CURRENT CONCEPTS & PRACTICES IN PEDIATRIC HEPATIC TRANSPLANTATION

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Objectives

• To learn about the current indications as well as the medical concepts which currently shape the care of pediatric hepatic transplant candidates.

• To learn about the current concepts in surgical approaches to pediatric hepatic transplantation.

• To learn about the listing process and current clinical practices in pediatric hepatic transplantation.

End Stage Liver Disease (ESLD)

2 Years after Liver Transplant

Courtesy of Dr. Peter Whitington

Pediatric Liver Transplant (OLT)

• Liver conditions leading to OLT

• Evaluation & Listing process of the candidates

• Surgery & Current Outcomes

First successful liver transplant - Children

• Starzl TE, Groth CG, Brettschneider L, Moon JB, Fulginiti VA, Cotton EK, Porter KA

First Successful Liver Transplants

- Denver - 1967
- Hepatoblastoma

Liver conditions leading to OLT

- Progressive liver disease → ESLD
- Acute liver failure
- Benign & malignant liver tumors
- Metabolic disease

Biliary Atresia - ESLD

Definition: A destructive inflammatory process that affects variable lengths of the biliary tract

- Progressive fibrosis
- Obstruction of extrahepatic biliary tree

Incidence

- 1:8,000 – 18,000 live births
- Female > Male
- No family history correlation (rare for 2 in 1 family)
- Higher incidence in Asian and African American population
Etiology
Perinatal or postnatal form
• Isolated defect in a healthy term newborn
• Wide speculations
  - Rhesus – rotavirus mouse animal model
Prenatal or embryonic form
• 10-25% have associated anomalies (BASM)
• Laterality genes implicated in animal model

Current model of Pathogenesis

Pathogenesis
• Bile duct obstruction
• Cholestasis
• Hepatic fibrosis
• Irreversible cirrhosis
• Liver failure

Diagnosis
• Blood tests
  - Evaluate for cholestasis, liver involvement and impaired function
• Ultrasound
• HIDA scan
• Liver Biopsy
• Intraoperative cholangiogram

What is the best test to make the diagnosis?
For every complex question there is a simple answer………………..
……………………and that is wrong!

Maternal Microchimerism in BA

A male cell, depicted by a red signal, the X chromosome, and green signal, a Y chromosome within the blue nuclear material can be seen in both male BA liver specimens. In the same specimen, one can also see a female cell, depicted by two red signals, both X-chromosomes with no green signal within the blue nuclear material.
Diagnosis

- Different phenotypes not one disease
- Evolving dynamic process
- Limited expression of liver injury in neonates to many insults
- Closing window of opportunity

Kasai Procedure - Outcomes

Poor Outcome Follow Late KP

Wadhwani S., Shepherd R. Pediatrics May 2008

Guideline for the Evaluation of Cholestatic Jaundice in Infants

Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary surveillance of infants with unexplained jaundice at 3 weeks of age is recommended</td>
<td>C</td>
</tr>
<tr>
<td>Retain any infant with an acute condition or other explanation for jaundice unless jaundice does not improve, resolves, or resolves and reappears</td>
<td>D</td>
</tr>
<tr>
<td>Differential is recommended for infants with cholestasis of prematurity</td>
<td>A</td>
</tr>
<tr>
<td>Liver biopsy is recommended for most infants with unexplained cholestasis of prematurity</td>
<td>A</td>
</tr>
<tr>
<td>GGTP and hypoalbuminemia are not routinely recommended</td>
<td>C</td>
</tr>
<tr>
<td>Only when liver test results are abnormal or other evidence of cholestasis is present is ERCP recommended but may be harmful in situations in which liver test results are unreliable or not available</td>
<td>B</td>
</tr>
<tr>
<td>Although the evidence is not wholly available, although ERCP may be useful in experienced hands</td>
<td>C</td>
</tr>
</tbody>
</table>

ESLD - Clinical picture

- Jaundice
- Malabsorption of lipids and lipid soluble vitamins → Failure to thrive
- Portal HTN → GI bleeding
- Pruritus
- Hepatosplenomegaly → Hypersplenism
- Ascites, Pleural effusion
- Xanthomas → rare in infancy
- Other organs- CF, AT deficiency, HPS, HRS, HE....

ESLD- Biochemical picture

- High Conjugated bilirubin
- High serum levels of bile salts
- High Alkaline phosphatase & GGT, AST, ALT
- Low or normal GGT – PFIC
- Bile acid synthesis defects
- Coagulation defect, low albumin
- Electrolyte, minerals, vitamins problems
- Low cell counts
ESLD Management

Supportive therapy:
- Increase bile flow - URSO, Rifampicin
- Elemental MCT rich feeding formulas
- Lipid soluble Vitamins (A,D,E,K) supplements
- Control of pruritus

Meet our Star

Liver conditions leading to OLT
- Progressive liver disease $\rightarrow$ ESLD
- Acute liver failure
- Benign & malignant liver tumors
- Metabolic disease

Acute liver failure
- Acute onset of coagulopathy, encephalopathy
- Indeterminate cause common, infections.....
- Hepatic encephalopathy, coagulopathy
- Fluid overload, HRS....CVVH/D, plasma exchange

Pediatric Liver Transplant (OLT)

Acute Liver Failure

Acetaminophen Toxicity
- Single dose of 100-150 mg/kg is the risk factor.
- Multiple small doses of therapeutic dosing as a second hit?
Acetaminophen Toxicity Current Concepts

- Glutathione reserve protects from the toxic intermediate NAPQI.
- Inducers of CP-450/depletion of glutathione due to malnutrition increases the risk.
- N-acetylcysteine is the substrate for Glutathione synthesis.
- Acetaminophen adducts formation parallels glutathione depletion.

Acetaminophen Adducts

Acetaminophen Toxicity Paradigm Shift

Detection of Acetaminophen Protein Adducts in Children With Acute Liver Failure of Inborn Errors Cause
Laura P. James, Estella M. Alonso, Linda S. Hyman, Jack A. Hinson, Timothy J. Davern, William M. Lee, Robert H. Squires and the Pediatric Acute Liver Failure Study Group
Pediatrics 2006;117;334-339 DOI: 10.1542/peds.2006-0069

Acute Liver Failure – Post OLT

Liver conditions leading to OLT
- Progressive liver disease\(\rightarrow\)ESLD
- Acute liver failure
- Benign & malignant liver tumors
- Metabolic disease

Pediatric Liver Transplant (OLT)

Hepatoblastoma Staging

Hepatoblastoma Current Algorithm
Liver Transplant for Liver Tumor

- Hepatoblastoma
- Other malignant tumors
- Benign tumors

Pediatric Liver Transplant (OLT)

Liver conditions leading to OLT

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Metabolic Liver Disease

Who has the AT Deficiency?

- #1. Alpha-1 AT deficiency is the most common cause of liver transplant in children with metabolic diseases.
- #2. Second most common in public after Cystic Fibrosis.
- #3. No medical cure yet available.

Progressive Familial Liver Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive Familial Intrahepatic Cholestasis (PFIC):</td>
<td></td>
</tr>
<tr>
<td>Type 1 (Byler’s disease)</td>
<td>Mutation in P-type ATPase</td>
</tr>
<tr>
<td>Type 2</td>
<td>Absence of sister of P-glycoprotein</td>
</tr>
<tr>
<td>Type 3</td>
<td>Absence of MDR3</td>
</tr>
<tr>
<td>Benign Recurrent Intrahepatic Cholestasis</td>
<td>Mutation in P-type ATPase</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>CFTR gene mutation</td>
</tr>
</tbody>
</table>

Bile Formation: Transporters

- Multidrug-resistant-3 (MDR3)
- Phospholipids
- Sister of P-glycoprotein
- Bile-salt export pump

Mitochondrial Disease - OLT

Fatal deterioration of neurological disease after orthotopic liver transplantation for valproic acid-induced liver damage
Medical Therapy for Tyrosinemia

Hypercoagulable Disorder

Pediatric Liver-Heart 2006

Pediatric Liver Transplant (OLT)
• Liver conditions leading to OLT
• Evaluation & Listing process of the candidates
• Surgery & Current Outcomes

Evaluation process - OLT
✓ Emergency; inpatient; outpatient
✓ Multidisciplinary team members
✓ Confirm cause & need for OLT
✓ No contraindications.....

Evaluation process - OLT
Table 21-3. BASICS OF THE PRETRANSPLANT EVALUATION
Confirm the diagnosis and need for transplantation.
Determine the urgency for transplantation.
Look for positive contraindications to transplantation.
Look for processes that might present a problem after transplantation.
Establish a relationship with parents and primary care providers.
Arrange for finances.
Arrange a mechanism for contacting parents and providing transport.
Establish a plan for interim management.
Listing process - OLT

- PELD score = (0.436[age]) – 0.687 log [albumin g/dl] + 0.480 log [total bilirubin mg/dl] + 1.857 log [INR] + 0.667 [growth failure]

- Exceptions to the rule......for non-standard patients.

- Acute liver failure –Status 1a or 1b.

Listing process – PELD scoring

Listing – Regional Sharing

Pediatric Liver Transplant (OLT)

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8 Functional Segments of the Liver

Standard Adult OLT
Technical Variants of OLT

- Live Donation of Segments 2 & 3
- Reduced Liver Transplant
- Split Liver Transplant
- Auxillary Liver Transplant
- Combined Organ Transplants

The Donor Liver

Anesthesia-Placing Lines

Mercedes Benz Incision

Thompson retractors-exposure
Hilar Dissection

..Mobilize Liver and Hepatectomy

The liver is out!

Liver is sent to pathology

Donor liver...

Implantation of the new liver...
The new liver is in and working! (abg, bile, sugars)

...look around and stop bleeders and roux en Y bile duct anastamosis

Patient arrives to ICU...

...accompanied by the anesthesiologist and the surgeon, there must be a smooth transition to the ICU. A full report should have details that include:

- Name, age, weight, underlying condition requiring transplantation
- Surgical details type of graft, ABO, type of vascular and biliary anastamosis
- Fluids infused during the OR should be itemized
- Blood losses/urine output
- Most recent ventilatory requirements
- Most recent labs, blood gases etc
- Post operative orders should be completed by the Surgeon (a pre printed sheet) and all orders explained to the ICU fellow/attending and nurses.

Combined Liver-Intestine

Multivisceral Transplant

Technical variant- Reduced
Texas First
Liver/Pancreas/Intestine 2006

Thank You