the circulation of the blood becomes more active (6-9).

This is predominantly due to the hepatocytes re-entering the cell cycle. That is, the hepatocytes go from the quiescent G0 phase to the G1 phase and undergo mitosis. This process is activated by the p75 receptors. There is also some evidence of bipotential stem cells, called hepatic oval cells or ovalocytes (not to be confused with oval red blood cells of ovalocytosis), which are thought to reside in the canals of Hering. These cells can differentiate into either hepatocytes or cholangiocytes. Cholangiocytes are the epithelial lining cells of the bile ducts. They are cuboidal epithelium in the small interlobular bile ducts, but become columnar and mucus secreting in larger bile ducts approaching the porta hepatis and the extrahepatic ducts (10, 11).

1-2. Liver tranplatation

Liver transplant is a last resort treatment measure that can help save patient's life when the liver no longer works. Also called a liver or hepatic transplantation, the treatment involves the surgical removal of the entire organ. It is then replaced with a healthy donor liver. Having a healthy liver is essential to longevity because the liver is responsible for nutrient distribution and toxin removal in the body (1, 2).

1-3. Liver transplant procedures

A liver transplant may involve the whole liver, a reduced liver, or a liver segment. Most transplants involve the whole organ but segmental transplants have been performed with increasing frequency in recent years. This would allow two liver recipients to be transplanted from one cadaveric donor or to allow for living donor liver donation. A reduced liver transplant may result if the donor liver is too large for the recipient (1, 3).

1-4. Introduction to pediatric liver transplantation

Liver transplantation is a treatment, used in appropriately selected patients, for acute and chronic liver failure due to any cause. It is not indicated if an acceptable alternative is available or if contraindications are present (eg, some cases of malignancy, terminal conditions, poor expected quality of outcome).

Pediatric patients account for about 12.5% of liver transplant recipients. When a pediatric patient is likely to require a liver transplant, the medical management is generally divided into pretransplant and posttransplant periods, with the posttransplant period further separated into early and late time frames.

Medical treatment, surgery, and postsurgical care can be broken into 4 basic steps:

1. Candidate evaluation;
2. Waiting period;
3. Surgery;
4. Postsurgical care (1).

2- MATERIALS AND METHODS

2-1. Literature Search

The following databases were searched for relevant papers and reports: MEDLINE, CINAHL, Embase, PsychINFO, Cochrane Collection, Google scholar, Pubmed and ISI Web of Knowledge. Key references from extracted papers were also hand-searched. These searches focused upon papers published between 1950 and 2015.

2-2. Search Terms

To evaluate the texts and websites, the singular or combination forms of the following keywords were used to search for the relevant literature: "Liver transplantation", "Risk factors", "Pediatric liver transplantation", "Survival", "Benefits" and "Mortality".

3- RESULTS

3-1. History

The first human liver transplant was performed in 1963 by a surgical team led by Dr. Thomas Starzl of Denver, Colorado, United States. Dr. Starzl performed several additional transplants over the next few years before the first short-term success was achieved in 1967 with the first one-year survival post transplantation. Despite the development of viable surgical techniques, liver transplantation remained experimental through the 1970s, with one year patient survival in the vicinity of 25%. The introduction of cyclosporin by Sir Roy Calne, Professor of Surgery Cambridge, markedly improved patient outcomes, and the 1980s saw recognition of liver transplantation as a standard clinical treatment for both adult and pediatric patients with appropriate indications. Liver transplantation is now performed at over one hundred centers in the US, as well as numerous centeres in Europe and elsewhere. One-year patient survival is 80–85%, and outcomes continue to improve, although liver transplantation remains a formidable procedure with frequent complications. The supply of liver allografts from non-living donors is far short of the number of potential recipients, a reality that has spurred the development of living donor liver transplantation. The first altruistic living liver donation in Britain was performed in December 2012 at St James University Hospital Leeds (12-14).

3-1. 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. Uncontrolled metastatic cancer outside liver, active drug or alcohol abuse and active septic infections are absolute contraindications. While HIV infection was once considered an absolute contraindication, this has been changing recently. Advanced age and serious heart, lung, or other disease may also prevent transplantation (relative contraindications). Most liver transplants are performed for chronic liver diseases that lead to irreversible scarring of the liver, or cirrhosis of the liver. Some centers use the Milan criteria to select patients with liver cancers for liver transplantation (15-17).

3-3. Indications for pediatric liver transplantation

About 50% of the pediatric patients who require a liver transplant have biliary atresia. Other disease states that progress to end-stage liver disease among pediatric patients and require liver transplantation include metabolic disorders and progressive intrahepatic cholestasis.

Examples of metabolic derangements include Wilson disease, alpha 1-antitrypsin deficiency, tyrosinemia, and hemochromatosis. Other metabolic disease states leading to hepatic dysfunction include the following (18) :

- Crigler-Najjar syndrome;
- Glycogenosis;
- Hyperoxaluria;
- Metabolic respiratory chain deficiencies;
- Familial hypercholesterolemia;
- Methylmalonyl aciduria.

3-2. Techniques

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.

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. 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) (19).

The donor's blood in the liver will be replaced by an ice-cold organ storage solution, such as UW (Viaspan) or HTK until the allograft liver is implanted. Implantation involves anastomoses (connections) 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. 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. The large majority of liver transplants use the entire liver from a non-living donor 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. Living donor liver transplantation for pediatric recipients involves removal of approximately 20% of the liver (Couinaud segments 2 and 3).

Further advance in liver transplant involves only resection of the lobe of the liver involved in tumors and the tumor-free lobe remains within the recipient. This speeds up the recovery and the patient stay in the hospital quickly shortens to within 5–7 days. Many major medical centers are now using radiofrequency ablation of the liver tumor as a bridge while awaiting for liver transplantation. This technique has not been used universally and further investigation is warranted (20, 21).

3-4. Immunosuppressive management

Like most other allografts, a liver transplant will be rejected by the recipient unless immunosuppressive drugs are used. The immunosuppressive regimens for all solid organ transplants are fairly similar, and a variety of agents are now available. Most liver transplant recipients receive corticosteroids plus a calcineurin inhibitor such as tacrolimus or cyclosporin plus a purine antagonist such as mycophenolate mofetil. Clinical outcome is better with tacrolimus than with cyclosporin during the first year of liver transplantation. If the patient has a co-morbidity such as active hepatitis B, high doses of hepatitis B immunoglubins are administrated in liver transplant patients (22, 23).

Liver transplantation is unique in that the risk of chronic rejection also decreases over time, although the great majority of recipients need to take immunosuppressive medication for the rest of their lives. It is possible to be slowly taken off anti rejection medication but only in certain cases. It is theorized that the liver may play a yet-unknown role in the maturation of certain cells pertaining to the immune system (24).

3-3. Graft rejection

After a liver transplantation, there are three types of graft rejection that may occur. They include hyperacute rejection, acute rejection and chronic rejection. Hyperacute rejection is caused by preformed anti-donor antibodies. It is characterized by the binding of these antibodies to antigens on vascular endothelial cells. Complement activation is involved and the effect is usually profound. Hyperacute rejection happens within minutes to hours after the transplant procedure. Unlike hyperacute rejection, which is B cell mediated, acute rejection is mediated by T cells. It involves direct cytotoxicity and cytokine mediated pathways. Acute rejection is the most common and the primary target of immunosuppressive agents. Acute rejection is usually seen within days or weeks of the transplant. Chronic rejection is the presence of any sign and symptom of rejection after 1 year. The cause of chronic rejection is still unknown but an acute rejection is a strong predictor of chronic rejections. Liver rejection may happen anytime after the transplant. Lab findings of a liver rejection include abnormal AST, ALT, GGT and liver function values such as prothrombin time, ammonia and bilirubin levels, albumin concentration, and blood glucose. Physical findings include encephalopathy, jaundice, bruising and bleeding tendency. Other nonspecific presentations are malaise, anorexia, muscle ache, low fever, slight increase in white blood count and graft-site tenderness (25).

3-4. Survival statistics

Prognosis is quite good, but those with certain illnesses may differ. There is no exact model to predict survival rates; 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. Others include technical flaws during surgery such as revascularization that may lead to a nonfunctioning graft (26, 27).

In the last decades, orthotopic liver transplantation has been associated with 1-year survival rates of 80-90% (Table.1) (28).

Table1: Graft and Patient Survival Rates for Pediatric Liver Transplantation

Donor Type	Graft Survival			Patient Survival		
	6 mo, %	1 y, %	3 y, %	6 mo, %	1 y, %	3 y, %
Split-liver, left lateral segment	72	68	64	79	78	75
Living donor, left lateral segment	76	74	71	86	86	84
Whole organ	79	77	73	83	83	81

3-5. 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 (29) the remarkable regenerative capacities of the human liver and (30) 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. 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. 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 (31).

3-6. 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, although some centeres now perform blood group incompatible transplants with special immuno suppression protocols;
- 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, 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 (32).

3-7. Complications

Living donor surgery is done at a major center. Very few individuals require any blood transfusions during or after surgery. All potential donors should know there is a 0.5 to 1.0 percent chance of death. Other risks of donating a liver include bleeding, infection, painful incision, possibility of blood clots and a prolonged recovery. The vast majority of donors enjoy complete and full recovery within 2–3 months (33).

3-8. Pediatric transplantation

In children, living liver donor transplantations have become very accepted. The accessibility of adult parents who want to donate a piece of the liver for their children/infants has reduced the number of children who would have otherwise died waiting for a transplant. Having a parent as a donor also has made it a lot easier for children - because both patients are in the same hospital and can help boost each other's morale (34).

3-9. Benefits of living liver donor transplantation

There are several advantages of living liver donor transplantation over cadaveric donor transplantation, including:

- Transplant can be done on an elective basis because the donor is readily available
- There are fewer possibilities for complications and death than there would be while waiting for a cadaveric organ donor
- Because of donor shortages, UNOS has placed limits on cadaveric organ allocation to foreigners who seek medical help in the USA. With the availability of living donor transplantation, this will now allow foreigners a new opportunity to seek medical care in the USA.
- Living donor transplantation is a multidisciplinary approach. All living liver donors undergo medical evaluation. Every hospital which performs transplants has dedicated nurses that provide specific information about the procedure and answer questions that families may have. During the evaluation process, confidentiality is assured on the potential donor. Every effort is made to ensure that organ donation is not made by coercion from other family members. The transplant team provides both the donor and family thorough counseling and support which continues until full recovery is made.
- All donors are assessed medically to ensure that they can undergo the surgery. Blood type of the donor and recipient must be compatible but not always identical. Other things assessed prior to surgery include the anatomy of the donor liver. However, even with mild variations in blood vessels and bile duct, surgeons today are able to perform transplantation without problems. The most important criterion for a living liver donor is to be in excellent health (6, 26, 34).

4- DISCUSSION

3-1. Pre-transplantation care

Pre-transplantation care needs to take into consideration potentially prolonged waiting periods and to project far in advance when transplantation might be required. By initiating the pretransplant workup early, one can work toward maximizing the nutritional status.

Nutritional status impacts both pretransplant and posttransplant outcomes, especially in the pediatric population, because of an increased incidence of cholestatic liver diseases. Cholestatic liver diseases lead to fat malabsorption, which causes a deficiency of calories as well as fat-soluble vitamins (35). Pediatric patients can greatly benefit from caloric assessments and supplemental tube feedings as indicated. Furthermore, parenteral feedings are sometimes warranted in the most nutritionally deprived patients with end-stage liver disease. The optimization of nutritional status in pediatric patients has translated into improved survival after transplantation, fewer infections, and a reduction of surgical complications (36).

3-2. Neonatal liver transplantation

Liver transplantation has been successfully extended to neonates (37). Acute liver failure from hemochromatosis, leading to a histologic diagnosis of giant-cell hepatitis, is the primary indication for liver transplantation in the neonatal population. Because of size discrepancies between the recipient and the donor pool, partial liver grafts are usually used for this population of patients (38). Although neonates appear to be more immunotolerant to transplanted organs, their immature immune systems

combined with immunosuppression increases the risk for infectious complications. Among neonatal transplant recipients, vascular thrombosis is the major complication, dramatically reducing survival.

3-3. Candidate evaluation

Once a liver transplant is considered, a team of specially trained staff usually evaluates the patient to establish whether the patient would be a good candidate for a liver transplant. The team includes the following specialists:

- Hepatologists (medical liver specialists);
- Transplant surgeons;
- Social workers;
- Psychologists, psychiatrists, or both;
- Nurses;
- Transplant coordinators.

When a pediatric patient is likely to require a liver transplantation, the medical management is generally divided into pretransplant and posttransplant periods, with the posttransplant follow-up further separated into early and late periods.

3-4. Waiting period

Once a pediatric patient is found to be a suitable candidate for a liver transplant, the patient's name is placed on a waiting list for an organ. Unfortunately, many more potential recipients are on the waiting list than there are organs available each year. At most transplantation centers, the decision to be placed on a waiting list is determined by a multidisciplinary committee. Although not pediatric specific, an observational multicenter study reported that the decision process primarily involves reviewing possible reasons for patient exclusion, which may include patients who are not sick enough, too sick, or too old; other reported factors were the presence of nonhepatic comorbid conditions, substance abuse problems, or other psychosocial barriers (39).

3-5. Anesthesia in pediatric liver transplantation

Living donors receive general anesthesia and immediate transplantation of a portion of their liver into the recipient (40, 41). Therefore, the patient receiving the transplant is prepared for surgery within the same time frame as the donor. A liver from a deceased donor must be transplanted into the recipient within 12-18 hours. A team of surgeons and anesthesiologists performs an operation to remove the liver from the donor. The liver is then preserved and packed for transport. These procedures are performed using standard surgical practices and sterile techniques.

3-6. Immediate postoperative care

Following liver transplant surgery, patients frequently remain on a ventilator for the first 24-48 hours. Patients are moved out of the pediatric ICU (PICU) in a few days, depending on their recovery. Reintroduction of oral intake can begin within the week following surgery. Typically, hospital stays range from 1-2 weeks. Blood tests are performed within the first few weeks following transplantation to confirm correct medication levels. Prior to discharge, the transplant team provides follow-up care and medication instructions. The patient's and caregivers' questions are answered, and signs of rejection are discussed with the patient in an age-appropriate manner and with the family. The patient and family should be instructed to continue a rehabilitation program that includes exercise, proper nutrition, and the continuation of immunosuppression and other medications. Generally, living donors do not have any restrictions or specific medications or special diet as a result of liver donation.

3-7. Long-term monitoring

Following liver transplantation, patients require at-home rehabilitation. Recommendations vary depending on the age of the patient. In general, if the pediatric patient is able to walk, walking is recommended to restore strength and prevent lung complications.

Follow-up visits are required for check-ups. These begin soon after the patient returns home. Initially, outpatient visits may occur weekly or even more often. As time passes, the frequency of follow-up visits usually decreases.

3-8. Growth and development after liver transplantation

Growth and development are important challenges to physicians caring for children with end-stage organ (ie, kidney, heart, liver) failure (42-44). Transplantation may successfully reverse the growth impairment in these children, for whom it remains the most physiologic treatment for growth retardation. Nutritional status improves after transplantation, and most children have the potential to experience accelerated growth, to obtain normal height, and to improve cognitive and developmental skills, including behavioral, motor, and social functions. Appropriate neurologic development can be expected after transplantation, and children have the potential to perform at levels that are adequate for their ages.

Many neuropsychological deficits, as well as physical impairments and growth failure, however, may still occur and persist. In one study, pediatric recipients of liver transplants, when compared with other groups of chronically ill children, scored lower in many motor and psychological tests and obtained fewer academic achievements (45). A mild functional impairment was present in 79% of children after liver transplantation, when the children were compared with a reference population.

Approximately 20% of pediatric liver transplant recipients are estimated to experience growth impairment at some point after transplantation. A recent suggestion was that a pretransplantation growth defect may not be completely corrected in liver transplant recipients, although an increasing percentage of children are demonstrating catch-up growth. Growth may initially worsen after transplantation (during the initial 6 months), but catch-up growth begins afterward.

The SPLIT 2000 (Studies of Pediatric Liver Transplantation) annual report demonstrated that growth failure was more significant in patients younger than 5 years but that these same patients also manifested the greatest improvement 18 months after transplantation. According to the report, some important pretransplantation factors affecting posttransplantation growth are age at transplantation (patients younger than 2 years had the greatest catch-up growth), Z-score at transplantation, and primary diagnosis (patients with biliary atresia seem to have the most catch-up growth) (46). A proper recognition of children with nutritional and growth deficits before solid-organ transplantation is therefore fundamental.

Analysis of 167 10-year survivors after pediatric liver transplantation found that linear height is significantly below the general population, with 69% of patients below the 50% percentile and 23% below the 10% percentile. There was a strong association between low linear height and ongoing use of corticosteroids as part of the immunosuppression regimen (47).

3-9. Frequency; International

Sarna et al. from Finland reported 79% of liver recipients as being below the reference range for height at 3 years after transplantation (48). In the same series, the catch-up growth after transplantation was reported to be 26% in the first year, 47% in the second year, and 56% in the third year (49, 50). In 1999, Viner et al from England reported severe growth retardation in 20% of patients at the time of liver transplantation (51).

4- CONCLUSION

A liver transplant is a surgical procedure done in some patients with liver failure to replace their diseased liver with a healthy liver. When a patient receives a liver transplant, his or her entire liver is removed. It is then replaced by a portion of the donor's healthy liver. In living liver donor surgery, the donor and the recipient are placed in side-by-side operating rooms. A surgeon removes a part of the donor's liver, typically the right half. This donated segment of the liver is then immediately placed in the recipient in the next operating room. The remaining part of the donor's liver is sufficient to maintain normal body functions. The recipient also receives a large enough segment of the donor liver to maintain body functions. During approximately the next two months, the remaining and transplanted parts of the donor liver grow to normal size, providing normal long-term liver function for the donor and the recipient. There are many benefits of receiving a liver from a living donor:

- No waiting period;
- Surgeries can be scheduled at a convenient time for both the donor and the recipient;
- A liver from a living donor typically lasts longer than a liver from a deceased donor;
- A living liver transplant can be scheduled electively and before the onset of life-threatening complications while waiting for a liver from a deceased donor.

Compared with adults, who may suffer from recurrence of their primary illness leading to hepatic dysfunction in their transplanted grafts, children largely do not experience recurrence. This fact is reflected in the overall better allograft survival rates in the pediatric population. Alternatives to liver transplantation that are currently being researched include liver support devices, artificial organ construction, and hepatocyte transplantation. Transplantation is not indicated if an acceptable alternative is available or if contraindications, such as malignancy, a terminal condition, or poor expected outcome exist. Complications of liver transplantation include the following:

- Hepatic artery thrombosis;
- Biliary complications;
- Infection;
- Nephrotoxicity;
- CNS toxicity;
- Osteoporosis;
- Cardiovascular disease;
- Lymphoproliferative disorders;
- Psychosocial stress.

6-CONFLICT OF INTERESTS: None.

7- REFERENCES

1. Cotran RS, Kumar V, Robbins SL. Robbins Pathological Basis of Disease. 5th ed. Philadelphia, PA: WB Saunders Co; 1994. P.841.

2. Abdel-Misih, Sherif R Z, Bloomston M. "Liver Anatomy". Surgical Clinics of North America 2010; 90(4): 643–53.

3. "Anatomy and physiology of the liver - Canadian Cancer Society". Cancer.ca. Retrieved 2015-06-26. Available at: http://www.cancer.ca/en/cancer-information/cancer-type/liver/anatomy-and-physiology/?region=on.

4. TortoraDerrickson 2008. p. 945.

5. Anthea M, Hopkins J, William McLaughlin Ch, Johnson S, Quon Warner M, LaHart D, et al. Human Biology and Health. Englewood Cliffs, New Jersey, USA: Prentice Hall; 1993. ISBN 0-13-981176-1. OCLC 32308337.

6. Häussinger D. Liver Regeneration. Berlin New York: NY De Gruyter; 2011. p. 1. ISBN 9783110250794.

7. Robbins and Cotran Pathologic Basis of Disease (7th ed.). 1999. p. 101. ISBN 0-8089-2302-1.

8. Jaime Ch, Kirsten CS. "New school in liver development: Lessons from zebrafish". Hepatology 2009; 50 (5): 1656–63.

9. W. T. Councilman (1913). "Two". Disease and Its Causes. New York Henry Holt and Company London Williams and Norgate The University Press, Cambridge, U.S.A. Available at: https://en.wikipedia.org/wiki/Liver.

10. Suzuki K, Tanaka M, Watanabe N, Saito S, Nonaka H, Miyajima A. "p75 Neurotrophin receptor is a marker for precursors of stellate cells and portal fibroblasts in mouse fetal liver". Gastroenterology 2008; 135 (1): 270–81.

11. Tietz PS, Larusso NF. "Cholangiocyte biology". Current Opinion in Gastroenterology2006; 22 (3): 279–87.

12. Cronin M. "Starzl, Tribune-Review reporters claim Carnegie Science Awards". Pittsburgh Tribune-Review. Retrieved 2010-01-29. Available at: https://en.wikipedia.org/wiki/Thomas_Starzl.

13. "Sir Roy Calne to give Strauss Lecture". University Week *(*University of Washington*)* 1998;15(35). Retrieved 2014-08-01.

14. "First UK live liver donation to a stranger takes place." BBC News. 23 January 2015. Retrieved 3 Dec 2015.

15. Vorvick, Linda J. A.D.A.M. Health Solutions, Ebix, Inc.; David Zieve, MD, MHA, David R. Eltz, Stephanie Slon, and Nissi Wang, eds. "Contraindication: MedlinePlus Medical Encyclopedia". MEDLINE. United States National Library of Medicine. Retrieved 7 November 2015.

16. Cirrhosis". April 23, 2014. Retrieved 19 Dec 2015. Available at: https://en.wikipedia.org/wiki/Cirrhosis.

17. Duffy JP, Vardanian A, Benjamin E, Watson M, Farmer DG, Ghobrial RM, et al. "Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA". Annals of Surgery 2007; 246 (3): 502–9.

18. Evrard V, Otte JB, Sokal E, Rochet JS, Haccourt F, Gennari F, et al. Impact of surgical and immunological parameters in pediatric liver transplantation: a multivariate analysis in 500 consecutive recipients of primary grafts. Ann Surg 2004; 239(2):272-80.

19. Information on different Liver Dialysis Systems. Available at: http://www.liver-products.com/liver-therapy/liver-dialysis.html. Accessed in Dec 2015.

20. Southard JH, Belzer FO. "Organ preservation". Annu Rev Med 1995; 46 (1): 235–47.

21. 510(k) Summary. Custodiol HTK Solution Common/Classification Name: Isolated Kidney Perfusion and Transport System and Accessories, 21 CFR 876.5880; Franz Kohler. Prepared December 14, 2004.

22. Frohn C, Fricke L, Puchta JC, Kirchner H. "The effect of HLA-C matching on acute renal transplant rejection.". Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2001;16 (2): 355–60.

23. Abbas, Abul K, Lichtman, Andrew H. Basic Immunology: Functions and Disorders of the Immune System. 2nd ed. Saunders/Elsevier. ISBN 978-1-4160-5569-3. Available at: http://www.amazon.com/Basic-Immunology-Functions-Disorders-Immune/dp/072160241X.

24. Kino T, Hatanaka H, Hashimoto M, Nishiyama M, Goto T, Okuhara M, et al. FK-506, a novel immunosuppressant isolated from aStreptomyces.1. Fermentation, isolation, and

physico-chemical and biological characteristics. J Antibiot (Tokyo) 1987; 40(9):1249-55.

25. Janeway CA Jr, Travers P, Walport M, et al. (2001). "The complement system and innate immunity". Immunobiology: The Immune System in Health and Disease. New York: Garland Science. Retrieved 25 February 2013.

26. Liver transplants result in excellent survival rates for patients with liver cancer. Available at: http://www.innovations-report.com//html/reports/medicine-health/report-22829.html.

27. Thomas Earl Starzl. (born March 11, 1926) is an American physician, researcher, and is an expert on organ transplants. He performed the first human liver transplants, and has often been referred to as "the father of modern transplantation. Encyclopedia of World Biography. Available at: http://www.encyclopedia.com/doc/1G2-3404707902.html

28. Yersiz H, Renz JF, Farmer DG, Hisatake GM, McDiarmid SV, Busuttil RW. One hundred in situ split-liver transplantations: a single-center experience. Ann Surg 2003; 238(4):496-505;

29. Haddad EM, McAlister VC, Renouf E, Malthaner R, Kjaer MS, Gluud LL. "Cyclosporin versus tacrolimus for liver transplanted patients". Cochrane Database of systematic reviews 2006;18 (4): CD005161.

30. O'Grady JG, Burroughs A, Hardy P, Elbourne D, Truesdale A. The UK and Ireland Liver Transplant Study Group. "Tacrolimus versus microemulsified ciclosporin in liver transplantation: the TMC randomised controlled trial". Lancet 2002; 360 (9340): 1119–25.

31. Strong RW. "Living-donor liver transplantation: an overview". J Hepatobiliary Pancreat Surg 2006;13 (5): 370–77.

32. Who can be a Donor? University of Maryland Medical Center. Available at: http://umm.edu/programs/transplant/services/liver/living-donor/who-can-be-a-donor.

33. Vohra V. "Liver transplantation in India". Int Anesthesiol Clin 2006; 44 (4): 137–49.

34. Tuttle-Newhall JE, Collins BH, Desai DM, Kuo PC, Heneghan MA. "The current status of living donor liver transplantation". Curr Probl Surg 2005; 42 (3): 144–83.

35. Balistreri WF, Bucuvalas JC, Ryckman FC. The effect of immunosuppression on growth and development.Liver Transpl Surg 1995;1(5 Suppl 1):64-73.

36. McDiarmid SV. Management of the pediatric liver transplant patient. Liver Transpl 2001; 7(11 Suppl 1):S77-86.

37. Sundaram SS, Alonso EM, Whitington PF. Liver transplantation in neonates. Liver Transpl 2003; 9(8):783-88.

38. Fine RN, Alonso EM, Fischel JE, Bucuvalas JC, Enos RA, GoreLangton RE. Pediatric transplantation of the kidney, liver and heart: summary report.Pediatr Transplant 2004; 8(1):75-86.

39. Volk ML, Biggins SW, Huang MA, Argo CK, Fontana RJ, Anspach RR. Decision making in liver transplant selection committees: a multicenter study. Ann Intern Med 2011; 155(8):503-8.

40. Takada Y, Tanaka K. Living related liver transplantation. Transplant Proc 2004; 36(2 Suppl):271S-3S.

41. Lopez-Santamaria M, de Vicente E, Gamez M, de la Vega A, Diaz MC, Jara P, et al. Pediatric living donor liver transplantation. Transplant Proc 2003; 35(5):1808-9.

42. Burdelski M, Nolkemper D, Ganschow R, Broering DC, Nolkemper D. Liver transplantation in children: long-term outcome and quality of life. Eur J Pediatr 1999; 158 Suppl 2:S34-42.

43. Melter M, Briscoe DM. Challenges after pediatric transplantation. Semin Nephrol 2000; 20(2):199-208.

44. Bartosh SM, Thomas SE, Sutton MM, Brady LM, Whitington PF. Linear growth after pediatric liver transplantation. J Pediatr 1999: 135(5):624-31.

45. van Mourik ID, Beath SV, Brook GA, Cash AJ, Mayer AD, Buckels JA, et al. Long-term nutritional and neurodevelopmental outcome of liver transplantation in infants

aged less than 12 months. J Pediatr Gastroenterol Nutr 2000; 30(3):269-75.

46. SPLIT research group. Studies of Pediatric Liver Transplantation (SPLIT): year 2000 outcomes.Transplantation 2001; 72(3):463-76.

47. Ng VL, Alonso EM, Bucuvalas JC, Cohen G, Limbers CA, Varni JW. Health status of children alive 10 years after pediatric liver transplantation performed in the US and Canada: report of the studies of pediatric liver transplantation experience. J Pediatr 2012; 160(5):820-6.e3.

48. Sarna S, Laine J, Sipila I, Koistinen R, Holmberg C. Differences in linear growth and cortisol production between liver and renal transplant recipients on similar immunosuppression. Transplantation 1995; 60(7):656-61.

49. Sarna S, Sipila I, Vihervuori E, Koistinen R, Holmberg C. Growth delay after liver transplantation in childhood: studies of underlying mechanisms. Pediatr Res 1995; 38(3):366-72.

50. Sarna S, Sipila I, Ronnholm K, Koistinen R, Holmberg C. Recombinant human growth hormone improves growth in children receiving glucocorticoid treatment after liver transplantation. J Clin Endocrinol Metab 1996; 81(4):1476-82.

51. Viner RM, Forton JT, Cole TJ, Clark IH, Noble-Jamieson G, Barnes ND. Growth of long-term survivors of liver transplantation. Arch Dis Child 1999; 80(3):235-40.