Global Outcomes in Pediatric Liver Transplantation

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The Hospital for Sick Children, University of Toronto

Seattle Children’s Hospital: Pediatric Liver Transplant Family Education Day – September 15, 2017
Learning Objectives

1. To review long-term outcomes for children after liver transplant on an international level

2. To review a research definition of “ideal survivor of pediatric LTx”

3. To highlight a few SPLIT efforts

4. To identify key opportunities to further improve durable outcomes for this patient population
Global Outcomes after Pediatric Liver Transplant

<table>
<thead>
<tr>
<th>Transplant Center</th>
<th>1-Year Patient Survival</th>
<th>1-Year Graft Survival</th>
<th>5-Year Patient Survival</th>
<th>5-Year Graft Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eurotransplant</td>
<td>76-95%</td>
<td>76%</td>
<td>71-86%</td>
<td>66%</td>
</tr>
<tr>
<td>Asia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>94%</td>
<td>87%</td>
<td>91%</td>
<td>83%</td>
</tr>
<tr>
<td>Korea</td>
<td>88%</td>
<td>87%</td>
<td>82%</td>
<td>80%</td>
</tr>
<tr>
<td>Latin America</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>91%</td>
<td>NA</td>
<td>84%</td>
<td>NA</td>
</tr>
<tr>
<td>Argentina</td>
<td>80 – 87%</td>
<td>NA</td>
<td>74%</td>
<td>NA</td>
</tr>
<tr>
<td>Mexico</td>
<td>85%</td>
<td>NA</td>
<td>75%</td>
<td>NA</td>
</tr>
<tr>
<td>North America</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNOS</td>
<td>94-96%</td>
<td>86% - 92%</td>
<td>85-93%</td>
<td>79% - 88%</td>
</tr>
<tr>
<td>SPLIT</td>
<td>94%</td>
<td>87%</td>
<td>91%</td>
<td>83%</td>
</tr>
<tr>
<td>SickKids</td>
<td>92-97%</td>
<td>90-96%</td>
<td>87-96%</td>
<td>87-96%</td>
</tr>
</tbody>
</table>

(UNOS, 2017; Ng et al., 2012; SickKids, 2015; Eurotransplant Database, 2017; Kasahara, 2016; Kim et al., 2013; Paolo et al, 2014)
Immune Suppression Needs at 10 Year Anniversary

- Tacrolimus: 68%
- CyA Monotherapy: 23%
- CyA Monotherapy: 15%
- Tac Monotherapy: 47%
- Other: 5%
- Missing data: 4%
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

Vicky L. Ng, MD, FRCP(C), Estella M. Alonso, MD, John C. Bucuvalas, MD, Geoff Cohen, PhD, Christine A. Limbers, PhD, James W. Varni, PhD, George Mazariegos, MD, John Magee, MD, Susan V. McDiarmid, MD, and Ravinder Anand, PhD, for the Studies of Pediatric Liver Transplantation (SPLIT) Research Group.

Extrahepatic complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal In.</td>
<td>9.3</td>
</tr>
<tr>
<td>PTLD</td>
<td>5</td>
</tr>
<tr>
<td>Overweight</td>
<td>10</td>
</tr>
<tr>
<td>Hgt &lt;10%</td>
<td>23</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>25</td>
</tr>
<tr>
<td>Increased Glu.</td>
<td>10</td>
</tr>
</tbody>
</table>
In 10-year survivors of LT (n=80), **Health Related Quality of Life (HRQOL)**, measured by PedsQL 4.0™, was lower compared to healthy matched children.

Studies of Pediatric Liver Transplantation (SPLIT) Group. Ng et al. J Peds 2012
Q. Is there really no difference...or could it be that our tools are just not asking the right questions?
More Than Just About the Liver

- Initial Graft non-function
- Surgical site infections
- Biliary leak
- Vascular complications

- PTLD
- Elevated BP
- Allograft rejection
- Chronic rejection

- Late allograft rejection
- Opportunistic Infections

- Chronic renal insufficiency
- Cancer
- Disease recurrence
- Cardiovascular risk
- Osteoporosis
- Late graft dysfunction (CR)

- **Non-immune Complications** – renal dysfunction, cardiovascular risks, diabetes, growth, cognitive development, HRQOL
- **Emerging Adulthood**
- **Nonadherence**
Learning Objectives - #2

1. To review long-term outcomes for children after liver transplant on an international level

2. To review a research definition of “ideal survivor of pediatric LTx”

3. To highlight ideal outcomes achieved from SPLIT

4. To identify key opportunities to further improve durable outcomes for this patient population
“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
Outcome Measures Hierarchy

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

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

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

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**Q.** What is the applicability in the pediatric LT patient population?

*Potter NEJM 2010*
The **Ideal** Liver Transplant Survivor
Findings from SPLIT

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**“Ideal 10-year Survivor after Pediatric Liver Transplantation”**

1. No Retransplantation
2. No Chronic Rejection
3. Normal ALT
4. Normal Total Bilirubin
5. Normal Albumin
6. Normal GGT
7. No PTLD
8. No renal dysfunction
9. Linear growth ≥-2SD
10. No diabetes
11. No antihypertensive
12. No antiseizure

Prevalence of (only) 31% of SPLIT 10-Year Survivors – Where are the opportunities to target?

*And – let’s not forget a patient-reported outcome like quality of life!*
Learning Objectives - #3

1. To review long-term outcomes for children after liver transplant on an international level

2. To review a research definition of “ideal survivor of pediatric LTx”

3. To highlight some research efforts to-date

4. To identify key opportunities to further improve durable outcomes for this patient population
Current Challenges

• “Our ability to restore a normal lifespan and quality of life after a liver transplant is challenged by a shortage of organs, the adverse effects of medications, long-term graft failure, and the adverse behavioural, emotional, and social effects of chronic illness and disease.”

NIH Workshop, Feb 2007
The SPLIT Research Agenda 2013

Estella M. Alonso¹, Vicky L. Ng²,
Ravinder Anand³, Christopher D.
Anderson⁴, Udeme D. Ekong¹, Emily M.
Fredericks⁵, Katryn N. Furuya⁶, Nitika A.
Gupta⁷, Stacee M. Lerret⁸, Shikha
Sundaram⁹, Greg Tiao¹⁰ and on behalf of
the Studies of Pediatric Liver
Transplantation (SPLIT) Research Group
Learning Objectives - #4

1. To review long-term outcomes for children after liver transplant on an international level

2. To review a research definition of “ideal survivor of pediatric LTx”

3. To highlight ideal outcomes achieved from SPLIT

4. To identify key opportunities to further improve durable outcomes for this patient population
“Facing the future”....what lies ahead?
Journey to Survive and Thrive

#1 Patient Selection

#2 Organ Allocation

#3 PRE-LTx Minimizing Risks while Waiting

#4 Peri-Transplant Minimizing Risks and Complications

#5 SHORT TERM OUTCOMES
PICU <30d 1 year

#6 LONG TERM OUTCOMES
>1 y 5y >10 y
Success after Pediatric LT: Moving Beyond Patient Survival

- Focus has shifted to encompass long term outcomes after pediatric liver transplantation

- Studies of Pediatric Liver Transplantation (SPLIT) is the largest detailed database of pediatric liver transplant recipients in the United States and Canada
SUMMARY

- 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
  - Prioritize access to children - decrease mortality on waiting list
  - Graft health long(est) term
  - Adherence
  - Long-term Immunosuppression
  - What matters to patients most? Patient reported outcomes, Parent Advocacy
  - Interventional clinical trials, Comparative Effectiveness research initiatives, Digital Tools/Social Media
Conclusions

• Success with survival after pediatric LT marks a new “era”
  = the refocusing of COLLABORATIVE efforts towards better understanding of the long-term issues for these children

• SPLIT aims to be the voice of pediatric liver transplantation towards the overarching goal of improving the quality and quantity of life for pediatric liver recipients.

“RESEARCH IS CREATING NEW KNOWLEDGE.”
NEIL ARMSTRONG
It takes a village to raise a child........
PARTICIPATING CENTERS

• Alfred I. DuPont Hospital
• Boston Children’s Hospital
• Cardinal Glennon Children’s Hospital
• Children’s Healthcare of Atlanta
• Children’s Hospital of Denver
• Children’s Hospital of Philadelphia
• Children’s Hospital of Pittsburgh
• Children’s Hospital Western Ont
• Children’s Hospital of Cincinnati
• Children’s Hospital of Wisconsin
• Children’s Med Ctr of Dallas
• Children’s Memorial Med Ctr, Chicago
• Children’s Mercy Hospital, Kansas City
• Hospital for Sick Children, Toronto
• John Hopkin’s Hospital
• LeBonheur Children’s, Memphis
• Mayo Medical School
• Med College of Virginia

Medical University of South Carolina
Mt Sina, New York
New York Presbyterian Hosp, NY
Ste Justine, Montreal
Stanford University
St Louis Children’s
Texas Children’s, Houston
UCLA
Stollery Children’s, Edmonton
UCSD
UCSF
University of Chicago
University of Florida, Gainsville
University of Miami
University of Michegan
University of Minnesota
University of Nebraska
University of North Carolina
University of Rochester
University of Texas, San Antonio
University of Wisconsin
“You have a rare condition called ‘good health’. Frankly, I’m not sure how to treat it.”
Questions?
### Paradigm Shift: Composite Analysis Strategy Approach

#### Has evidence of a stable allograft

<table>
<thead>
<tr>
<th>Medical Variable (result at 10 yr visit)</th>
<th>#pts in which data available</th>
<th>Answering YES n(%) patients</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>2 (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>126 (85%)</td>
<td>18 (11%)</td>
</tr>
</tbody>
</table>

#### Has avoided Immunosuppression-Induced Co-Morbid Conditions AND avoided additional treatments

<table>
<thead>
<tr>
<th>Medical Variable</th>
<th>#pts in which data available</th>
<th>Answering YES n(%)</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 (&lt;-2SD)</td>
<td>121</td>
<td>112 (93%)</td>
<td>46 (27%)</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>135 (81%)</td>
<td>0</td>
</tr>
<tr>
<td>12 No anti-HT agent use</td>
<td>167</td>
<td>146 (87%)</td>
<td>0</td>
</tr>
<tr>
<td>13 No use of anti-Sz meds</td>
<td>167</td>
<td>167 (100%)</td>
<td>0</td>
</tr>
</tbody>
</table>