“Biliary atresia is the darkest chapter in pediatrics ...”

Potts
Biliary Atresia

- Incidence ~ 1:10,000-15,000
- Predominantly female
- Unknown etiology
  - viral insult
  - congenital hepatic embryopathy
  - genetic predisposition
  - immune dysregulation
- Associated abnormalities in ~10%
  - polysplenia (90%), situs inversus (50%), preduodenal portal vein (40-60%), absent vena cava (40-50%), malrotation (30-40%), cardiac anomalies (30-40%), and asplenia (10%)

M Davenport, Sem Ped Surg 14:42-48, 2005
Biliary Atresia - Pathology

- Three types
  - Type 1 (~5%)
    → level of obstruction with in common duct
  - Type 2 (~3%)
    → obstruction with in common hepatic duct
  - Type 3 (>90%)
    → obstruction with in porta hepatis

M Davenport, Sem Ped Surg 14:42-48,2005
Biliary Atresia – Clinical Features

- Jaundice
  - acholic stool
  - dark urine
  - hyperbilirubinemia – direct
- Ddx
  - α1-antitrypsin
  - cystic fibrosis
  - hepatitis (multiple etiologies)
  - choledochal malformation
- Natural course
  - universally fatal
  - almost all fatalities by 2 yrs

M Davenport, Sem Ped Surg 14:42-48,2005
Biliary Atresia and Denver

John R. Lilly, MD
Biliary Atresia and Denver

Thomas E. Starzl, MD
What I’m up Against

• “Kasai should be used as initial therapy for extrahepatic biliary atresia”

• “Kasai performed in the first 2 months of life provides significant improvement for at least 5 years in one-third of the patients, although cirrhosis and disappearance of the intrahepatic bile ducts occurs with increasing age.”

NIH Consensus Development Conference Statement, 1983
Kasai “Cures” Biliary Atresia

- Post-Kasai bile flow
  - 33% no flow
  - 33% achieve short term flow
  - 33% achieve long term flow

- Bilirubin < 2 mg/dL at 6 mos = 37%
- Went on to transplant = 67%

MA Escobar, Jour Ped Surg, 2006
Kasai “Cures” Biliary Atresia

- Progression of disease
  - Kasai at 15-30 days old
    - early stage biliary obstruction
    - histologic scarring
    - slight fibrosis
    - portal inflammation
  - native liver at transplant, 6 mos – 8 yrs
    - cirrhotic
    - remarkable fibrosis
    - cholestasis
    - less prominent ductule proliferation

I Shirahase, Jour Ped Surg, 1994
Kasai “Cures” Biliary Atresia

- Complications
  - cholangitis (50-60%)
    - 25% with > 1 episode
    - of those who survived > 2 yrs
      25% still with cholangitis
    - significantly decreased survival

ET Wu, Ped Surg Int, 2001
PY Hung, Jour Ped Gastro and Nut, 2006
### Kasai “Cures” Biliary Atresia

#### Cholangitis and Survival

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>≥ 1 episode cholangitis</th>
<th>≥ 2 episodes cholangitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 year</td>
<td>61.5</td>
<td>58.2</td>
<td>35.5</td>
</tr>
<tr>
<td>5 year</td>
<td>39.1</td>
<td>40.4</td>
<td>14.2</td>
</tr>
<tr>
<td>10 year</td>
<td>33.8</td>
<td>35.0</td>
<td>14.2</td>
</tr>
</tbody>
</table>

PY Hung, Jour Ped Gastro and Nut, 2006
Kasai “Cures” Biliary Atresia

- Complications
  - 21/76 pts surviving with Kasai > 10 yrs.
  - 13 (62%) with comps
    - esoph varices hemorrhage
    - duod ulcer
    - gastric ulcer/erosion

A Toyosaka, Jour Ped Surg, 1993
Kasai “Cures” Biliary Atresia

• Ascites
  – BARC
  – 24% children developed ascites
    • esophageal varices
    • SBP
  – ascites 8%, no ascites 69%
• Worse outcomes with associated anomalies
  – 1 = 75%, >1 = 25%
  – BASM 18%, no BASM 58%
Long-term Outcomes for Kasai

- 104 children with BA over 13 years
- 35 survived >10 years
  - 12/35 required transplant
  - 2/3 with 1 or more episodes of cholangitis
  - 55% with esophageal bleeding
  - 20% with hypersplenism requiring therapy
- One quarter of children with Kasai can be expected to survive 10 yrs or more

FM Karrer, Arch Surg, 1996
“... only 10-15% will have a truly excellent long-term, symptom-free, hospital-free, normal liver biochemistry existence although even in those their liver histology is still very abnormal.”

M Davenport, Sem Ped Surg, 2005
Transplantation for Biliary Atresia

• Failed Kasai needs liver transplantation
• Most pediatric liver transplants are for BA
• Donor graft
  – cadaveric whole organ
  – cadaveric reduced size or split liver
  – living donor
Transplant as Primary Therapy?

- Age
- Size
- Nutrition
- Lack of small organs
- Who will benefit from Kasai
- Age > 90 days, cirrhosis

*Kasai is a bridge to transplantation*
Kasai vs. Transplant

- Retrospective review, single institution
- 63 pts over 10 yrs
- 57 pts underwent liver transplant
  - 49 after Kasai
  - 8 as primary treatment

AD Sandler, Jour Ped Surg, 1997
# Transplantation for Biliary Atresia

## Table 1. Liver Transplant Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n = 8), No Kasai</th>
<th>Group 2 (n = 49), Previous Kasai</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>0.7 ± 0.2</td>
<td>2.3 ± 0.4</td>
<td>.06</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>6.9 ± 0.4</td>
<td>11.6 ± 1.2</td>
<td>.07</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>3.5</td>
<td>24.25</td>
<td></td>
</tr>
<tr>
<td>Time on list (days)</td>
<td>63.3 ± 7.1</td>
<td>170.3 ± 24.6</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Deaths on list</td>
<td>0</td>
<td>6/55</td>
<td>.3</td>
</tr>
<tr>
<td>Status 1</td>
<td>2</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Status 2</td>
<td>4</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Status 3</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Status 4</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Operative time (min)</td>
<td>476.8 ± 53.3</td>
<td>593.9 ± 29.3</td>
<td>.06</td>
</tr>
<tr>
<td>Blood transfusion (mL/kg)</td>
<td>199.8 ± 46.2</td>
<td>466.0 ± 122.5</td>
<td>.1</td>
</tr>
<tr>
<td>Type of transplant, whole v reduced</td>
<td>2:6</td>
<td>19:30</td>
<td></td>
</tr>
</tbody>
</table>

AD Sandler, Jour Ped Surg, 1997
Transplantation for Biliary Atresia

[Line graph showing percent survival over time after listing for patients with Kasai and those without Kasai.]
Long-term Results of Transplant

- 45 children undergoing transplant for BA
- 79% with post-Kasai pre-transplant comps
- Survival
  - transplanted < 1 yr
    - 7 yr actuarial survival 85%
  - transplanted > 1 yr
    - 7 yr actuarial survival 88%

M Kalayoglu, Surgery, 1993
Long-term Results of Transplant

- Transplants 2001-2003
  - 77% 3 yr graft survival
  - 87% 3 yr patient survival (US)
  - 87% 3 yr survival (Denver)
Long-term Results of Transplant

- UNOS data
- Transplant for BA, 1988-2003
- 1,976 patients
- Median follow-up 4.2 years

NR Barshes, Liver Trans, 2005
Long-term Results of Transplant

- Patient survival (1, 5, and 10-year)
  - 90%, 87%, 86%
- Graft survival (1, 5, 10-year)
  - 79%, 76%, 72%
- 1 year mortality by graft type
  - 6% whole liver cadaveric
  - 7% cadaveric split-liver
  - 9% living donor
  - 16% cadaveric partial/reduced

NR Barshes, Liver Trans, 2005
When Kasai vs. Transplantation?

- 31 pts with perc liver bx
- Failure of Kasai associated with
  - syncitial giant cells
  - focal necrosis
  - bridging necrosis
  - lobular inflammation
  - cholangitis

KS Azarow, Jour Ped Surg, 1997
What is the Truth?

- **Kasai**
  - most kids fail
  - some succeed long term
  - most successes have serious complications
  - little room for improvement

- **Transplant**
  - some mortality
  - most succeed long term
  - complications
  + huge opportunity to improve
    → tissue engineering
    → immunotolerance
Thank You

Baby Liver Transplant

Dr. Kam’s Hand