Pediatric Primary Sclerosing Cholangitis and Potential Therapies

Philip Rosenthal, M.D.
Professor of Pediatrics & Surgery
University of California,
San Francisco

DISCLOSURE

- I have the following financial relationships with the manufacturers of any commercial product(s) and/or provider of commercial services discussed in this CME activity:
- Research Support from: Roche, Bristol Myers Squibb, NIH
- I am the Pediatric Principal Investigator at the UCSF Clinical Site for the STOPSC and DHHS-FDA Grant (FD-003709-01) Ursodeoxycholic Acid Therapy in Pediatric Primary Sclerosing Cholangitis: A Pilot Withdrawal/Reinstitution Trial
- Consultant for: HepaLife, Roche, Hyperion

- I do intend to discuss an unapproved/investigative use of a commercial product/device in my presentation

PSC in Children-Definition

- Chronic liver disease of unknown etiology
- Probable autoimmune process
- Irregular damage and scarring of extrahepatic and medium to large intrahepatic bile ducts
- Progresses to biliary cirrhosis

Differences: Children vs. Adults

- Cause
- Age and course
- Auto-antibodies
- Response to immunologic suppression therapy

Causes of Sclerosing Cholangitis in Children

- Immune deficiencies
- Cystic fibrosis
- Infections of bile ducts
- Autoimmune : Associated with Ulcerative colitis or Crohn's disease = 50-80%
  - 30-50%
- Primary SC

Clinical differences: Child vs. Adult

- Incidence
  - <18 years old 0.23 per 100,000
  - Adults 1.11 per 100,000
- Males = Females in young children
- Females > Males in teens
- Males > Females in adults

Symptoms of PSC in Children

- Initial Symptoms
  - Fatigue, poor appetite, nausea, weight loss, itching
  - Delayed puberty
  - Jaundice is rare
  - No symptoms-elevated liver blood tests found on testing
    - Ulcerative colitis and Crohn's disease
  - Large liver or spleen on exam
  - Gastrointestinal bleeding

Diagnosis

- Blood tests suggestive (elevated GGT)
- Imaging of bile ducts
  - Ultrasound
  - CT scan
  - Magnetic resonance cholangiography (MRCP)
  - Endoscopic retrograde cholangiography (ERCP)
- Liver biopsy
  - Look for damage to bile ducts
  - How much scarring is present?
  - Exclude other liver diseases

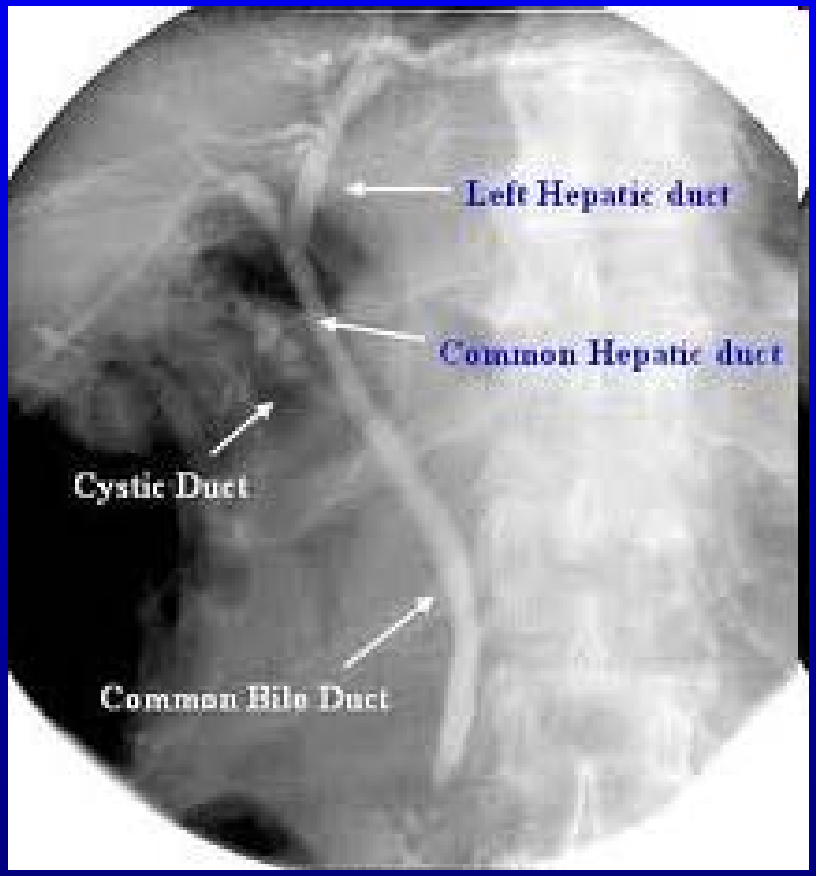
Autoimmune SC (overlap) – common in children

- Autoimmune Hepatitis (AIH)
  - Chronic liver disease
  - No bile duct injury!!!
  - Elevated IgG
  - Presence of auto-antibodies in blood
  - Characteristic appearance to liver biopsy
  - Teenage girls-most common
  - Associated with other autoimmune diseases (40%) such as IBD
  - Felt to be a true autoimmune disease

Autoimmune SC (overlap)

- ASC/overlap
  - About one third or more of PSC children present with picture of AIH (vs. 10% of adults)
  - Elevated IgG
  - Liver biopsy- AIH
  - Auto-antibodies present
    - ANA, anti-smooth muscle antibody, p-ANCA, rarely anti-LKM
  - Eventually, evidence of bile duct injury and strictures present on MRCP or ERCP

Teen with Ulcerative Colitis



AIH Normal bile ducts

8 years later- PSC with strictures

Autoimmune SC (overlap)

- Treatment Response of ASC
  - Steroids and Imuran: 70-90% normalized liver blood tests
  - Progression of bile duct injury can still happen in many

Treatment

- If ASC/AIH Overlap
  - Treat for AIH component (not done in adults)
  - Corticosteroids and Imuran (Azathioprine)
  - If normal blood tests for 1-2 years, attempt to wean off therapy if liver biopsy is normal
- Ursodeoxycholic acid: 10-20 mg/kg/day
  - No proof of long-term benefit, but improves liver blood tests and some symptoms
  - Basis for FDA study

Treatment

- Fatigue
  - Exclude low thyroid or adrenal gland function, or other autoimmune disease
  - Exclude anemia
  - Daytime somnolence
  - Did not work: fluoxetine, ondansetron
- Itching
  - Urso, rifampicin, cholestyramine, others
  - Exclude bile duct stricture that needs to be dilated
- ? Use of probiotics, Remicade, vancomycin, others

Vancomycin ?

- 14 children with PSC and IBD
- Improvement in ALT, GGT, ESR and clinical symptoms-
  - 10 normalized without cirrhosis
  - 4 improved with cirrhosis
- Concern for long-term Vancomycin use-VRE
- Not randomized- all patients had IBD, not just PSC
- Larger randomized trials in PSC with and without IBD required

Davies et al. JPGN 2008; 47;61-67

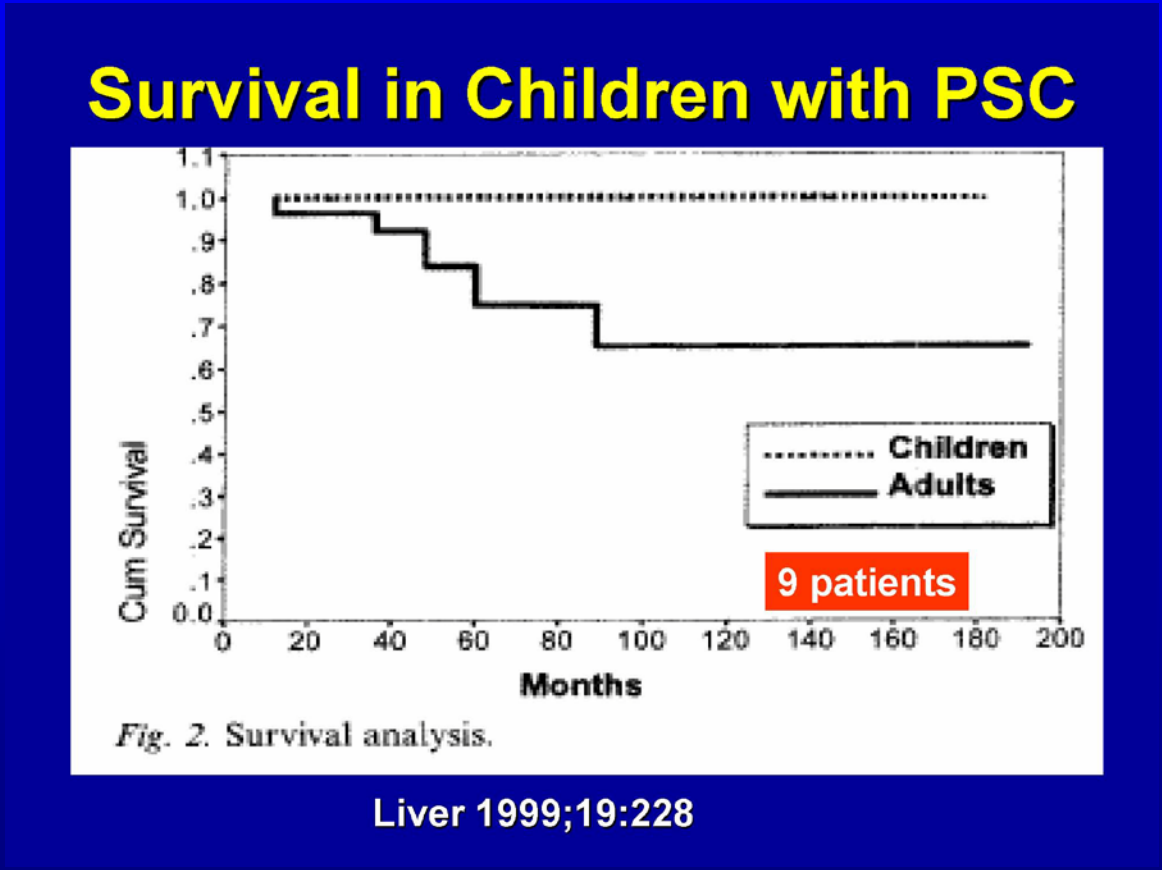
Treatment

- Complications of PSC
  - Strictures
  - Cholangitis
- Complications of Cirrhosis
  - Varices
  - Ascites
  - Fatigue
  - Others
- Bile Duct cancer exceedingly rare in children
- Liver Transplantation

Liver Transplant

- Ultimate treatment for majority, if not all, children with PSC
- Outcome very good
  - SPLIT data under evaluation
- Surveillance for colitis and its complications post-liver transplant
- Recurrent disease a concern, as in adults

Survival in Children with PSC



Liver 1999;19:228

Survival-Mayo Series

Survival – Mayo Series

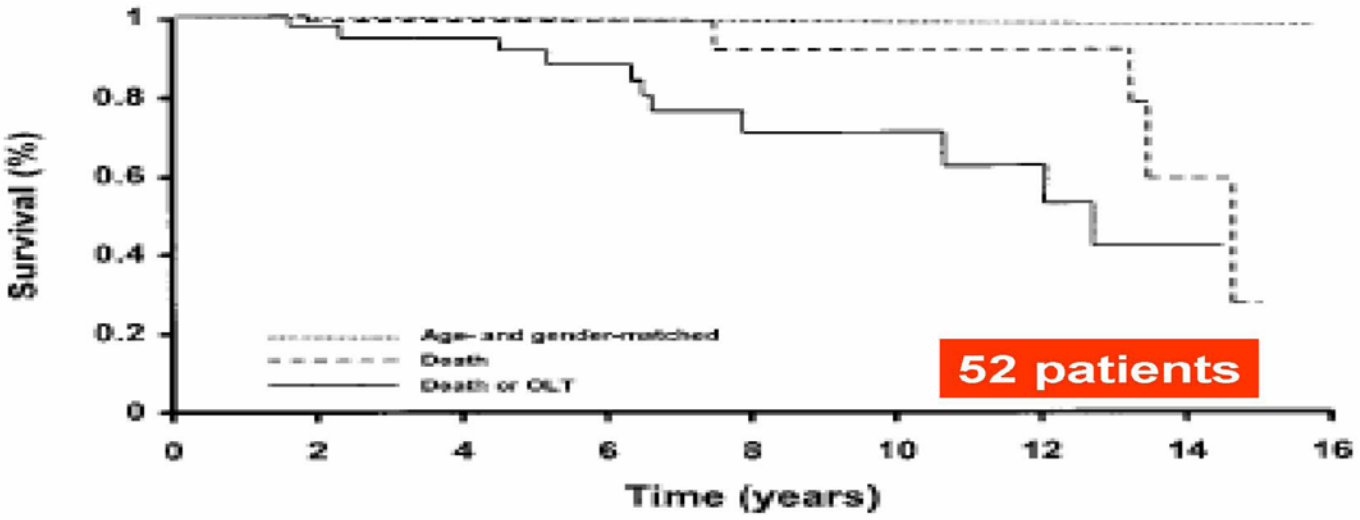


Fig. 1. Actual survival of children with PSC and the expected survival for a cohort of a U.S. Caucasian population matched by age and sex and

Hepatology 2003;38:210

Survival- PSC vs. ASC

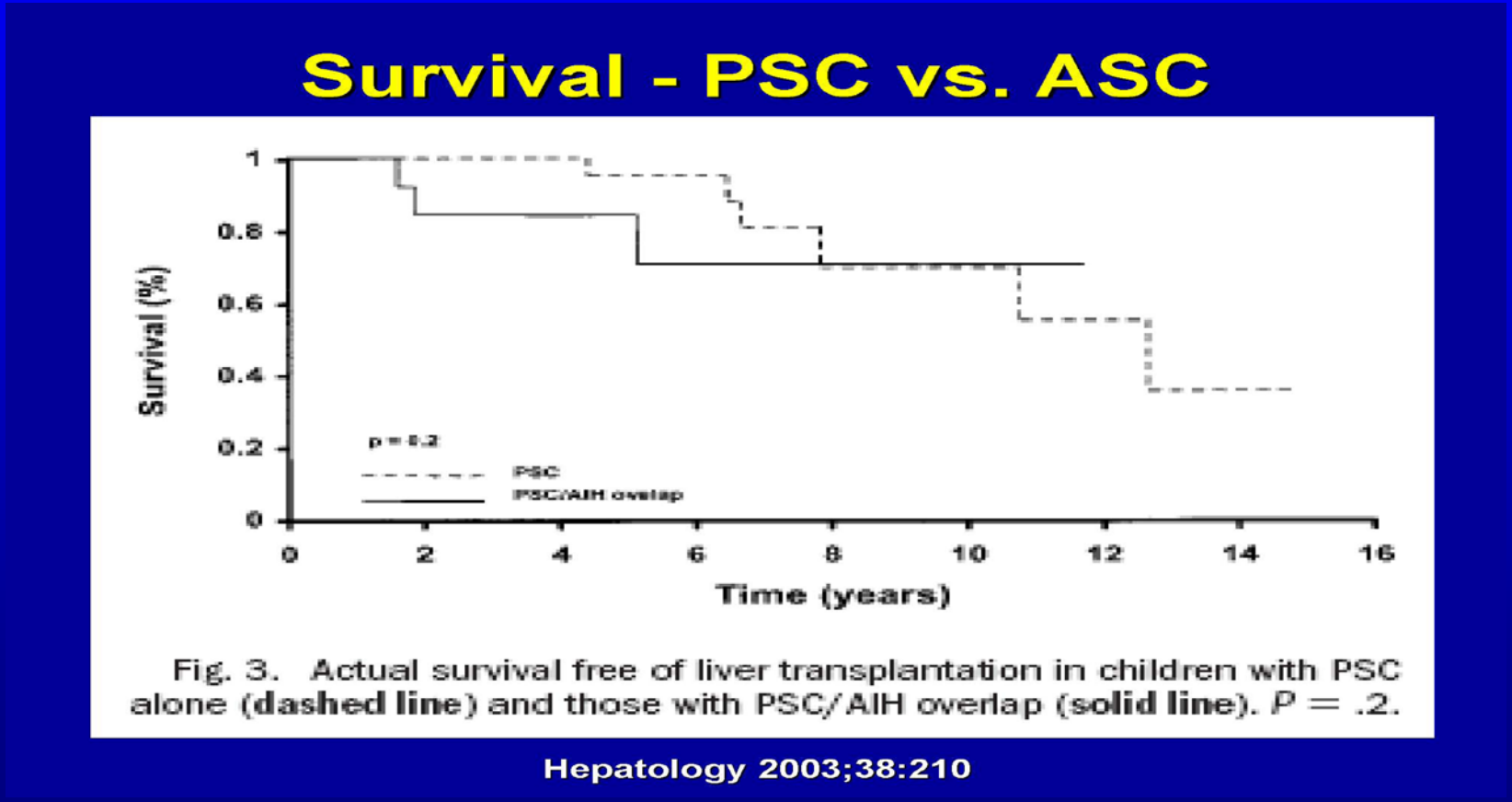


Fig. 3. Actual survival free of liver transplantation in children with PSC alone (**dashed line**) and those with PSC/AIH overlap (**solid line**). $P = .2$.

Hepatology 2003;38:210

Survival- Effect of Treatment

Survival – Effect of Treatment

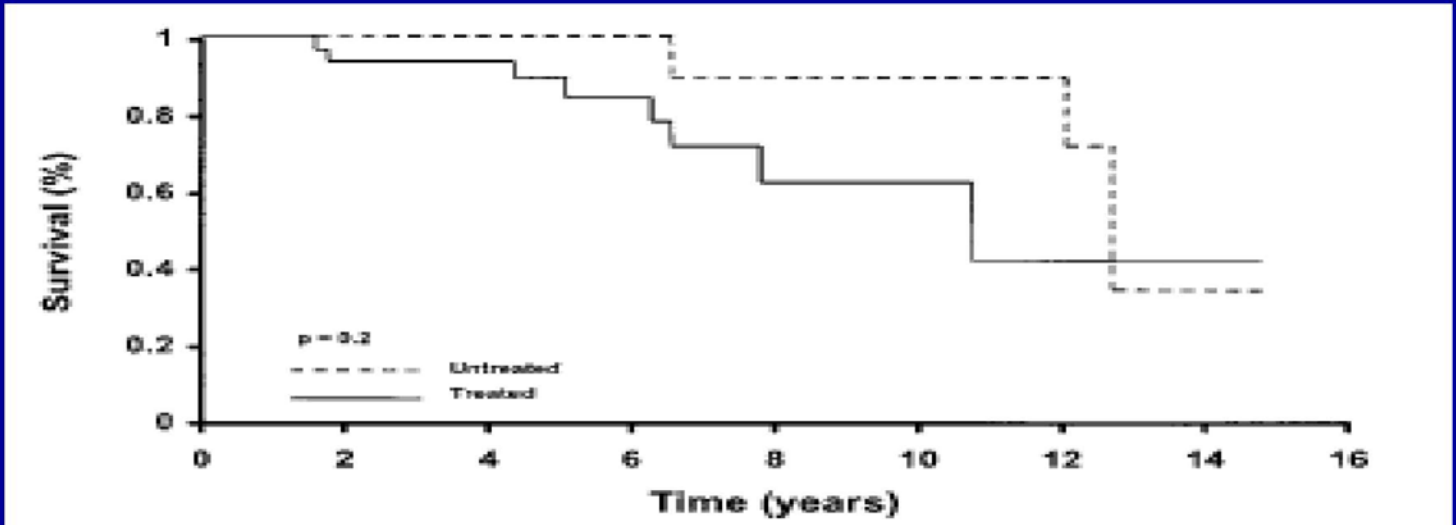


Fig. 2. Actual survival free of liver transplantation in treated (**solid line**) and untreated (**dashed line**) children with PSC. $P = .2$.

Hepatology 2003;38:210

Bottom Line-Take Home Messages

- PSC is a rare disease in children
- No controlled clinical trials in children yet performed
- Need more multi-center collaboration to learn more about cause, ASC overlap, why disease progresses, test treatments
- STOPSC study is now attempting to do this