A Global View – Current Status of Liver Disease in the United States

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Objectives

• Review current understanding of burden of pediatric liver diseases in the United States

• Review opportunities and goals for research and improvement in current status

• Describe plan for future efforts to achieve these goals
Pediatric Liver Diseases

- Chronic Hepatitis
- Cirrhosis and End-stage Liver Disease
- Autoimmune Liver Diseases
- Viral and Toxic Hepatitis
- Inherited Metabolic Liver Diseases
- Steatohepatitis
- Neonatal Cholestasis
- Biliary Atresia

TRANSPLANTATION

FHF
How does one measure burden of disease?

- Number of patients
- Cost of care, burden on health care system
- Lost income
- Mortality
- Morbidity
  - Physical
  - Cognitive
  - Emotional
  - Social
  - Economic
Epidemiology - Pediatric Liver Disease

- Poorly studied
- Many diseases not reportable or reported
- Incidence and prevalence lower than adults
- Impact of these diseases is high
  - mortality, need for liver transplantation, family disruption, precursor of adult disease, number of years of life lost
National Demand

- Demand for pediatric liver specialists has risen
  - unique spectrum of liver diseases affecting infants and children
  - developmental changes in the liver have broad physiologic effects
  - new and changing approaches to diagnosis and treatment and prevention
  - liver transplantation expertise needed
  - ongoing research creates changing landscape
New Developments

- Understanding of molecular and cellular control of bile secretion
- Embryologic development of the liver and biliary tree
- Disease mechanisms being unraveled
- Genetic underpinning and modification of many pediatric liver diseases
- Enthusiasm for development of new treatments using novel technologies
Prevalence & Incidence of Liver Disease

- Not known for children
- Hospitalizations – 15,000 children/yr.
- Deaths from liver disease
  - not one of top 15 in children
  - in adults – chronic liver disease and cirrhosis are 12th most common cause of death
    - ~ 28,000 deaths per year
Incidence of Specific Diseases

- **Incidence of neonatal cholestasis:**
  - all causes = 1 in 2,500
  - biliary atresia = 1 in 13,000 (U.S.)
  - about 350-400 new BA patients per year
  - about 2464 Alagille syndrome pts.

- **Hepatitis C virus chronic infection**
  - 1 in 500 age 6-11 yrs. in U.S.
  - 1 in 250 age 12-19 yrs.

- **NAFLD**
  - 2 - 10% of all children
Impact of Pediatric Liver Diseases

- Treatment for most is inadequate  → Liver transplantation only option for many
- Treatment and prevention would be highly cost-effective – many decades of productivity
- Many are precursors of adult chronic liver disease, cirrhosis and hepatocellular carcinoma: EtOH, NASH, HBV and HCV
**Liver Transplantation Impact**

- **Pediatric OLTs** – 12-15% of all OLTs
- **500-600 per year U.S.**
- **Major indications**
  - Cholestasis/biliary atresia 40-45%
  - Metabolic liver disease 10-15%
  - Acute liver failure 10%
  - Autoimmune 5-6%
  - Tumors 3-6%
  - Cirrhosis 5%
  - TPN related 5%
Liver Transplantation Impact

- Annual cost - $134 million for pediatric OLTs
- Perspective:
  - 0.3% of annual total U.S. health care expenditures directed to children with liver disease
  - These children = 0.0006% of pediatric population
  - Thus – major use of health care dollar
Burden of Specific Diseases
Biliary Atresia

• 1 in 10,000 to 13,000 in U.S.

• 30-40% of cases of neonatal cholestasis

• leading indication for transplantation

• African American, low birthweight, girls

• Annual U.S. cost estimated at $56 million
  – modest, probably underestimate
  – $7.6 million/yr. initial for first year care
  – $47.8 million/yr. for transplant care
Burden of Specific Diseases

Intrahepatic Cholestasis

• Heterogeneous group of disorders
  – Infectious
  – Genetic
    – transport defects, embryologic development, bile acid synthesis defects, mitochondrial
  – Metabolic diseases
    – Alpha-1AT deficiency
    – Tyrosinemia, Galactosemia, Tyrosinemia
    – Cystic Fibrosis
  – Storage Diseases
  – Idiopathic neonatal cholestasis
Burden of Specific Diseases
Intrahepatic Cholestasis

• Incidence overall: 1 in 7,000 live births
• 5-8% of Liver Transplants
• Discovery of genetic causes have had major effect on entire field of hepatology, with benefits to adults
  – *Jagged 1*: Alagille syndrome gene, Cong. Heart Disease
  – *FIC1*: PFIC 1 and BRIC 1
  – *BSEP*: PFIC 2 and BRIC 2
  – *MDR3*: PFIC 3, ICP, Gallstones, ? PSC
Burden of Specific Diseases

Metabolic Liver Diseases

- **Incidence:**
  - alpha-1AT def.: 1 in 1800 (10-15%)
  - Wilson’s disease: 1 in 30,000
  - Cystic fibrosis: 1 in 2000 (3-5% neonatal, 15-20% overall)

- Account for 10-15% of liver transplants

- New diseases discovered (↓ idiopathic)
  - A1AT, bile acid synthesis defects, mitochondrial hepatopathies

- Enormous opportunity for development of novel diagnostics and treatments
Burden of Specific Diseases
Non-alcoholic Fatty Liver Disease

- Roots of NAFLD and NASH begin in childhood – precursor of adult disease
- Growing incidence in parallel with obesity and type II DM epidemic
  - 20-30% of 12-17 yr. olds are obese or overweight
  - 10-20% of 6-12 yr. olds
  - Half have fatty liver
  - 10-20% have steatohepatitis
- Up to 5% of adolescents have NASH
Burden of Specific Diseases
Non-alcoholic Fatty Liver Disease

• Need to control childhood obesity:
  – diet, snacks and junk food, sugar beverages
  – exercise, “screen-time”
  – social implementation at school, home, family

• Understand effects of insulin resistance on the childhood liver

• Understand risks associated with pediatric NASH – cirrhosis, HCC, drug metabolism, others
Burden of Specific Diseases

Acute Liver Failure

- Incidence unknown for children
- Accounts for 10-15% of liver transplants
  - Outcome poorer with & without OLT
- PALF data
  - Metabolic cause in < 2 yr. olds
  - Indeterminate in older patients
  - Autoimmune or immune-mediated – more common than appreciated
  - Acetaminophen less common vs. adults
Burden of Specific Diseases

Acute Liver Failure

- Estimated costs:
  - > $100 million per year (minimum) for OLTs (40-60 per year), $8 M for follow-up
  - additional ICU care, financial impact on family, loss of life

- Major opportunity for better understanding of causes, pathogenesis, & earlier prognosis and critical need for better therapies
  - LIU score to predict outcome
    - Based on bilirubin, ammonia and INR/Protime

*Liu E et al. J Hepatology 2005*
Burden of Specific Diseases
Autoimmune Diseases

- AIH and PSC – incidence unknown
  - 4% of pediatric liver transplants
- AIH – girls, PSC - boys
- Onset of adult disease in childhood
- Best chance of preventing cirrhosis for AIH rests in treating in childhood
- Risks of post-transplant recurrence persist
- Need better understanding of these diseases
Burden of Specific Diseases
Hepatitis C


• Burden in children over next 10 years
  – 240,000 children born to 400,000 HCV infected women
  – 3% develop chronic infection – 7,200
  – 20,000 to 40,000 existing pediatric cases
  – Total number 30,000 to 40,000
Burden of Specific Diseases
Hepatitis C

- **Cost Estimates** (several scenarios tested)
  - Screening exposed infants
    $26 million
  - Monitoring chronically infected
    $117-162 million
  - Treatment
    $56 to 104 million
- **Total costs** $167 to 434 million for 2007-2017
Burden of Specific Diseases
Hepatitis A and B

- Successful prevention of both HAV and HBV possible with universal vaccination programs

*Pediatr Infect Disease Journal 20005;24:755*

Burden of Specific Diseases
Hepatitis A and B

- Reduction in HBV childhood infections in all ethnic groups
Burden of Specific Diseases
Hepatitis A and B

Burden of Specific Diseases
Hepatitis A and B

FIGURE 3. Hepatitis A incidence in Israel by age group before (1993-1998) versus after (2002-2004) universal mass vaccination of children aged 18 to 24 months (Dagan et al., 2005). Note: The percentage values shown represent the reduction in hepatitis A incidence observed for each age group following universal mass vaccination.
Burden of Specific Diseases
Hepatitis A and B

• May, 2006 ACIP new recommendations
  – Universal childhood vaccination recommended at age 12-23 months
  – Should prevent 180,000 new cases per year
  – Cost of $45 million
  – Acceptable cost-benefit ratio for dollars per life year gained

• We should eradicate (or close) pediatric cases of HAV!
Going Forward

• How do we address the needs of children with liver disease?
• How do we obtain the data, discover the cause and pathogenesis, develop screening methods, develop newer and better therapies and cures?
• Most of these are RARE DISEASES require collaboration – doctors, scientists, PAG

require government support
Collaborative Pediatric Liver Disease Research Networks

- SPLIT: Studies of Pediatric Liver Transplantation: Exclusively Pediatric
- PALF: Pediatric Acute Liver Failure: Initially adult/pediatric, now exclusively pediatric
- NASH: Nonalcoholic Steatohepatitis: Adult and Pediatric
- BARC: Biliary Atresia Research Consortium: Exclusively Pediatric
- PEDSC: Clinical trial of Pegylated Interferon with or without Ribavirin in Children: Exclusively Pediatric
- CLiC: Cholestatic Liver Disease Consortium: Rare Liver Disease Network: Exclusively Pediatric
- STOP SC: Privately funded for investigation of PSC and AIH
Why?

- Increased emphasis on clinical translational research as part of the NIH roadmap
- Almost all pediatric liver diseases qualify as orphan diseases
- No single center will have adequate volumes for clinical translational studies
  - Natural history at single centers changes due to changes in care
  - Uniformity of definitions and data collection is lacking
  - Clinical trials are impossible in this setting
- Led to a concept of collaborative research efforts with success in adults (HALTC as an example)
- Extended to Pediatric: Inclusion of Pediatrics in Collaborations and development of collaborations focused on pediatric diseases
Formation of Networks

- Investigator initiated multicenter studies:
  - SPLIT, PALF, PEDSC
- NIH initiated RFA:
  - NASH, BARC, CLiC (RDN)
- Foundation:
  - STOP SC, CFLD
Network Internal Structure

• Much of the structure is determined by guidance from the NIH, cooperative agreements: U01 mechanism
• Data Coordinating Center
• Executive Committee: Limited Group Day to Day Management
• Steering Committee: Larger Group of Participants Guide Overall direction
• Ancillary Study Committee: Screen Ancillary Study Applications
• Publication Committee: Screen, Guide and Direct Publication Suggestions
• NIH input and participation: different from R01
Key parts of collaborative networks: Registry/Database

- Generally designed to determine the natural history of a particular disorder in pediatrics
  - SPLIT, PALF, NASH, BARC, CLiC
- Significant collection of clinical data
  - SPLIT: Current data forms: 21 different data collection forms
- Collection and storage of biological specimens
  - PALF: serum and plasma, bile
  - NASH: serum, plasma
  - BARC & CLiC: serum, urine, liver tissue, bile duct, DNA or cell lines
  - PEDSC: serum, histology, viral RNA
# Key parts of collaborative networks: Clinical Trial

- Investigator initiated clinical trial
- Generally developed by the collaborative network
- PALF: NAC trial
- NASH: TONIC trial
- PEDSC: Developed for a clinical trial PEG-IFN +/- Ribavirin
- BARC: START Trial
## Characteristics of Networks

<table>
<thead>
<tr>
<th>Study</th>
<th>Registry</th>
<th>Specimens</th>
<th>Clinical Trial</th>
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<tbody>
<tr>
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<tr>
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<td>Yes</td>
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<td>BARC</td>
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<tr>
<td>PEDSC</td>
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<tr>
<td>CLiC</td>
<td>Planned</td>
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Ancillary Studies

• Study proposed separate from the core network study using some component of the network

• Ancillary Study Policy

• Rich database and linked specimen repository for translational studies

• Must have a collaborating/sponsoring investigator in the network

• Specific NIH RFA to fund these studies
Biliary Atresia Research Consortium

- NIH RFA outgrowth of NIH strategic plan
- Individual Centers Submitted Applications
- DCC Applications separate from center applications
- Special Study Section Ranked Applications
- Consortium Formed
- Centers: Cincinnati, Denver, Houston (Texas Children’s), John’s Hopkins, Mount Sinai, Northwestern, Philadelphia (CHOP), Pittsburgh, San Francisco, St. Louis (Washington University)
- DCC: Michigan
Five Current BARC Studies

- Retrospective study of outcome after HPE at 9 BARC centers (1997-2000)
- Prospective study of infants with cholestasis and biliary atresia epidemiology (PROBE) < 6 mo Old (187 enrolled)
  - extensive prospective database
  - biobanking of serum, urine, flash frozen liver/bile duct remnants/gallbladder and lymph nodes
  - EBV-transformed cell lines for DNA (and serum and DNA on parents)  
    *Abst AASLD 2006*
Outcome at 24 months

- Cumulative Total
- Time Period:
  - 0 - 3 Mo PO
  - 3 - 6 Mo PO
  - 6 Mo Po - 18 Mo Age
  - 18 - 24 Mo Age
- Alive with Native Liver
- Transplant
- Dead
## Clinical Factors and Outcome

<table>
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<tr>
<th>Factor</th>
<th>Outcome</th>
<th>Percent</th>
<th>p-value</th>
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<td>Presence of anomalies</td>
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<td>None</td>
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<td>Factors that did not impact outcome and percent of centers that use the treatment</td>
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<td>Urso</td>
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<td>75-80%</td>
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<td>Antibiotics</td>
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<td>60-70%</td>
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<td>Steroids</td>
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<td>22%</td>
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<td>Age at portoenterostomy</td>
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<td>&lt;30 days</td>
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<td>&lt;60 days</td>
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<td>60-90 days</td>
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<td>50%</td>
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*J Pediatr 2006, 148:467*
Five Current BARC Studies

- **Histopathology study**
  - to establish definitions, criteria, reproducibility, and scoring system liver histology in BA and neonatal cholestasis
  - *Abst – AASLD 2006*

- **Prospective study of BA patients over 1 year of age, and not in PROBE (BASIC)**
  - database – limited
  - DNA on patients and parents
  - serum, urine, tissue
Five Current BARC Studies

- Randomized, placebo controlled, double-blinded trial of high dose corticosteroids for biliary atresia post-portoenterostomy (START)
  - Enrollment goal: 140 patients
  - Extensive outcome data at 6 months and 12 and 24 months
    - Percent bilirubin <1.5 at 6 months with native liver
    - Survival with native liver, Growth, Development, Fat soluble vitamin status, Biochemistries, Vaccine responsiveness, HRQOL
Cholestatic Liver Disease Consortium

- Rare Disease Clinical Research Consortium to study 5 genetic causes of intrahepatic cholestasis
- Rare Disease Clinical Research Network: 10 consortia, ORD & NCRR
- CLiC funded by ORD and NIDDK
- 2004-2009
- U54 cooperative grant
- Pat Robuck, RN, PhD – project scientist
CLiC Diseases

1. Alagille syndrome
2. Alpha-1 antitrypsin deficiency
3. Progressive intrahepatic cholestasis (PFIC)
4. Bile acid synthesis defects
5. Mitochondrial hepatopathies
Patient Advocacy Groups

- Alagille Syndrome Alliance
- Alpha One Foundation
- American Liver Foundation
- Children’s Liver Alliance for Support Services
- Children’s Liver Disease Foundation
- United Mitochondrial Disease Foundation
• Initiative at the NIH

• Group dynamics:
  – Use evidence based approach for management decisions where available
  – Come to consensus for areas that there is not evidence to minimize variability of care between groups
  – Compromise
Keys to Success

- Approximately similar patient volume between centers (helps with finances, enrollment issues, publications)
- Partnering with centers with CRC resources to help with funding and support
- NIH personnel involved

Get buy-in from Patricia Robuck, PhD, RN
Future of Pediatric Liver Disease Progress

- National and International Cooperative Groups
- Involvement of Federal Agencies
- Involvement of Patient Advocacy Groups (Foundations) and Parent Groups
- Institutional Support from our Hospitals and Schools
- Leverage new era of translational research and human genome project discoveries to allow for better treatment, prevention and cure of childhood liver diseases
THANK YOU