Liver transplantation (LTx) has gained popularity and is being discussed more and more in pediatric circles now. Though there are a few established transplant programs in our country, they are predominantly adult programs which do few children and even fewer small children (<10 kg, <1 year of age). The Pediatric Liver transplantation program at Narayana Hrudyalaya has carried out 22 liver transplants to date—the mean weight is 9 kg and the mean age 1.5 years. This unique Indian experience along with other international data forms the basis of this article.

1. WHAT IS LIVER TRANSPLANTATION?

Liver transplantation (LTx) is an operation where in a diseased liver is replaced with a liver graft from another healthy person. After kidney transplantation, liver transplantation is the commonest solid organ to be transplanted. About 300 liver transplants are performed annually in India (a large majority of this number are adults) and this number is rapidly growing.

2. WHY DOES ONE REQUIRE A LIVER TRANSPLANTATION?

LTx is the only option for a person with chronic or end stage liver disease. Unlike patients with renal failure who do have the option of a dialysis program, patients of liver failure have no other treatment option. A hepatic “dialysis” is available, but this is only in acute liver failure to facilitate stabilisation of a very unstable patient until a transplantation can be organised. In certain other conditions, there is no liver failure as such, but there is a chronic liver dysfunction that results in poor quality of life (intense pruritus with PFIC, dietary restrictions with Tyrosinemia and Glycogen Storage Disease) and delayed physical and mental development. With improving results of pediatric LTx, even patients belonging to the latter group are offered transplantation.

3. WHAT ARE THE INDICATIONS FOR LIVER TRANSPLANTATION IN CHILDREN?

Biliary atresia is by far the commonest indication for liver transplantation in children. Upto 45-40% of all liver transplants in children are for this indication. The other indication for liver transplantation are listed in the Table 1.
TABLE 1: INDICATIONS FOR LIVER TRANSPLANTATION IN CHILDREN:

<table>
<thead>
<tr>
<th>Problems needing LTx</th>
<th>Indications for LTx</th>
<th>Diseases/examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulminant Liver Failure</td>
<td>Risk of death</td>
<td>Acetaminophen induced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute fulminant hepatitis</td>
</tr>
<tr>
<td>Chronic Liver Disease</td>
<td>Poor outcomes, certain death</td>
<td>Biliary atresia</td>
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<tr>
<td></td>
<td></td>
<td>Cirrhosis from other causes Wilson’s</td>
</tr>
<tr>
<td>Metabolic diseases</td>
<td>Life style issues</td>
<td>PFIC (persistent familial intrahepatic cholestasis)</td>
</tr>
<tr>
<td></td>
<td>(intense pruritus, dietary limitations)</td>
<td>Glycogen storage disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tyrosinemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bile acid synthetic defects</td>
</tr>
<tr>
<td>Premalignant Conditions</td>
<td>Risk of hepatic malignancy</td>
<td>Glycogen storage disease</td>
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<tr>
<td></td>
<td></td>
<td>Tyrosinemia</td>
</tr>
<tr>
<td>Hepatic Malignancy</td>
<td>limited only to liver</td>
<td>Hepatoblastoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metastatic tumours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(localised to liver)</td>
</tr>
<tr>
<td>Hepatic vascular diseases</td>
<td>To cure vascular problems</td>
<td>Budd Chiari syndrome</td>
</tr>
</tbody>
</table>

4. THE PELD SCORE:

The PELD (Pediatric End Stage Liver Disease Score) is a scoring system that is popularly used. It is based on a formula that includes the following parameters: age less than 1 year, presence or absence of growth failure (weight <2SD), serum albumin, serum bilirubin and INR. A higher score suggests an increased risk of death from complications of liver failure and indicates the degree of urgency to transplant. Children with serious end stage disease and fulminant failure have scores in excess of 30. In a cadaveric nation wide program such as in the US, this score is used to allocate organs. In a living donor scenario such as here in India, it is not as relevant.

5. WHEN DOES ONE REFER A CHILD WITH LIVER DISEASE FOR TRANSPLANTATION?

The next question that arises is when does one refer a child with chronic liver disease for transplantation. Once the diagnosis is confirmed to be a problem that will benefit with a liver transplantation, it is imperative that this child be referred to a Transplant Centre as soon as possible—even if the LTx is not immediately required. This early referral has several advantages:

i. allows time to counsel that family
ii. allows time for the family to come to terms with the procedure and plan for it

iii. allows time to optimize the child’s condition. This nutritional and medical optimization has a definite role in reducing the risks of the LTx and improve it’s outcomes. Often immunisation is incomplete and this can be rectified. Several additional vaccines are given to reduce the problems of infections when the child is on immune suppression.

iv. allows time for the transplant centre to complete their evaluation of the child and potential donors.

v. allows time for the legal and other formalities to be completed

6. WHERE DOES THE GRAFT COME FROM?

The liver graft can come from one of two sources:

i. *Cadaveric donor* (also called deceased donor liver transplantation): There are guidelines laid out by Law regarding the assessment and declaration of brain death-and these are to be adhered to. In the West, 80-90% LTx are cadaveric/deceased donor liver transplants. Unfortunately, in India, only a handful of cadaveric organs are available each year.

ii. *Liver Donor Liver Transplantation*: Due to a paucity of cadaveric organs overall, and the difficulty in finding size matched grafts for children, live donor liver transplantation has gained popularity. It has several advantages:

1. the donor operation for pediatric transplantation often involves only a left lateral segment resection, which is a much safer operation for the donor

2. the donor is often a first degree relative-the mother in most instances-and this reduces the problems of rejection in the long run

3. the operation can be planned procedures-with a greater degree of success

4. the ischemia time for the graft is minimum and this translates into excellent graft function in the post op period.

7. WHAT TYPES OF GRAFTS ARE POSSIBLE?

The liver is a unique organ in that it is capable of regeneration. Normally the liver has 2 lobes, a left and a right-each of these lobes is composed of 4 segments each. For pediatric transplantation, often it is the left lateral segment (segments II, III) that is used, For children above 15 kg, the full left lobe (segments II,III,IV) is used.(Figure 1) In a live donor scenario, the operation in the donor involves taking out the required segments while ensuring that the remanent liver is left undisturbed and healthy. In cadaveric organs, a size matched donor is preferred. if this is not available, an adult liver graft is
cut down to the size required (reduced grafts) or the liver is split into two halves for two different recipients (split grafts).

**FIGURE 1: SEGMENTAL ANATOMY OF LIVER AND TYPES OF GRAFTS FOR CHILDREN**

8. IS THE NATIVE LIVER REMOVED?

Yes, in a majority of cases the diseased liver is removed and the new liver is placed in its place. This is called orthotopic liver transplants. Occasionally, the native liver is not removed and the liver is placed in a remote location in the abdomen as an extra-this is called auxiliary liver transplantation. Auxiliary transplants are performed in situations where the native liver is expected to recover function-as in some cases of fulminant hepatic failure.
9. WHO CAN BE A DONOR?

The criterion for being a donor are the following:

i. age between 18-50 years.

ii. same blood group as the recipient. Occasionally, in specific circumstances, compatible but not similar blood groups are accepted.

iii. should be healthy individuals with no medical problems

iv. should understand the issues involved and the fact that it is not a zero risk procedure

v. should have normal hematology and biochemistry

vi. should have a normal BMI, increasing BMI results in increasing fat in the liver and increasing surgical risk for the donor

vii. should have a liver anatomy that is favorable for resection-the arterial and portal supply and the biliary and hepatic venous drainage should allow for a safe splitting of the liver.

viii. should belong to the patient’s immediate family, so called “related donor”. The definition includes parents, siblings and children. This definition is to be extended in the near future to include grandparents and grand children. Anything beyond this becomes “unrelated or altruistic donor” and this will require prior approval from appropriate governmental authorities.

ix. by far, in majority of cases in our practice, the mother has been the donor (in 16 out of 22).

10. WHAT DOES THE WORKUP INVOLVE?

a. Donor work up is centered around trying the clarify the following:

i. suitable physical health-hematology, biochemistry, serology

ii. blood group

iii. serology status with respect to TORCH titers- some of these infections can be transmitted to the recipient and hence care needs to be taken.

iv. liver imaging-USG Doppler and Triphasic Contrast enhanced CT scan for evaluating the anatomy. A MRCP is done in selected cases
v. other basic tests for undergoing major surgery - ECG, chest xray, etc.

vi. psychological and psychosocial evaluation

b. Recipient Work-up

i. blood group

ii. basic hematolgy and biochemical work-up

iii. USG and Doppler of the liver and abdomen. Some children have obstruction to the portal vein or IVC. In these further imaging will be required.

iv. serology evaluation

11. HOW IS THE OPERATION PLANNED?

As far as is possible, the procedure is carried out as a planned operation with full preparation of both the donor and the recipient. It is carried out in 2 adjacent operation theaters. Both theaters are fully equipped to allow major hepato-biliary surgery and the 2 teams are in constant contact. This is done to meet 2 objectives:

i. nothing irreversible is done in either patient until it is certain that the transplantation will go ahead.

ii. the operation times are kept to a minimum

iii. the ischemia times are kept to a minimum

12. WHAT HAPPENS IN THE DONOR OPERATION?

The patient is prepared as for any major operative procedure. After incision the liver is inspected and an operative cholangiogram is carried out to confirm the biliary anatomy. The blood vessels supplying the left lateral segments are identified and isolated. The liver parenchyma is then split. The biliary duct and vessels are then divided and the graft removed. On the back table, this graft is then perfused with cold HDK - this washes away the blood and also reduces the temperature of the cells to reduce their metabolic demands. The liver is then double bagged in ice and then shifted to the recipient theatre. The donor operation is completed.

13. WHAT HAPPENS IN THE RECIPIENT OPERATION?

The recipient operation is a whole lot more complex. There are several specific issues that need to be addressed. The factors that play a role include:

i. previous surgery with severe adhesions
ii. each adhesion is vascular due to portal hypertension

iii. copious neo-vascularisation due to portal hypertension

iv. serositis due to ascites and subacute bacterial peritonitis

v. severe coagulopathy

vi. prolonged operation that has a high risk of hypothermia and acidosis

14. WHAT ARE THE STAGES OF THE RECIPIENT OPERATION?

The recipient operation includes the following steps:

i. Anesthetic preparation - vascular access and lines, temperature regulation, monitoring physiology, biochemistry, hematology and coagulation

ii. Native hepatectomy:

A large inverted “T” shaped incision is made on the upper abdomen. All the adhesions are divided and the liver is approached. All the ligaments of the liver are divided. The portal structures are dissected and the hepatic artery, portal vein and roux loop/bile duct are identified and dissected. The inferior vena-cava is isolated and controlled below and above (at the diaphragmatic inlet) the liver. A large number of small vessels drain the liver into the inferior vena-cava. These are carefully identified and divided after ligature. The liver is now attached only by the vascular pedicles. This stage of the operation is challenging due to the severe portal hypertension and coagulopathy. There is a potential for serious blood loss.

iii. Anhepatic Phase:

Once the graft has come into the recipient operation room, the IVC is clamped above and below the liver, the hepatic artery and portal vein are ligated and divided close to the hilum. The liver is removed. At this stage, the IVC and the portal vein are clamped. This leads to decrease venous return fall in blood pressure. The blood pressure is maintained by a combination of fluid and inotropes. This phase also is associated with increased oozing as the portal pressure shoots up due to the portal vein clamping.

iv. Implantation Phase:

Now the liver graft is positioned within the liver bed and the implantation is commenced. The hepatic vein is anastomosed to the IVC to establish venous drainage. The graft portal vein is now anastomosed to the recipient portal vein.
v. Re-perfusion Phase:

After the hepatic vein-IVC and the portal vein anastomosis are completed, the IVC and portal veins clamps are opened and the liver perfused with portal blood. This period of reperfusion results in a large load of acid and potassium from the ischemic bowel and inferior extremities to rush into the heart. This can cause serious problems of arrhythmia, hypotension and potential cardiac arrest. The anesthetic team will have all emergency medications and measures ready to counter any eventuality. This perhaps is physiologically the most crucial phase of the liver transplant operation. Once re-perfusion is completed, a period is allowed for the liver to perfuse and the patient to stabilise. A good perfusion is marked by a sudden return of portal pressures to normal and improving hemodynamic and coagulation markers.

vi. Arterial anastomosis:

This is performed only after the portal perfusion and venous outflow are optimal. This step is crucial from the long term perspective. Hepatic artery thrombosis is a dreaded complication and can potentially result in graft loss and need for urgent re-transplantation. A doppler examination is perform intra-op to confirm good arterial, portal inflows and hepatic venous outflows. Bile flow too commenced by this time.

vii. Biliary drainage:

Biliary drainage is established-usually into a roux loop of jejunum. Usually, the roux loop constructed at the time of the initial Kasai procedure (for biliary atresia) is freshened and used. Hence, in some ways, the previous operation in a bonus!

viii. Completion of procedure:

Once the graft is well settled as evidenced by clinical, radiological and lab data and hemostasis has been achieved, drains are placed and closure of the abdomen is commenced. Often the size of the graft is large and a full anatomical closure is not possible. In the rare instance, the abdomen is left open with a silo-the child is taken back to theater after 3-4 days to achieve abdominal closure. The child is then returned to the ICU ventilated.

15. WHAT IS THE POST-OPERATIVE COURSE?

a. Immediate Post-operative period:

i. The aims of treatment in the early post-operative period is to achieve hemodynamic stability and extubate the child over a period of 24-48 hours as is
required. Coagulation and albumin are supported. Watch is kept for bleeding from the drains.

ii. Immune suppression is commenced—a dose of Methyprednisone is given prior to re-perfusion. Tacrolimus is administered on the evening of surgery.

b. Intermediate term:

i. The aims are to initiate early enteral feeding and facilitate weaning of all supports. Renal function, liver functions are monitored. The liver functions improve rapidly in the face of a healthy graft.

ii. Attention is paid to the cardiac and pulmonary functions.

iii. Daily ultrasound dopplers are performed to assess the health of the liver, its vasculature and collections. Bile leakage is a problem that needs to be looked for. Drains are removed once the output falls.

iv. Immune suppression is continued and levels are monitored to achieve target levels.

v. The child is moved out of the ICU once on full feeds with good graft function.

c. Discharge and Long Term:

i. The child is usually discharged 3-4 weeks time. Prior to this the parents are roomed in with the child to allow them to learn to care for the child and also administer the multiple drugs that the child receives. It is especially important for them to become comfortable in administering the immunesuppression—especially since these are usually available in tablet form only.

ii. The family is encouraged to prepare their homes to receive the child and they are instructed in various aspects of the child’s care at home. They are left to look after the child in the wards for a couple of days before they are discharged.

16. WHAT IS IMMUNE SUPPRESSION?

a. Immune suppression is mandatory as the recipient’s body treats the graft as “non-self” and sets off a destructive immune mediated inflammatory response against it. This process is called rejection and this can result in loss of graft and can be potentially fatal. Some degree of rejection occurs in all transplants—but an optimal program of immune suppression keeps this under control—without increasing the child’s susceptibility to opportunistic infections.

b. Newer immune suppression agents selectively block pathways in the rejection cycle and do not cause non-specific immune suppression like with steroids.
c. The common agents used as Calcineurin Inhibitors (eg. Tacrolimus, Serolimus, Cyclosporine), anti-nucleotide agents (eg. mycophenolate), steroids, monoclonal antibodies (eg. basiliximab, dacluzimab etc)

d. All immune suppression has it’s side effects and it is mandatory to monitor these children to identify adverse effects and treat them before permanent damage occurs. Renal failure in the long term is a common event and needs special care.

17. WHAT ARE THE POST-OPERATIVE COMPLICATIONS?

a. Early post-operative complications:
   i. bleeding, dyselectrolytemia, renal dysfunction, pulmonary problems
   ii. early acute rejection and graft dysfunction
   iii. hepatic artery thrombosis, portal vein thrombosis, biliary leaks

b. Medium term complications
   i. delayed vascular problems
   ii. acute rejection
   iii. infections and sepsis
   iv. renal dysfunction
   v. chronic graft dysfunction
   vi. biliary leaks, strictures

c. Long Term complications
   i. chronic rejection
   ii. renal dysfunction
   iii. portal vein and biliary strictures
   iv. adverse effects of drugs
   v. opportunistic infections
18. WHAT ARE THE OUTCOMES?

The graft survival at the end of the first year is >90%. Five year graft survival is >75%. Generally, if the child remains well during the first year, the long term outcome is better. Children generally recover completely, have catch-up physical and mental development and return to age appropriate activities by the end of the first year-schooling is also commenced after 6 months. Paradoxically, it is the sicker children who bounce back more dramatically.

19. PHENOMENON OF IMMUNE TOLERANCE:

The risks of very long term immune suppression are not fully understood. Experience with poor compliance with immune suppression in the adolescent population has shown that there is a group of children who can completely come off immune-suppression. This is an area of intense study as the advantages of this are self evident.

20. WHAT ARE THE DONOR OUTCOMES?

The donor operation, especially the left lateral heptectomy or the left heptectomy are safe operations. They are major procedures, but with due care and diligence, the donors make an uneventful recovery. They are out of hospital by the end of 1 week and participate in the care of their child gradually over the next few weeks. The liver too regenerates and returns to its original volume by 6-8 weeks. Minor complications such as wound problems can occur. Major complications are rare and can include hematoma, bile leaks, deep vein thrombosis, lung atelectasis. Mortality has been reports and is under 0.2%. Hence all efforts are made to screen the donors carefully to identify high-risk factors and only those who are physically and mentally fit are accepted. Extreme care is taken during surgery and thereafter as these are essentially healthy individuals who have chosen to undergo very major surgery for to benefit some one else. They are continued on followup for at least 2 years post-op to ensure a full return to health and activities.

SUMMARY:

To summarise, liver transplantation in children, even very small ones is a feasible and established intervention. The outcomes are excellent and the children do remarkably well after their transplantation. The financial implications are large, but not insurmountable. Several agencies and public at large have come forward in large numbers to provide financial assistance to these families. As a larger number of transplants are performed, the results will improve even further and the costs will come down further too.

It is also not out of place to highlight the need for a robust Cadaveric Program in our Country. Cadaveric donation is abysmally low and it falls upon all of us to promote this aspect of medical care. However difficult it may seem, we owe it to the large number of patients waiting for various transplants, to broach the issue of organ donation in brain dead individuals-there is no doubt, that if handles sensitively, there is a high chance of success.