Long-Term Management of the Post-Liver Transplant Patient
Something for Everyone to Care About

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Disclosures

• I have no financial relationships with a commercial entity to disclose

Learning Objectives

• To provide a 2015 update on survival and health status achievable by pediatric liver transplantation
• To understand that long-term management of this patient population involves combined and integrated efforts
• To consider key gap opportunities available for focused strategies and new discoveries
Kaplan-Meier Probability of Patient Survival after Pediatric Liver Transplantation

BY PRIMARY DIAGNOSIS

PERCENT SURVIVAL

0 20 40 60 80 100

MONTHS

0 1 2 3 4 5 6 7 8 9 10 11 12

Survival of Children in 2 yrs according to the Main Indication in Europe

BY PRIMARY DIAGNOSIS

Biliary Atresia
Other Chole. or Metabolic
Fulminant Liver Failure
Cirrhosis
Other

Tacrolimus
68%

CyA
23%

Other
5%

Missing data
4%

More Than Just About the Liver

Risk of Complication

Initial Graft non-function
Surgical site infections
Biliary leak
Vascular complications
PTLD
Elevated BP
Allograft rejection
Chronic rejection
Chronic renal insufficiency
Disease recurrence
CV risks/dyslipidemia
Osteoporosis
Growth – obesity vs short
Late infections
Cancer
Late graft dysfunction (CR)
Non-adherence

More Than Just About the Liver
Medical Complications
• Renal insufficiency in 9.3%
• PTLD in 5%
• Overweight in 10%
• Hgt <10th percentile in 23%
• Hyperlipidemia in 25%
• Requiring insulin/anti-hyperglycemic medication in 10%
• PedsQL Total Scale Score >2 SD below mean score for healthy population in 14%

Case #1
11 year old female underwent living donor (Dad) liver transplantation at age 11 months for BA. Her post transplant course was remarkable for prolonged antibiotics for fever and ascites NYD, early allograft rejection, and challenges with feeding. She presently has excellent functional health, growing beautifully, AST, ALT and GGT <20 while on tacrolimus monotherapy with FK levels 2-3 ng/mL.

Patient and parents have zero concerns.
Is she the “ideal” patient?

“Ideal” Outcome Feasible or Futile?
“IDEAL” is defined as....

- existing only in the imagination; desirable or perfect but not likely to become a reality
  - synonyms: unattainable, unachievable, impracticable

- “satisfying one’s conception of what is perfect; most suitable”
  - synonyms: perfect, best possible, excellent, flawless, faultless, exemplary, model, ultimate quintessential, picture-perfect

- exactly right for a particular situation or person

From Oxford Advanced Learner’s Dictionary (Language Matters) AND Merriam-Webster dictionary

“Ideal” life post transplant: How could/do we measure it?

- Value- defined as health outcomes per $ spent
  - not synonym for cost reduction
  - should reflect full cycle of care
  - requires tracking patient outcomes and costs longitudinally

From What is Value in Health Care? Michael E. Porter, MD NEJM 363:26 December 23, 2010

Outcome Measures Hierarchy

- Tier 1 Health Status achieved or retained
  - Degree of health or recovery

- Tier 2 Process of recovery
  - Time to recovery and time to return to normal activities
  - Disability of care or treatment process (e.g., treatment-related discomfort, complication, adverse effects)

- Tier 3 Sustainability of health or recovery and nature of recurrences
  - Long-term consequences of therapy (e.g., care-induced illness)
  - Sustainability of health or recovery and nature of recurrences

Q. What is the applicability in the pediatric LT patient population?
Paradigm Shift: Composite Analysis Strategy Approach

<table>
<thead>
<tr>
<th>Medical Variable</th>
<th>#pts in which data available</th>
<th>Answering YES (% pts)</th>
<th>Data missing n(%) pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 No Retransplantation</td>
<td>167</td>
<td>147(88%)</td>
<td>0</td>
</tr>
<tr>
<td>2 Chronic rejection-free</td>
<td>167</td>
<td>152 (91%)</td>
<td>0</td>
</tr>
<tr>
<td>3 Normal ALT</td>
<td>166</td>
<td>148(89%)</td>
<td>1(1%)</td>
</tr>
<tr>
<td>4 Normal TB</td>
<td>165</td>
<td>161(98%)</td>
<td>4(2%)</td>
</tr>
<tr>
<td>5 Normal Alb</td>
<td>162</td>
<td>160(99%)</td>
<td>5(3%)</td>
</tr>
<tr>
<td>6 Normal GGT</td>
<td>149</td>
<td>128(80%)</td>
<td>18(11%)</td>
</tr>
</tbody>
</table>

Has evidence of a stable allograft

Has avoided immunosuppression-induced co-morbidities AND avoided additional treatments

<table>
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<th>Medical Variable</th>
<th>#pts in which data available</th>
<th>Answering YES (% pts)</th>
<th>Data missing n(%) pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 No PTLD</td>
<td>167</td>
<td>158(94%)</td>
<td>0</td>
</tr>
<tr>
<td>8 No renal dysfunction</td>
<td>118</td>
<td>107 (91%)</td>
<td>49 (29%)</td>
</tr>
<tr>
<td>9 Normal growth (z&lt;2SD)</td>
<td>121</td>
<td>112 (93%)</td>
<td>46 (37%)</td>
</tr>
<tr>
<td>10 No Diabetes</td>
<td>167</td>
<td>165(99%)</td>
<td>0</td>
</tr>
<tr>
<td>11 No Prednisone use</td>
<td>167</td>
<td>115(68%)</td>
<td>0</td>
</tr>
<tr>
<td>12 No antihypertensive use</td>
<td>167</td>
<td>148(87%)</td>
<td>0</td>
</tr>
<tr>
<td>13 No use of anti-seizure drugs</td>
<td>167</td>
<td>167(100%)</td>
<td>0</td>
</tr>
</tbody>
</table>

32% of SPLIT 10 y Survivors = IDEAL

OUTCOMES
10 years post LT

COMORBIDITIES

< 1/3 of the n=167 ten-year survivors enrolled in the SPLIT Registry met the requisite composite definition of "Ideal 10-year survivor of pediatric LT"

"Ideal 10-year Survivor after Pediatric Liver Transplantation"

1. No Retransplantation 7. No PTLD 10. No ongoing use of prednisone
2. No Chronic Rejection 8. No renal dysfunction 11. No antihypertensive

23% PeLTQL subjects = Ideal

Health Status of all 10 year-survivors (n=57)

Prevalence of comorbidities in nIDL-5 (n=44)
**Case #1**

A patient who has achieved an “ideal outcome” — normal allograft health as defined by liver tests, absence of biliary or vascular changes (and normal histology) without immune or non-immune complications of IS medications with excellent functional health and effective self-management – achievable in 25-32% of patients.

**Learning Objective #2**

- To provide a 2015 update on survival and health status achievable by pediatric liver transplantation
- To understand that long-term management of this patient population involves combined and integrated efforts
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**Long-Term Medical Management of the Pediatric Patient After Liver Transplantation:**

*2013 Practice Guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation*

- Routine Monitoring & Management – Growth & Nutrition, Endocrine (bones), Psychosocial, Neurocognitive (and HRQOL) monitoring, Adherence
- Graft surveillance – late surgical complications (HAT, PVT, IVH/HV), late biliary strictures, protocol liver biopsies
- General – skin cancer surveillance, safe living
- Immunosuppression – ACR, CR, A/E’s, iWITH
- Disease - specific issues – recurrent ds, CFLD
- Late infections – viral, PCP, PTLD
- Adolescent Health – STD, menstrual anomalies, OCP, Pregnancy, non-adherence, risk behaviours
- Transition – self-management components
Case #2

6 year old boy with missed BA, s/p DD (whole) LT age 8 months.

- IS treatment with CyA, prednisone and azathioprine. Early post-operative course was complicated by persistent elevated LFTs, concerns with HA flow, no rejection or infection.
- Age 4 years - switched to Tacrolimus for AST, ALT, GGT in mid 100-200’s. CB 0, INR normal, Alb normal. Plts > 300. Told to remain on steroids.
- Age 5 years – clinical onset of pruritus and jaundice → U/S and diagnostic PTC revealed multiple intrahepatic duct dilations, and anastomotic stricture. IR intervention – guidewire unsuccessful, external drain left in – lots of admissions, refractory pruritus.
- Age 6 years - referred for 2nd opinion.

Case #2

- Meds – FK 0.6 mg BID, Pred 5 mg po QD, amlodipine multi-vitamin, iron, ASA.
- Labs – AST 354, ALT 288, GGT 362, plts 268. CB, Alb, INR normal. Hb 92, MCV 62?

Q. Parents ask about - growth, anemia, BP, biliary complications, graft life, QOL after liver transplant, graft life?

Catch-up growth patterns of children who undergo LT is incomplete

MVA suggests that some risk factors are modifiable – including pre-LT nutritional status, duration of steroid use post-LT, graft function (lower TB and GGT levels at 12 months post LT)
• Linear growth impairment (20%)
• Delayed puberty (39% girls, 42% boys ages 16-18 years were not yet Tanner 5)
• Independent predictors of growth impairment included:
  • impaired growth at time of LTx (OR 11.53, p<=0.001), re-transplantation (OR 4.37, p=0.991), non-white race and primary diagnosis other than BA.

Risk factors for chronic anemia in pediatric orthotopic liver transplantation: Analysis of data from the SPLIT registry

• Chronic anemia was common in children following LT \( \rightarrow \) 242/1026 (24%)
• MVA identified use of cyclosporine, steroid use, GI bleeding, presence of leukopenia, and renal insufficiency (cGFR<90 mL/min/1.73 m²) = independent risk factors associated with chronic anemia
• Screening and attention to chronic anemia important – impact on growth and development, overall graft health, as well as important outcome measures including QOL and physical function

Blood Pressure Elevation in Long-Term Survivors of Pediatric Liver Transplantation

The prevalence of elevated BP measurements in 5-10 yr LTx survivors - 17% to 28%

How can Pediatric Health Care Teams Help?
• Check BP with any encounter
• Evaluate for cardiovascular risk factors
## Biliary complications

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>N</th>
<th># (%) BC</th>
<th>Graft type</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laurence</td>
<td>2015 Toronto</td>
<td>2001-2011</td>
<td>173</td>
<td>29 (17%)</td>
<td>75 LRD, 98 DD</td>
</tr>
<tr>
<td>Darius</td>
<td>Belgium</td>
<td>1993-2010</td>
<td>429</td>
<td>98 (23%)</td>
<td>203 LRD, 326 DD</td>
</tr>
<tr>
<td>Feier</td>
<td>Brazil</td>
<td>1995-2012</td>
<td>489</td>
<td>71 (15%)</td>
<td>All DD</td>
</tr>
<tr>
<td>Luthold</td>
<td>Geneva</td>
<td>1990-2011</td>
<td>116</td>
<td>29 (24%)</td>
<td>All DD</td>
</tr>
</tbody>
</table>

### Mental Health Issues – Focus Moving Forward

**Anxiety**

<table>
<thead>
<tr>
<th>SCARED® score</th>
<th>n</th>
<th>SD</th>
<th>cut off for anxiety (n, %)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.2 ± 13.4</td>
<td>44</td>
<td>12</td>
<td>17 (27%)</td>
<td>≥14.6</td>
</tr>
</tbody>
</table>

*Screen for Child Anxiety Related Disorders (20 Items)*

C/W 5-17% incidence of anxiety in general population
5  Ask Amy for analysis
   Mar Miserachs, 4/28/2015

6  Should we include parents results?? I am not sure we have them, need to look at PeLTQL database
   Mar Miserachs, 4/28/2015
Case #2
• Patient seen by Liver Transplant multi-disciplinary team members plus various consultants.
• Re-reviewed all films
• Interventional radiology
• Currently – with internal-external drain, no longer pruritic, stools pigmented, “his eyes are whiter than mine”. CB 0, GGT from 338 to 258, INR and Alb normal, plts continue to be normal.
• Parents advised will need re-LT in future

It takes a village to raise a child.........

Learning Objective #3
• To provide a 2015 update on survival and health status achievable by pediatric liver transplantation
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**Key Drivers over the Full Cycle of Care**

- Patient Selection
- Pre-Transplant Considerations
- Organ Allocation
- Donor Selection
- Peri-Transplant Challenges
- Short-Term Outcomes
- Long-Term and Longer-Term Outcomes

Current active efforts:
1) Understanding long term graft dysfunction – DSA, protocol liver biopsies
2) Biliary complications – diagnostic and treatment subgroups
3) Infectious Disease – CMV, immunization practices
4) Ideal Outcomes – heat map analyses
Summary and Take-Home Messages

- Multiple outcomes collectively define success of pediatric LT
  - Composite Outcome inclusive of sustainability of health – both for the allograft (maximizing longevity) AND for the patient (minimizing immunosuppression-induced comorbidities and its treatment effects)
  - Definition of “ideal” Tiers 1, 2 and 3 outcomes may be further refined – histopathology, clinical event and biochemical markers

- Still LOTS to do - collaborative opportunities
  - Longitudinal tracking as the cohort ages - standardization of follow-up, innovative ways (web-based etc)
  - Well-designed interventional clinical trials, Comparative Effectiveness research initiatives, etc

Standardization of follow-up

“If you hadn’t done those tests to find out what’s wrong with me, I’d still be healthy!”

“You have a rare condition called ‘good health’. Frankly, I’m not sure how to treat it.”
Acknowledgments

- Studies of Pediatric Liver Transplantation (SPLIT)
  - EMMES
  - All SPLIT coordinators and PIs

- Pediatric Liver Transplant Quality of Life (PeLTQL) Research Group

- Patients and families

- The “Teams”

Thank you for your attention!

QUESTIONS?
Glucose intolerance or post-transplant diabetes was found in 214 (13%) patients, of whom 166 (78%) were diagnosed within 30 days of transplantation (early GI/PTDM).

Multivariate analyses - age >5 yr at transplant, hospitalization at transplant, a primary diagnosis other than BA, early steroid use, and tacrolimus use are associated with increased incidence of early glucose intolerance.

Routine monitoring for the development of glucose intolerance and post-transplant diabetes is indicated in the short- and long-term care of children following LTx.

Survey study – 823 SPLIT participants

- 33% of patients missed >10 days of school per year
- 34% of participants were receiving special education services
- 20% participants repeated a grade level
- Parents reported a diagnosis of learning disorder made previously in 17% of patients.

PTLD developed in 2% of patients by 12 months post-transplant, and 3.6% by 5 years.

Outcomes of PTLD include: Death = 8/78 (10.3%) and Graft loss = 10/78 (12.8%).

How can Pediatricians/Health care provider teams help?

- Every visit by a LTx survivor to a primary care provider represents an opportunity for surveillance for malignancy/PTLD
- Know the signs and symptoms of PTLD
  - Common sites – lymphoid (adenotonsillar) tissues, GIT, lung and liver
  - Can be insidious and non-specific – ie. fever (episodic/unexplained), weight loss, fatigue etc before developing more significant symptomatology → high index of suspicion
  - May present as constitutional symptoms, lymphadenopathy, new onset anemia, new onset mouth-breathing, new onset encephalopathy, new onset mouth-breathing, new onset encephalopathy

Decreasing Incidence of Symptomatic Epstein-Barr Virus Disease and Posttransplant Lymphoproliferative Disorder in Pediatric Liver Transplant Recipients: Report of the Studies of Pediatric Liver Transplantation Experience 2283 pts

PTLD developed in 2% of patients by 12 months post-transplant, and 3.6% by 5 years.

Outcomes of PTLD include: Death = 8/78 (10.3%) and Graft loss = 10/78 (12.8%).
• Prevalence of obesity at 1 year was 19%, and at 3 years was 18%
• MVA – Hispanic ethnicity, prolonged steroid use, overweight and obesity at time of LT

How can Health Care Provider Teams help?
A need to broaden standard care to include obesity assessment and intervention in routine pre- and post-LT care

Reducing Pediatric Liver Transplant Complications: A Potential Roadmap for Transplant Quality Improvement Initiatives Within North America
Incidence of PTLD among pediatric patients receiving a liver transplant, 2000–2010, by recipient Epstein-Barr virus (EBV) status at transplant

The cumulative incidence is estimated using Kaplan-Meier competing risks methods. PTLD is defined as a histopathologic diagnosis of lymphoproliferative disease within 1 year or cause of death on the Transplant Recipient Follow-up Form or on the NIH transplant. Malignancy form is polymorphic PTLD, monocytoid PTLD, or Hodgkin’s Disease. Only the earliest date of PTLD diagnosis is considered.