The Alphabet Soup of Pediatric Viral Hepatitis

- Hepatitis A – dramatic vaccine success
- Hepatitis B – triumphs & tribulations
- Hepatitis C – 5M children $$$$$$$
- Hepatitis E – hopes for a vaccine??
Hepatitis A in Children

- Acute infection in children below the age of five years - asymptomatic in 80%–95%.
- 1% of cases - acute liver failure
- Half - liver transplantation or fatality
- Formalin inactivated vaccine highly effective and safe – 40,000 children
- 79% fall in acute HAV in US since the 70’s and mandatory vaccine for infants 1 year old
HAV: Remaining Challenges

- Vaccination - part of a comprehensive plan
- Improvement of overall sanitation levels
- During outbreaks of HAV, measures to assess overall immunization status and sanitation
  Countries registries re national burden of HAV.
- Cost-effectiveness analyses of relevant immunization strategies including immunity up to 25 years
HEPATITIS B AND C IN CHILDREN: THE TIP OF THE ICEBERG

ESLD, HCC < 3%

Laboratory findings

SOCIAL STIGMA
FEARS
SOCIAL ISOLATION

INFLAMMATION FIBROSIS
HBV Genotype By Birthplace – pediatric US
Transmission of HBV Infection

- Transfusion (blood, blood products)
- Fluids (blood, semen)
- Organs and tissue transplantation
- Mother to baby (Vertical)
- Contaminated needles and syringes
- Close contact to contact (Horizontal)

- Transmitted via blood or body fluids similar to HIV
- 50–100 times more infectious than HIV.

PEDIATRIC ISSUES
Pregnant women
Newborns
Breast feeding
School
Immunosuppression
Don’t ask don’t tell
SINCE 1982, MORE THAN 1 BILLION DOSES OF HEPATITIS B VACCINE HAVE BEEN ADMINISTERED TO CHILDREN WORLDWIDE
Hepatitis B Incidence, Children (<19 years) 1990-2001

Estimated cases per 100,000

<19 years


ICVH 2016 INTERNATIONAL CONFERENCE ON VIRAL HEPATITIS
Routine Hepatitis B Immunization and the Incidence of Hepatocellular Carcinoma Among Children: Taiwan

Therapy for Chronic Hepatitis B

- 1992: IFN alfa
- 1998: LAM, "The New Era"
- 2002: ADV
- 2005: ETV, PegIFN alfa-2a
- 2006: LdT
- 2008: TDF, Combination Rx?
- 2009 and beyond...
HBRN Pediatric Subcommittee

Kathleen Schwarz, Chair
Peter Lee and Doug Mogul Hopkins; Karen Murray – Seattle; Phil Rosenthal UCSF, Sarah Jane Schwarzenberg U of Minn; Jeff Teckman, SLU; Norberto Rodriguez-Baez, UTSW; Simon Ling, U of Toronto
New and important knowledge gained in children with Hepatitis B in N Am

- Largest study (n=342) of children with HBV in N America: epidemiology, natural history, and genotypes
- Median HBV DNA 158,489,319 IU/mL
- Majority (97.5%)—immigrants/born to immigrant parents
- More than half (53%) - international adoptees.
- Sizeable proportion (18.3%) - indeterminate phenotype.
- Largest study (n = 182) of antiviral drug resistance variants, basal core promoter, pre-core stop mutations
- Detailed evaluation of HRQOL revealed negative impact on parents of males
HBV: Remaining Challenges

Improve screening for HBV-infected children
Increase vaccine coverage and immunogenicity
Improve management of pregnant HBV+ females
Improve educational tools
Identify children with active disease for treatment
Understand immunology so as to develop better treatments
Global Burden of Hepatitis C
Hepatitis C in Children Around the World

• 115 M subjects globally (1.6% world’s population)
  - 11 M < 15 years
• 5 M viremic and in need of therapy
• China, Pakistan, Nigeria, Egypt, India, and Russia account for >50% of the total pediatric infections
• Prevalence varies ranging from 0.05% to 0.36% in the United States and Europe to 1.8% to 5.8% in some developing countries
• Children : adults varies from 1:25 in high income countries to 1:4 in middle-income countries, as high as 1:2 in low-income countries
Scant Attention to Pediatric Hepatitis C Means Most Children Are Left Behind

Rebecca Voelker

The great unknown in pediatric hepatitis C infection is what course the disease will take as patients mature from childhood to adolescence and into adulthood. Some will spontaneously clear the infection, while others eventually may develop liver cancer. But researchers find it difficult, if not impossible, to arrive at any conclusions about disease progression because so few children infected with hepatitis C virus (HCV) are identified early in their lives.

The Institute of Medicine made the case in a January report for stepped-up surveillance of hepatitis B and C infection, but a recent study highlights the particular inadequacies in diagnosing and treating children and teens infected with hepatitis C. “There’s a frightening lack of awareness among both the public and clinicians about hepatitis C virus infection in pediatric patients,” said lead author Armin

Applying the national 0.3% prevalence rate, the researchers calculated that Florida would have 12,155 cases of pediatric hepatitis C infection. But a state database contained 1,755 unique States; it’s not just specific to Florida,” said Philip Rosenthal, MD, director of pediatric hepatology at the University of California, San Francisco, School of Medicine. “This is underappreciated within the pediatric community.”

Usually, adults are infected through contact with contaminated blood. Transfusions prior to 1992 (when screening of the blood supply began), injection drug use, and needlesticks in health care settings are common transmission routes. But Rosenthal, who was not involved with the study, said most children acquire the infection through maternal neonatal transmission. “The majority of the time, the child looks well,” he said. “If you don’t ask about risk factors, then [HCV] is not even going to be on the radar screen.”

Of approximately 3.2 million individuals living with HCV in the United States, an estimated 240,000 are children, said John Ward, MD, director of the division of viral hepatitis at the Centers for Disease Control and Prevention.

Expected and Actual Case Ascertainment and Treatment Rates for Children Infected with Hepatitis C in Florida and the United States: Epidemiologic Evidence from Statewide and Nationwide Surveys

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Objective To evaluate the rate of pediatric hepatitis C virus (HCV) case ascertainment relative to the estimated number of actual cases.

Study design Data from Florida and United States health departments were used to assess pediatric HCV case ascertainment rates in Florida and nationwide. The percentage of children infected with HCV from Miami-Dade County receiving medical care by a pediatric gastroenterologist was estimated based on data obtained from physician questionnaires.

Results From 2000 through 2009, 2007 children were identified as having positive HCV antibody tests in Florida, only 12% of the expected number (n = 12 155). An estimated 1.6% of the expected children with HCV who tested Ab-positive (37 of 1935) were actively followed by a pediatric gastroenterologist in Miami-Dade County, Florida. Across the United States, only 4.9% of the expected cases have been identified.

Conclusions The identification of children infected with HCV in the nation as a whole is grossly inadequate. Only a small fraction of cases are identified. In Florida, less than 2% of children identified receive treatment. Lack of identification and lack of treatment of children infected with HCV constitute critical public health problems. Strategies to increase awareness of HCV infection and to screen at-risk individuals could substantially improve morbidity and mortality while reducing health care costs. (J Pediatr 2012; □:□ - □).
Newly reported cases of HCV infection

Rate per 100,000 population

All age groups

Ages 15-24 yrs

Most common risk factor = IDU

MMWR 60:537, 2011
Potential Routes of Acquisition of Hepatitis C in Children

a. Maternal-infant
   » Intra-uterine
   » Intra-partum
   » Post-natal
b. IV Drug Abuse
   c. Intrafamilial (?)
   d. Post-transfusion (despite screening)

No means of prevention yet!!
Perinatal Transmission of HCV

Maternal viremia

- Prolonged duration of membrane rupture (>6 hrs)
- Infection of maternal PBMC's
- History of IVDU
- Sexual partner of mother also HCV infected

Female sex

- Invasive internal fetal monitoring
- Coinfection with HIV
- HLA antigen class II compatibility (Mother & Child)
- Elevated AST (last yr before pregnancy and at delivery)

Outcome of Perinatal HCV Infection

• Recovery from perinatal HCV infection unlikely
• *Patients asymptomatic*
• Chronic hepatitis in most
• Histology variable (several studies)
What about children?

Only One FDA approved option
5 year follow in the PEDS C study – 100% of children who cleared HCV RNA 5 years ago are still HCV-free!!
Open-Label, Multicenter, Multi-cohort, Single-Arm Phase 2 Trials

1. Investigate Safety & Efficacy of Sofosbuvir + Ribavirin in Children With Genotype 2 or 3 Chronic HCV infection  
   NCT02175758

2. Investigate Safety & Efficacy of Sofosbuvir + Ledispavir in Children With Genotype 1 Chronic HCV infection  
   NCT02249182

3. Open-Label Study - Pharmacokinetics, Safety, and Efficacy of Ombitasvir, Paritaprevir, Ritonavir +/- Dasabuvir +/- Ribavirin in Genotype 1 or 4
HCV: Remaining challenge$$

- Interruption of maternal-fetal transmission
- Developing an effective vaccine
- Detecting HCV in high risk children
- Using Peg/ribavirin for those who might benefit most
- Getting FDA approval of safe effective DAA’s for children
- Figuring out whom to treat and how to pay for it
Hepatitis E
HEV: Remaining challenges

• Global safe and effective HEV vaccine?
• Who should receive it?
• How long will the neutralizing protective antibodies last?
• Dramatic effect on global disease burden?