PAEDIATRIC LIVER TRANSPLANTATION

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Paediatric Liver Transplantation

- Paediatric liver transplantation
  - well established as treatment for end-stage chronic liver disease and acute liver failure

Main focus

- Prevention of immunosuppression related complications
- Promotion of normal growth and psychosocial development
- Management of recurrent disease
- Management of nonadherence and the risk of late rejection and graft loss
Indications for Paediatric Liver Transplantation

• Extrahepatic cholestasis
  - Biliary atresia

• Intrahepatic cholestasis
  - Alagille’s syndrome
  - Nonsyndromic paucity of intrahepatic bile ducts
  - Progressive familial intrahepatic cholestasis
  - Sclerosing cholangitis

• Metabolic diseases
  - Crigler-Najjar syndrome
  - Inborn errors of bile acid metabolism
  - Wilson’s disease
  - $\alpha_1$-antitrypsin deficiency
Indications for Paediatric Liver Transplantation

- **Metabolic diseases**
  - Tyrosinemia
  - Disorders of the urea cycle
  - Organic acidemia
  - Acid lipase defect
  - Oxaluria type 1
  - Disorders of carbohydrate metabolism

- **Acute liver failure**

- **Others**
  - Autoimmune hepatitis
  - Viral hepatitis
  - Primary liver tumours
  - Cystic fibrosis
Contraindications to Liver Transplantation

- Uncontrolled sepsis
- Concomitant end-stage organ failure that cannot be corrected by a combined transplant
- Irreversible serious neurological damage
- Non-resectable extrahepatic malignancies
- Psycho-socioeconomic reasons
  - history of non-compliance
  - inadequate access to medical care
  - living conditions – no electricity, running water / sanitation
Evaluation of Paediatric Transplant Candidate

• Confirm indication for transplant
• Determine severity of disease
• Alternative treatments to transplant
• Identify active infections / assess immunological status
• Identify cardiac malformations that need correction pre-Tx
• Pre-transplantation
  - immunisations up to date especially live vaccines
  - nutritional support to optimise growth
  - dental care
Evaluation of Paediatric Transplant Candidate

Evaluate psycho-socioeconomic factors and logistics

- Parents unemployed
- Reliant on child support grants
- Lack of electricity; inadequate sanitation and water supply
  ~ bucket / pit toilets
  ~ no running water - river
  ~ shared amenities – community taps, toilets
- Access to medical care
- Distance to hospital
  ~ clinic, primary, secondary, tertiary
- Transport
Evaluation of Paediatric Transplant Candidate

Evaluate psycho-socioeconomic factors and logistics

Level of medical care

• Monitor graft function
• Monitor drug levels
• Secure access to lifelong immunosuppression

Ongoing intensive medical support whilst awaiting transplant

Ability to relocate temporarily to Transplant Centre
Evaluation of Paediatric Transplant Candidate

Educate parents / patients

• Pre-transplant waiting period
• Transplant procedure
  - risk of surgery
  - technical complications
• Post transplant
  - rejection
  - risks of immunosuppression
  - malignancy
  - recurrent disease
Often wide socioeconomic disparity
Differences in level of facilities and care in rural and urban areas
Types of Paediatric Liver Transplants

Cadaveric liver transplantation

• Whole liver transplantation

• Reduced liver transplant
  - right lobe (segment 5-8)
  - left lobe (segment 1-4)
  - left lateral segment (segment 2-3)
  
  → reduced paediatric mortality on waiting list,
  withdraws organs from adult recipient pool

Piggy-back technique - preserves recipient’s IVC
Types of Paediatric Liver Transplants

Cadaveric liver transplantation

Split – liver transplantation

• Whole liver
  - segment 2-3 → child
  - segment 1, 4 - 8 → adult

• Higher incidence of biliary and vascular complications, primary non-function

• Avoid using marginal donors
Types of Paediatric Liver Transplants

Living-related liver transplantation

- Left lateral segment (segment 2 and 3)
- >1200 cases worldwide
  - donor mortality 0.2%
  - donor morbidity 10%
    ~ biliary complications
    ~ bleeding
    ~ incisional hernias
- Centres need to perform >50 living related transplants/year
Types of Paediatric Liver Transplants

Living-related liver transplantation

• Main benefits
  - planned procedure
  - performed before child’s clinical condition deteriorates

• Donor - extensive evaluation of physical and psychiatric fitness
  - only 30% found suitable to donate
Donor Selection

- Donor characteristics
  - donor age
  - ICU stay
  - infections
  - haemodynamic stability
  - use of inotropes

- Adequate donor mass

- Hepatocyte injury
  - donor injury (ischaemia)
  - preservation injury
  - reperfusion injury
  - rejection
Donor Selection

• Donor-to-recipient body weight ratio
  - 2-12 : split liver or reduced size liver
  - $\leq 2$ use whole liver

• Donors with extended criteria
  - whole liver if cold ischaemia time limited

• Donor liver biopsy helpful
Post Transplant Complications

Early post operative period

• Primary non-function

• Technical complications
  - biliary
  - vascular

• Infections

• Immunological
Post Transplant Complications

Primary non-function

• Within hours of transplantation
  - high lactate levels
  - ↑ ammonia, coagulopathy
  - failure to wake up

• Management
  - IVI Prostaglandin E1
  - IVI Mannitol and hyperventilation

• Urgent retransplantation

• Risk factors
  - ischaemic / hypoxic injury
  - macrovesicular steatosis > 40-50%

• Hyperacute rejection
Hepatic artery thrombosis

- 15-18% incidence (1st 30 days)
- 3-4 x more frequent than in adults
- Early thrombosis → graft necrosis
- Early identification → attempt reconstruction
  - graft failure → Re Tx
- Later thrombosis (weeks post Tx)
  - biliary complications – stenosis, anastomotic breakdown, intrahepatic abscesses
Vascular complications

Hepatic artery anastomosis stenosis

- Cholestasis, graft failure
- Rx - revision of anastomosis
  - balloon angioplasty / stenting
Post Transplant Complications

Vascular complications

Portal vein thrombosis

• 5-10%
• Biliary atresia – portal vein hypoplasia
• Early thrombosis – ultrasound screen
  → immediate anastomotic revision / thrombectomy
• Later thrombosis
  - ↓ platelet count,
  - ↑ spleen size
  - GIT bleeding
    → Mesorex shunt

Portal vein anastomotic stenosis
• Balloon dilatation / stenting
Post Transplant Complications

Biliary complications

• 10-30%

• Bile leaks

• Anastomotic strictures

• Intrahepatic biliary strictures
  - secondary sclerosing cholangitis
Post Transplant Complications

Retransplantation

- 8 - 30%
  - hepatic artery thrombosis
  - primary non-function
  - biliary complications
  - chronic rejection

• Early retransplant
  - patient survival > 80%

• Re Tx following prolonged immunosuppression for chronic rejection
  - survival 50%
Post Transplant Complications

Immunological

Acute rejection

• 20-50% - acute rejection within first 6 weeks

• Malaise, fever, irritability, poor feeding

• Leukocytosis

• Abnormal liver profile
  - ↑ALP, GGT, ALT, AST
  - jaundice late feature
Post Transplant Complications

Acute Rejection - Histology

• Liver biopsy – Triad of
  - endothelialitis
  - portal tract infiltration with bile duct targeting
  - parenchymal cell damage

• Endothelialitis – most reliable, but transitory sign of rejection

• Portal tract infiltrate – activated T cells, immunoblasts, plasma cells, neutrophils, eosinophils

• Cholangitis maybe destructive / non-destructive
Post Transplant Complications

Acute rejection - Histology

• Cellular rejection – other features
  - inflammatory infiltrate mainly T cells in the sinusoids
  - canalicular cholestasis
  - apoptosis

• Severity of acute rejection
  - scored according to Banff scheme

• Rejection activity index score 0 - 3
  - prevalence + severity of portal inflammation, bile duct injury + subendothelial inflammation

• Descriptive grades
  - indeterminate (1-2), mild (3-4), moderate (5-6) and severe (>6)
Post Transplant Complications

Infections

- Most common source of morbidity post transplantation

Immediate post transplant period

Bacterial infections

- G-ve enteric organisms
  - Enterococcus
  - Staphlococcus

- Remove invasive monitoring lines as soon as possible

- Limit use of prophylactic antibodies
  - ↓ rates of resistance

- ↑ Vancomycin-resistant enterococcus and Methicillin - resistant Stapholoccoal infections
Post Transplant Complications

Infections: Immediate post transplant period

Fungal infections

• High risk patients
  - multiple operations
  - re-transplantation
  - haemodialysis
  - pre-transplant antibiotics
  - marked cholestasis
Infections: Immediate post transplant period

Viral

- Early and severe viral infections
  - Herpes family
    ~ EBV, CMV and Herpes simplex
    ~ Herpes virus 6 and 7

- Risk of CMV and EBV infections
  - pre-operative serological status of recipient and donor
  - D+ / R- greatest risk of primary infection
Post Transplant Complications

Infections: Immediate post transplant period

Viral

- CMV infection
  - fever, leukopenia, rash
  - hepatitis
  - pneumonitis
  - GIT involvement
    ~ CMV colitis frequently serum PCR negative
      needs tissue diagnosis
- EBV infection
  - mononucleosis-like syndrome
  - hepatitis resembling rejection
  - post transplant lymphoproliferative disease
Infections: Immediate post transplant period

Viral

• Monitor CMV and EBV PCR
  - all children receive IVI Gancyclovir
  - conversion to oral Valgancyclovir

Pneumocystosis

• Nearly eliminated by the prophylactic use of Cotrimoxazole
Post transplant lymphoproliferative disease

- Heterogenous group of disorders ranging from
  - benign reactive plasmacytic hyperplasia
  - polymorphic PTLD - polyclonal or monoclonal
  - monomorphic PTLD - T or B cell lymphomas

- Most frequent malignancy in children post Tx - usually in 1st 2 years

- Late forms – aggressive clinical course and poor prognosis

- Risk factors
  - high total immunosuppression load
  - EBV naïve patients – 60-80%
  - high EBV replication rate
Post transplant lymphoproliferative disease: Management

- Decrease or withdraw immunosuppression
- Rituximab – anti-CD20 mAb has been used successfully if tumour expresses C20
- Cyclophosphamide, Prednisone, Rituximab
- Debulking surgery
- Aggressive monoclonal disease – poor prognosis
- Autologous EBV-specific cytotoxic T lymphocytes
  - enhance EBV-specific immune responses
    → reduced EBV viral load
  - successfully used as 1st line Rx
Post Transplant Complications

Late liver allograft dysfunction

• Usually detected on routine screening of LFTs

• Usually asymptomatic

• Recurrent disease less common in paediatric liver transplantation

• Liver biopsy usually necessary to establish diagnosis
Post Transplant Complications

Late liver allograft dysfunction

Late onset acute rejection

• < 30% incidence at 5 years

Risk factors

• Inadequate immunosuppression
• Non-adherence
• Treatment with immune activating drugs eg. IFN
• History of autoimmune liver disease
Post Transplant Complications

Late liver allograft dysfunction

Late onset acute rejection

Histology

• Predominantly mononuclear portal tract inflammation
• Venous endothelial inflammation of portal or central veins
• Perivenular inflammation
• Bile duct inflammation and damage
• Central perivenulitis

Management: Optimise immunosuppression
Post Transplant Complications

Late liver allograft dysfunction

Chronic rejection

• 5-10% transplants

Risk factors

• Inadequate immunosuppression
• Non-adherence
• Treatment with immune activating drugs - IFN
• Refractory acute rejection
• Chronic rejection in a previous failed allograft
Late liver allograft dysfunction

Chronic rejection

Clinical manifestation

• Can occur within weeks of transplantation

• Follows unresponsive acute rejection or inadequate immunosuppression

• Asymptomatic or presents with progressive cholestasis
Chronic rejection

2 Clinical forms

Vanishing bile duct syndrome
- Biliary epithelium primarily injured with changes ranging from senescence (early) to severe ductopaenia in > 50% portal tracts
  - retransplantation if not responsive to Tacrolimus / MMF

Progressive ischaemic injury to bile ducts and hepatocytes
- Ductopaenia, ischaemic necrosis with fibrosis
- Difficult to diagnose on biopsy – arteries with pathognomonic changes rarely seen
- Retransplantation usually necessary
Post Transplant Complications

Late liver allograft dysfunction

Bile duct injury and ductopaenia can also be caused by
• Biliary strictures
• Hepatic artery pathology
• CMV infection
• Adverse drug reactions

Recurrent disease
• Autoimmune hepatitis
• Primary sclerosing cholangitis
Post Transplant Complications

Late liver allograft dysfunction

Recurrent autoimmune hepatitis / De Novo autoimmune hepatitis

- Positive autoantibodies
  - ANF, ASA, LKM-1 Ab

- Hypergammaglobulinaemia

- Histology
  - Interface hepatitis with portal lympho-plasmocytic infiltrates

- Exclusion of viral or drug-induced hepatitis
Post Transplant Complications

Late liver allograft dysfunction

Recurrent autoimmune hepatitis

- 30% at 5 years
- Usually associated AIH type 1
- Severe inflammation in native liver
- HLA DR3 and DR4
- Suboptimal immunosuppression
- Should not withdraw steroids
Late liver allograft dysfunction

De Novo autoimmune hepatitis

• < 5% at 5 years

• Protocol biopsies in asymptomatic children at 1, 5 and 10 years post Tx
  - steroids withdrawn at 3 months
  - chronic hepatitis with progressive fibrosis → cirrhosis
  - associated autoantibodies

• Need to monitor children carefully with liver biopsies if steroids withdrawn
Post Transplant Complications

Idiopathic post transplant hepatitis

• Chronic hepatitis

• < 5 - 60% at 5 years

• Central perivenulitis
  - centrilobular-based acute rejection
  - de novo autoimmune hepatitis if autoantibodies positive

• Does not always respond to increased immunosuppression
  → progressive fibrosis
Paediatric Liver Transplantation

Immunosuppression

Triple immunosuppression

- Cyclosporine / Prednisone / Azathioprine
- Tacrolimus / Prednisone / Azathioprine
- Tacrolimus / Prednisone / Mycophenolate mofetil
- Interleukin-2 receptor blockers - renal dysfunction

Rejection

- Adequate Tacrolimus levels, mycophenolate mofetil and boostered steroids
- Rarely need to pulse with IVI medrol
**Paediatric Liver Transplantation**

**Outcome following Transplantation**

**UNOS Paediatric Kaplan-Meier Survival figures**

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Overall 10 year patient survival 75%
Paediatric Liver Transplantation

Outcome following Transplantation

UNOS Paediatric Kaplan-Meier Survival figures

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Overall 10 year graft survival 61%
Paediatric Liver Transplantation

Factors affecting outcome

Age

• < 1 yr or < 10 kg
  - technical problems
    ~ hepatic artery thrombosis
    ~ portal vein thrombosis

Diagnosis and patient status

• Survival similar for cholestatic and metabolic disease
• Early survival worse for acute liver failure and liver tumours
  - associated multi-organ failure
• Rapidly deteriorating PELD scores
• Severe malnutrition
Paediatric Liver Transplantation

Factors affecting outcome

Long-term survival influenced by

- Consequences of prolonged immunosuppression
  - infection
  - PTLD
  - Renal insufficiency
  - Hypertension
  - Diabetes mellitus

- Non-adherence especially in adolescents
Psychosocial issues pre and post transplantation

- Chronic liver disease has impact on
  - growth and neuro-development
    → later psychosocial adjustment and quality of life

- Behavioural problems

- Learning difficulties (26%)
  - special education needs

- Depression and anxiety

- Parents, patient and family need support

- Lifelong immunosuppression and regular follow-up required
Paediatric Liver Transplantation

• Transplantation - established treatment for acute liver failure and chronic endstage liver disease

• Longterm patient and graft survival figures are excellent

• Improves overall quality of life, but still inferior to healthy children
  - lifelong medication and follow-up required
  - complications of immunosuppression
  - neurocognitive disability

• Non-adherence - major cause of late mortality especially on adolescents

• Continuous multidisciplinary support, follow-up and education required

• Cannot underestimate psychosocial and economic impact of transplantation on families particularly when complications arise