Paediatric Liver Transplantation

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Director
Paediatric Liver GI and Nutrition Centre
King’s College Hospital
London
1980s

Liver transplant
Liver anatomy - The Couinaud classification
Left lobe segmental graft
Metabolic bone disease
Ileus

Perforation
Effusion need for intervention
ARDS like picture:
There is diffuse opacification throughout both lungs

Right upper lobe opacity
Diagnosis of HPS

- **Abnormal** Tech 99 - Macroaggregated albumin (MAA) lung scan

Tracer uptake in brain

Tracer uptake in kidneys
Immunosuppression /Graft Function

• **Immunosuppression**
  - Tacrolimus 0.15 mg/kg bd po
  - Methylprednisolone 2mg/kg iv, weaned to 0.01 mg/k by 4 weeks

• **Risk of organ failure**
  - Track eosinophils along with AST/ALT
  - Intelligent tailored immunosuppression

• Ultrasound + CT if develop new transaminitis
• Graft non function: acidosis, coagulopathy, cvs failure, hypoglycaemia
Viral Complications / Management

Anti CMV prophylaxis only in CMV mismatch CMV positive Donor and negative Recipient (IgG pos children up to 2 years are considered negative)

Weekly surveillance

CMV negative blood products to CMV naïve patients
Scenario 1

• 1 year old, Biliary atresia, failed Kasai
• Admitted from home for Ltx
• PICU stay 16 hrs
• Immunosuppression, Prograf, Steroids
• Antibiotics for 72 hrs, CMV -ve donor
• Drain out 4 days
• Discharged out day 12 local accommodation, home day 21
Scenario 2
Alagille Syndrome with decompensated cirrhosis

• Pre Tx cardiac assessment, dobutamine challenge, >50% increase in cardiac output
• High Cystatin C (1.5)
• Post op, poor urine output, inotropes
• CVVH
• Immunosuppression IL2 induction, low dose Prograf, Steroids, MMF.
• Antifungals, Antivirals (CMV mismatch)
• Prolonged ITU stay 4 weeks
Scenario 3
Acute Liver Failure

- ALF of indeterminate aetiology
- Transplant from PICU, CVVH, Inotropes, ICP monitor
- Graft dysfunction, liver biopsy /allograft rejection.
- Prograf levels 12, IL2 antibody 2 doses, MMF
- Further deterioration of graft dysfunction re transplant 4 weeks later.
- Graft dysfunction returns, retransplant 4 weeks later, ATG 2 weeks
- Planned 4th transplant with matched unrelated BMT in the 2-3rd week
- Died of MOF while awaiting Tx
- Liver histology ????? Not diagnostic
Post-transplant haemodynamics

• Haemodynamic depression caused by hypocalcemia induced citrate intoxication from massive transfusion or as a result of reperfusion syndrome

• Pulmonary oedema following OLT most common complication with at least 50% of these episodes in the first 24 hours

• Metabolic derangements, in the form of:
  ✓ Acidosis
  ✓ Hypothermia
  ✓ Electrolyte disturbance
Outcome and Complications
Paediatric Liver Transplants

Living related
Survival 1 year 5 years
94% 94%

Graft survival 91%

Mother makes history to save her son from death

A tough choice, but well worth the risk

Daily Mail

Newspaper of the Year 1995
Paediatric LTX, KCH
Survival by era

Paediatric Survival

Cum Survival

DATE
< 2000
> 2000
Outcome: patient survival

KCH London

Survival Plot

Presentation
- chronic liver failure
- acute liver failure

Survival %

Survival (years)
INDICATIONS FOR LIVER TRANSPLANTATION IN THE PEDIATRIC POPULATION STRATIFIED BY RECIPIENT AGE

- **0-2 years**
  - Acute hepatic necrosis: 6.92%
  - Benign neoplasms: 0.18%
  - Biliary atresia: 22.25%
  - Cholestatic liver disease/ Cirrhosis: 48.52%
  - Malignant neoplasms: 1.11%
  - Metabolic diseases: 5.76%
  - Non-cholestatic cirrhosis: 3.33%
  - Others: 8.92%

- **3-10 years**
  - Acute hepatic necrosis: 26.76%
  - Benign neoplasms: 6.69%
  - Biliary atresia: 12.89%
  - Cholestatic liver disease/ Cirrhosis: 21.18%
  - Malignant neoplasms: 0.43%
  - Metabolic diseases: 21.18%
  - Non-cholestatic cirrhosis: 8.04%
  - Others: 17.93%

- **11-18 years**
  - Acute hepatic necrosis: 21.60%
  - Benign neoplasms: 22.20%
  - Biliary atresia: 10.89%
  - Cholestatic liver disease/ Cirrhosis: 21.60%
  - Malignant neoplasms: 0.72%
  - Metabolic diseases: 18.67%
  - Non-cholestatic cirrhosis: 10.71%
  - Others: 4.01%
Primary Diseases leading to Liver Transplantation in Europe: 01/1988 - 12/2008

- **Cirrhosis**: 41,696 (58%)
- **Acute hepatic failure**: 6,155 (9%)
- ***Others***: 2,209 (3%)
- **Cancers**: 10,199 (14%)
- **Cholestatic diseases**: 7,552 (10%)
- **Metabolic diseases**: 4,542 (6%)
- **Primary Biliary**: 4,277 (10%)
- **Autoimmune**: 1,786 (5%)
- **Secondary Biliary**: 495 (1%)
- **Unknown causes**: 3,274 (8%)
- **Viral + Alcoholic**: 1,759 (4%)
- **Primary Biliary**: 4,277 (10%)
- **Virus related**: 15,936 (38%)
- **Alcoholic**: 13,638 (33%)
- **Others**: 531 (1%)

**ELTR 12/2008**
USA-UNOS GRAFT SURVIVAL ACCORDING TO RECIPIENT AGE

- 2-3 years
- 3-10 years
- 11-18 years

- Acute hepatic necrosis
- Biliary atresia
- Malignant neoplasms
- Metabolic disease
- Cholestatic liver disease / Cirrhosis
- Non-cholestatic cirrhosis
- All diagnoses
Immunosuppression
The Game Changer

THE SURGEON LOOKS LEFT, PIVOTS TO THE RIGHT, TRANSPLANTS THE ORGAN AND... WHOA! REJECTED!
The history of immunosuppression

- **Pre 1959:** total body irradiation
- **1959:** 6-mercaptopurine
- **1960:** Azathioprine
- **1962:** Glucocorticoids
- **1983:** Cyclosporin (Ciclosporin) [Neoral]
- **1989:** Tacrolimus [FK506]
- **1995:** Mycophenolate [CellCept, Myfortic]
- **1999:** Sirolimus (Rapamycin) [Rapamune]
- **2000:** Basiliximab [Simulect]
  Dacluzamab [Zenapax]

- Coming soon... FTY720; FK778; Myfortic; SDZ-RAD (Everolimus) etc
Rejection

- Occurs where the tissue type of a donor (allo) graft and the recipient differ and HLAs on the allograft are recognised as foreign

- Recognition occurs either directly via an attack by host’s cytotoxic T lymphocytes (TC) on allograft HLA class 1 antigens

- or indirectly after presentation of allograft HLA class II antigens to the recipient’s T helper (TH) cells

- The interaction of HLA II antigen with the T helper cells signals the intracellular production and secretion of interleukin 2 (IL-2)

- The combined signal from the allospecific T-cell receptor (TCR) stimulated by antigen presentation and IL-2 bound to the IL-2 (IL-2R) receptor causes clonal expansion

  i.e., the expansion and maturation of a cell population carrying the allospecific T-cell receptor or producing specific antibodies

- These cells infiltrate the graft, mediating inflammation, immune attack of the foreign antigen and cell death
5 years Follow-up
Surgical Complications
(n=146)
The PV, HV and IVC are patent. Note is made again of thrombosis of the common hepatic artery; a few small intrahepatic arterial collaterals are noted. There is intrahepatic biliary dilatation. There are multiple areas of low attenuation in the liver graft, seen in both phases, in keeping with 'soft' ischaemic liver.
Chronology of Bilairy complications  Seehofer et al AJT 2013

- Bile leak
- Anastomotic stricture
- Non-anastomotic strictures
- Ampullary dysfunction

T-tube removal
especially DCD, HAT
Medical

- Disease Recurrence
- Ductopenic rejection
- Parasitic infestations
- Cholangitis
- Drug reaction (Drugs causing cholestasis)
PTC: A diagnostic study was carried out via an anterior approach to the left lobe segmental graft and confirmed evidence of a moderate anastomotic stricture and an intrahepatic stricture at second-order level of the segment III duct. Following the diagnostic study dilatation of these strictures to 7 mm was conducted with placement of a transhepatic internal and external drain into the unobstructed roux loop.
**Management Protocol**

**Suspect Biliary complication** (Elevated biliary enzymes, bile leak, gut bacteria associated septicaemia)

- **Doppler USS**
  - Bile leak/Duct dilatation
  - Normal
  - Hepatic artery Thrombosis

  - Bile leak
  - Aspiration, MR Cholangiography
  - Liver Biopsy Biliary features
  - MR Cholangiography
  - Angiography

- **PTC/ ERCP**
  - Stricture dilatation +/- stent/ external biliary drain
  - Surgical reconstruction/ Retransplantation

- Surgical reconstruction likely to be unsuccessful could disrupt collaterals
Paediatric Liver Transplantation
Triumphs and Challenges (KCH)

Immunosuppression related Complications
EBV in the Immunosuppressed Patient

- An infection of B-lymphocytes
- EBV infection progresses to lymphoproliferative disorder (PTLPD)
  - If inadequate anti-EBV cytotoxic T-cells
  - Incidence ≈ 50% - over days to months
- Eventual progression of EBV-driven PTLPD to EBV-independent lymphoma
PTLD in Intestine

Intramural lymphoid mass – absent follicular organization

CD-20 (B-cell marker) Stain
PTLD – Symptoms

*Alone or in combination:*

- Subcutaneous nodules, hard & immobile
- Generalized lymphadenopathy
- Snoring (adenoidal hypertrophy)
- Mouth breathing with ulcerating palatine tonsils
- Pneumonia (lung & mediastinal masses)
- Diarrhea (diffuse small bowel mucosal infiltration)
- Abdominal pain (bowel obstruction)
PTLD

- Mainly following primary EBV infection
- GI lesions common after other SOT
- Blood EBV DNA-PCR not 100% sensitive
- Falling incidence
  - Less acute rejection (and its treatment)
  - Quantitative EBV-DNA monitoring
PTLD

Endoscopic findings

- Protruding intramural mass with central umbilication
- Distinguish from benign lymphoid follicles
Treatment of EBV-PTLD

- Reduce immunosuppression
- Rituximab (Rituxan®) – anti-B cell monoclonal antibody
- Chemotherapy (based on cyclophosphamide & steroids)
- IV ganciclovir & CMV immune globulin (Cytogam®)
PTLD KCH experience

Liver transplant n=658
PTLD, N=24

Incidence = 3.7%.

• Median age at diagnosis of PTLD: 62 (range, 17-148) months.
• Median interval for PTLD presentation from liver transplantation:
  – 30.5 (range, 3-103) months.
• Positive In-situ hybridization of EBV RNA in cells: 19 cases
### Presenting Symptoms & clinical features:

<table>
<thead>
<tr>
<th>Presenting Symptom</th>
<th>Clinical Examination</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Gen. Lymphadenopathy</td>
<td>4 (18%)</td>
</tr>
<tr>
<td>16 (72%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting/ Diarrhoea</td>
<td>Cervical Lymphadenopathy</td>
<td>4 (18%)</td>
</tr>
<tr>
<td>5 (22%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI Bleed</td>
<td>Axillary Lymphadenopathy</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>4 (18%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Lumps” in neck &amp; body</td>
<td>Abdominal mass/ distension</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>4 (18%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>Nerve Palsy</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>2 (9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological problems</td>
<td>Enlarged Tonsils</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>2 (9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stridor</td>
<td>Normal clinical examination</td>
<td>5 (22%)</td>
</tr>
<tr>
<td>1 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td></td>
<td></td>
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<tr>
<td>1 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep apnoea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (5%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Underlying Aetiology for Liver Transplantation

- **Biliary atresia** (16)
- **Crigler-Najjar** (2)
- **Primary Sclerosing Cholangitis** (2)
- **Neonatal Sclerosing Cholangitis** (1)
- **Hepatoblastoma** (1)
- **Portal Vein Sclerosis** (1)
- **N/A** (1)
Site(s) of PTLD involvement:

- BM+LN (5)
- BM+Intestine (3)
- BM+Liver (2)
- LN (5)
- Intestine (2)
- Nervous system (1)
- Liver (1)
- Lung (1)
- Tonsils (1)
- BM (1)

Number of patients:

BM - Bone marrow; LN - Lymph node
• **Histological sub types:**

  - B cell lymphoma = 16
  - T cell lymphoma = 1
  - Polymorphous sub type (B + T cell) = 5
  - Data not available = 2
Management & outcome of PTLD

- Immunosuppression withdrawal (n=21)
  - Not responded (n=18)
    - Rituximab (n=7)
      - Not responded (n=5)
        - Died (n=1)
      - Responded (n=2)
        - Responded to Chemotherapy (n=4)
    - Rituximab + chemotherapy (n=2)
      - Responded (n=2)
  - Responded (n=3)
    - Chemotherapy (n=9)
      - Died (n=2)
      - Responded (n=7)
        - Death unrelated to PTLD (n=2)
72% were alive after a median follow up of 44 months.
Disease Recurrence

• Giant cell hepatitis with Coomb’s positive hemolytic anemia
• Sclerosing cholangitis
• PFIC
• Chronic viral hepatitis
  • Hep C
  • Hep b
Bile Salt Export Pump Def

• Recurrence  N=4 (KCH)
• ? Antibody to the missing BSEP protein
• Symptoms-Pruritus
• Liver Biopsy –Cholestasis
• Treatment
  – Steroids
  – IV Ig
  – Rituximab, plasma exchange, retransplant
Longterm graft function and QoL
Progressive Histological Damage in Liver Allografts Following Pediatric Liver Transplantation

Helen M. Evans, Deirdre A. Kelly, Patrick J. McKiernan, and Stefan Hilscher

(Hepatology 2006;43:1109-1117.)
• Non compliance to medication is common in all chronic
• Non compliance common cause of late mortality in 10-17 yrs old post LTx recipients (Sudan et al Ann Surg 1998)
• *Non compliance higher in teenagers!*
Non compliance in younger children

Dunn et al Ped Trans 2004

$n=200$

Non-compliance 40

< 10 years of age 28

50% single parents

- other factors like socio economic status, ethnicity (Renal Tx Data)
• Adequate (levels)  =5 Immunosupp
• Low immunosuppression levels  =15
• Causes of low Immunosuppression
  • Unknown  =7
  • Admitted poor compliance  =3
  • PTLD  =2
  • HCC recurrence  =1
  • Tuberculosis treatment  =1
37 Young People >5 Years after LTx

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Function</td>
<td>92 +/- 10</td>
<td>0.001</td>
</tr>
<tr>
<td>Social Behavioral</td>
<td>94 +/-13</td>
<td>0.21</td>
</tr>
<tr>
<td>Social Emotional</td>
<td>88 +/-22</td>
<td>0.03</td>
</tr>
<tr>
<td>Social Physical</td>
<td>90 +/-18</td>
<td>0.009</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>73 +/-21</td>
<td>0.004</td>
</tr>
<tr>
<td>Behaviour</td>
<td>78 +/-15</td>
<td>0.007</td>
</tr>
<tr>
<td>Mental Health</td>
<td>75 +/-18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Self Esteem</td>
<td>77 +/-16</td>
<td>0.001</td>
</tr>
<tr>
<td>Global health perception</td>
<td>56 +/-18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family activities</td>
<td>77 +/-20</td>
<td>0.49</td>
</tr>
<tr>
<td>Family Cohesion</td>
<td>76 +/-22</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Significance compared with normal young people

Taylor and Dhawan, KCH experience 2006
Paediatric liver transplantation complications

Complications Identified in the last decade -

- Small Bowel Bacterial Overgrowth - Mack and Dhawan, Liver Trans 1997

- Eosinophilic gastroenteritis Dhawan et al Liver Trans 1998

- Hypertrophic cardiomyopathy (role of Mangenese def.) Dhawan et al Lancet 1996

Threats to health and longevity

- Malignant disease
- Renal failure
- Cardiovascular disease
- Metabolic disease
- Obesity
- Bone disease
Are children after liver transplant more prone to NAFLD?

Nobili and Dhawan, Pediatr Transplantation 2008: 12: 611-613
Recurrence of non-alcoholic steatohepatitis after liver transplantation in a 13-yr-old boy

Metabolic Syndrome in Liver Transplant Recipients: Prevalence and Association With Major Vascular Events

Marie Laryea,1,4 Kymberly D. Watt,1,4 Michele Molinari,1,2 Mark J. Walsh,1,2 Vivian C. McAlister,3 Paul J. Marotta,3 Bjorn Nashan,1,2 and Kevork M. Pellekian1,4
Food Allergies after Liver Transplantation
Hind and Dhawan 2006 Ped Transplant.

Th1/Th2 imbalance ?calcineurin inhibitor related more with Tacrolimus
De novo allergies

- Allergies ↑ recognised in patients on IS post-transplantation
- Eosinophilia and atopy more prevalent in solid organ recipients treated with FK506
- New onset food allergy ~ liver and/or small bowel transplantation only
- Not ↑ reported in other solid organ recipients despite = IS (often with FK506)
New onset food allergy

• In +- 20% of paediatric liver tx patients
• Acquired > liver transplantation
  • No atopic symptoms prior to transplant, no familial history
• Passive transmission of sIgE donor → recipient
  • Transfer of symptomatic peanut allergy to the recipient of a combined liver- and kidney transplant. N Engl J Med 1997: 337:822-4
• Prospective study in paediatric living related liver tx → no donors with FA
New onset food allergy

- Symptoms
  - Life-threatening type 1 reactions!
  - Often GI symptoms
    - Chronic diarrhea, faltering growth, eosinophilic enteropathy, oral lesions,...
  - Often mulitple FA
- > in young children (<1 yr) and infants at time of transplant
- Mechanism?
  - > unexplained
  - > FK506:
    - Shift in Th1/Th2 towards Th2
    - ↑ intestinal permeability
  - Role of the liver in immunotolerance???

Saalman, Robert; Transplantation. 89(5):606-611, March 15, 2010.
ANATOMY OF A TEENAGER'S BRAIN

THE BIRDS AND THE BEES LOBE

REBELLION CENTER
SUPERTURBO REBELLION CENTER
CENTER OF UNIVERSE CENTER

SELF IMAGE
FITTING IN GLAND
INARY ADDICTIONS

EVERY EPISODE OF THE SIMPSONS
INDESTRUCTIBILITY CORTEX

PEER PRESSURE RESISTANCE

PRONE TO BRUISING

"COOL" GAUGE

SLANG DECORDER
JUDGEMENT GLAND
MEMORY FOR MUSIC
MEMORY FOR CHORES, HOMEWORK, ETC.

SLAM DOOR REFLEX
CAR KEYS CRAVING

ALL THE ANSWERS

ABILITY TO BE SEEN IN PUBLIC WITH PARENTS

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# Adherence in Liver Transplant Recipients

Patrizia Burra, Giacomo Germani, Francesca Gnoato, Silvia Lazzaro, Francesco Paolo Russo, Umberto Cillo, and Marco Senzolo

LIVER TRANSPLANTATION 2011

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study population</th>
<th>No. of Patients</th>
<th>Time since LT (mo)</th>
<th>Nonadherence rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falkenstein et al. 2004</td>
<td>Pediatric</td>
<td>234</td>
<td>NR</td>
<td>17</td>
</tr>
<tr>
<td>Venkat et al., 2008</td>
<td>Pediatric</td>
<td>101</td>
<td>63.6</td>
<td>31.6</td>
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<tr>
<td>Berquist et al., 2006</td>
<td>Adolescent</td>
<td>97</td>
<td>&gt;12</td>
<td>38.1</td>
</tr>
<tr>
<td>Berquist et al., 2008</td>
<td>Adolescent</td>
<td>111</td>
<td>&gt;6</td>
<td>22.5</td>
</tr>
<tr>
<td>Berlakovich et al., 2000</td>
<td>Adult</td>
<td>118</td>
<td>&gt;9</td>
<td>16</td>
</tr>
<tr>
<td>O’ Carroll et al., 2006</td>
<td>Adult</td>
<td>435</td>
<td>68</td>
<td>15</td>
</tr>
</tbody>
</table>
## Factors Associated With Nonadherence in Adult and Pediatric Liver Transplant Patients

### Adult Patients
- High cost of medication
- Young age (<40 yr)
- Psychiatric disorders
- Conviction that the medication is harmful
- Side effects of medication

### Pediatric Patients
- Psychological distress
- Social adjustment problem
- Behavioral difficulties
- Family functional status
- Side effect of medication
Late cellular rejection and Compliance
Danitga and Dhawan Trans 2002

n=20
• Adequate Immunosupp (levels) = 5
• Low immunosuppression levels = 15
• Causes of low Immunosuppression
  • Unknown = 7
  • Admitted poor compliance = 3
  • PTLD = 2
  • HCC recurrence = 1
  • Tuberculosis treatment = 1

Detection of non-compliers should be a permanent concern of the transplant team
## Tolerance: Is It Achievable in Pediatric Solid Organ Transplantation?

<table>
<thead>
<tr>
<th>Center (year)</th>
<th>Study population</th>
<th>No. of Patients</th>
<th>Tolerant (%)</th>
<th>Acute Rejection</th>
<th>Chronic Rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miami (2005)</td>
<td>Adult</td>
<td>104</td>
<td>20 (19%)</td>
<td>70</td>
<td>2</td>
</tr>
<tr>
<td>King’s College 1998,2005</td>
<td>Adult</td>
<td>18</td>
<td>5 (17%)</td>
<td>13</td>
<td>1</td>
</tr>
</tbody>
</table>

Vicki Seyfert-Margolis, PhD, Sandy Feng, MD, PhD
Obstacles for tolerance in pediatric transplant recipients

• Difficulty in conducting clinical trial for novel unproven safety and/or efficacy treatment in children

• No validated biomarkers for predicting the tolerant state
  • Gene expression has been developing as a new tool