Viral Hepatitis
What’s new in Children?

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## Conflict of Interest Disclosure: Dr. Karen Murray

<table>
<thead>
<tr>
<th>Commercial or Non-Profit Interest</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilead</td>
<td>Research Support, DMC member</td>
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<tr>
<td>Shire</td>
<td>Research Support</td>
</tr>
<tr>
<td>Merck</td>
<td>Stockholder</td>
</tr>
<tr>
<td>NIH</td>
<td>Research Support</td>
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</table>
### CanMEDS Roles Covered

<table>
<thead>
<tr>
<th>Role</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Expert</strong></td>
<td>As <em>Medical Experts</em>, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. <em>Medical Expert</em> is the central physician Role in the CanMEDS Framework and defines the physician’s clinical scope of practice.</td>
</tr>
<tr>
<td><strong>Communicator</strong></td>
<td>As <em>Communicators</em>, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.</td>
</tr>
<tr>
<td><strong>Collaborator</strong></td>
<td>As <em>Collaborators</em>, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.</td>
</tr>
<tr>
<td><strong>Leader</strong></td>
<td>As <em>Leaders</em>, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.</td>
</tr>
<tr>
<td><strong>Health Advocate</strong></td>
<td>As <em>Health Advocates</em>, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.</td>
</tr>
<tr>
<td><strong>Scholar</strong></td>
<td>As <em>Scholars</em>, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.</td>
</tr>
<tr>
<td><strong>Professional</strong></td>
<td>As <em>Professionals</em>, physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.</td>
</tr>
</tbody>
</table>
Hepatitis B in Children

Some slides adapted from those of Dr. Gonzalez-Peralta
Burden of HBV: United States

New cases of HBV infection

- 1.25 million HBV carriers
- 3,000 deaths annually
- 22,000 HBV (+) women deliver every year
Screening for Chronic HBV Infection in Children

- Children born in countries endemic for HBV
- Children born in the US to immigrant parents from endemic areas
- Infants born to HBsAg+ mothers
- Children living with an HBsAg+ individual
  - Including children who received hepatitis B vaccine after birth who were not screened before vaccination

### HBV Genotypes in US-Canada

<table>
<thead>
<tr>
<th>HBV genotype</th>
<th>Children (n=230)</th>
<th>Adults (n=1615)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5%</td>
<td>18%</td>
</tr>
<tr>
<td>B</td>
<td>43%</td>
<td>39%</td>
</tr>
<tr>
<td>C</td>
<td>32%</td>
<td>33%</td>
</tr>
</tbody>
</table>

Children with B/C compared to others:
- Asian
- HBeAg positive
- Higher HBV DNA levels
- Less ALT elevations

Can we Prevent Vertical HBV Transmission?

- Delivery mode, breast feeding: NO effect
- Vaccine+HBIG: from 90% to 10%
- Nucleos(t)ide analogues?
- Systematic review
  - 26 studies
  - N=3,622 pregnant women
  - HBV DNA > 4.3x10^7 IU/mL
  - LAM, Telbivudine, TDF

Reduced Transmission (12 mo):
- HBsAg: 17% → 4%
- HBV DNA: 27% → 8%

No effect:
- congenital malformation
- prematurity
- Apgar scores

Preventing Vertical HBV Transmission

Infant serology

Chang K-C et al, AASLD 2017
90% of young children infected become chronically infected
HBV Treatment in Children
HBV Treatment Goals in Children

- Decrease chronic liver disease
- Reduce viral replication
- Eliminate stigma

HBV DNA suppression
HBeAg loss/HBeAb conversion
HBsAg loss/HBsAb conversion
Who to treat?

- **Immune Tolerance**
  - HBeAg (+)
  - HBV-DNA: >2,000 IU/mL
- **Immune Reactive**
  - HBeAg (+)
  - HBV-DNA: >2,000 IU/mL
  - ALT: HBeAg (+) hepatitis
- **Inactive infection**
  - HBeAg (-)
  - HBV-DNA: >20,000 IU/mL
  - ALT: Inactive (carrier)
- **Immune escape Reactivation**
  - HBeAg (-)
  - HBV-DNA: >20,000 IU/mL
  - ALT: HBeAg (-) hepatitis

AASLD, Hepatology 2015
ESPGHAN, J Hepatol 2013
<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon-α2b</td>
<td>≥ 1 year</td>
<td>5-10 MU SQ TIW x 6 mo</td>
</tr>
<tr>
<td>Entecavir</td>
<td>≥ 2 years</td>
<td>0.015 mg/kg PO QD (+6 mo after HBeAb conversion)</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>≥ 3 years</td>
<td>3 mg/kg PO QD x ≥ 1 year</td>
</tr>
<tr>
<td>Adefovir</td>
<td>≥ 12 years</td>
<td>10 mg PO QD ≥ 1 year (+6 mo after HBeAb conversion)</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>≥ 12 years</td>
<td>300 mg PO QD x ≥ 1 year</td>
</tr>
</tbody>
</table>

Haber, et al. *Pediatrics* 2009

ESPGHAN, *J Hepatol* 2013
HBV Treatment in Children

Treatment of Immune Tolerant HBV?

- **Immune Tolerance**
  - HBeAg (+)
  - HBV-DNA
  - ALT

- **Immune Reactive**
  - HBeAg (+) hepatitis

- **Inactive infection**
  - Inactive (carrier) state

- **Immune escape Reactivation**
  - HBeAg (-) Hepatitis

Slide adapted from Peters, M. IVHC 2011
HBV Treatment: Immune Tolerant

Study Group (n=60)
Age: 10.9 (3.4-17.9) yrs
Asians: 90%
ALT <40 IU/ml
HBV DNA: 170 x10^6 IU/mL

Results

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Completed trial</td>
<td>55 (92%)</td>
</tr>
<tr>
<td>HBeAg loss</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>HBV DNA (&lt;1,000 U/mL)</td>
<td></td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>2 (3%)</td>
</tr>
</tbody>
</table>

Rosenthal, et al. AASLD 2017

ClinicalTrials.gov Identifier: NCT02263079
• Treatment for HBV in children is improving, but still limited
• Pediatric viral hepatitis research and trials are imperative to advance care
• Careful selection of children to be treated is important, with attention to potential duration and outcomes
• The future for children with HBV is bright
Hepatitis C in Children
Chronic Hepatitis C in Children

HCV Antibody positivity in North America:
- 0.2% of 6-11 year olds (31,000)
- 0.4% of 12-19 year olds (101,000)

Chronic HCV infection:
- 0.1-2% of all children
- 1.3% children >6 years old in USA

Mack et al. NASPGHAN Practice Guidelines. JPN 2012;54:838-55
Zou et al. Can J Gastroenterol 2000;14:575-80
HCV Infection in Children: Transmission and Clearance

- ~5% of infants are born to HCV-RNA positive women
- Vertical transmission accounts for most pediatric HCV (>60% in most studies)
- Spontaneous clearance of HCV-RNA (vertically acquired):
  - 25-40% of infants by 2-3 years (highest with genotype 3)
  - 6-12% of children up to 7 years

Granot and Sokal. *IMAJ* 2015;17:707-11
Bortolotti et al. *Gastroenterology* 2008;134:1900-7
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Patients</th>
<th>Inflammation</th>
<th>Fibrosis</th>
<th>Steatosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kage et al.⁴</td>
<td>1997</td>
<td>Japan</td>
<td>109</td>
<td>Less than adults</td>
<td>4% bridging</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Badizadegan et al.⁵</td>
<td>1998</td>
<td>US</td>
<td>40</td>
<td>Generally mild</td>
<td>44% bridging</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8% cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Guido et al.⁶,⁸,⁹</td>
<td>1998</td>
<td>Italy/Spain</td>
<td>80*</td>
<td>Generally mild</td>
<td>16% bridging</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.2% cirrhosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>Italy/Spain</td>
<td>112*</td>
<td>–</td>
<td>26% bridging</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.9% cirrhosis</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>Italy/Spain</td>
<td>66*</td>
<td>–</td>
<td>–</td>
<td>27%</td>
</tr>
<tr>
<td>Fujisawa et al.⁷</td>
<td>2000</td>
<td>Japan</td>
<td>49</td>
<td>Generally mild</td>
<td>20% bridging</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Mohan et al.¹⁰</td>
<td>2007</td>
<td>US</td>
<td>42</td>
<td>Generally mild</td>
<td>12% bridging</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Goodman et al.</td>
<td>2007</td>
<td>US</td>
<td>121</td>
<td>Less than adults</td>
<td>4.2% bridging</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.7% cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Schwarz et al.</td>
<td>2011</td>
<td>US</td>
<td>114</td>
<td>Less than adults</td>
<td>4% bridging</td>
<td>2% cirrhosis</td>
</tr>
<tr>
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</table>
Impact of Childhood Chronic HCV on Quality of Life

HCV in adults is strongly associated with decrements in:

(compared to healthy controls and patients with other types of liver disease)

- quality of life (QOL)
- cognitive performance (attention and higher executive functioning)
- psychological functioning (anxiety and depression)

HCV in children (19 subjects) compared to healthy children:

- greatest decrease in Global health and parental emotional impact
- children reporting reduced physical functioning despite being “asymptomatic”
- parents increasingly concerned about their child’s future health

Younossi et al. Hepatology 2007;45:806-16
Spiegel et al. Hepatology 2005;41:790-800
Nydegger et al. J Gastroenterol Hepatol 2008;23(2):226-30 (n=19)
Impact of Childhood Chronic HCV on Quality of Life

- 114 children 10.7 years (mean, SD 3 years)
- Caregivers: 46 +/- 7 years
  39% biological mothers HCV+
- Tools:
  - Child Health Questionnaire-Parent Form 50
  - Behavior Rating Inventory of Executive Functioning
  - Child Behavior Checklist
  - Children’s Depression Inventory
  - SF 36 Health Survey
- Comparison populations:
  - normative data from the U.S. general population
  - children with other chronic conditions (ADHD, evaluated for transplantation)

Rodrique et al. *JPEN* 2009;48:341-7
Impact of Chronic HCV on Child’s Quality of Life

- QOL, Cognitive, Behavioral, and Emotional functioning not globally impaired in children with HCV
- Symptoms of stress, depression, and anxiety not pervasive in children and adolescents with HCV
- Executive function impairments in 20% of infected children: planning, organizational skills, and inhibiting own behaviors
- Children with HCV had worse cognitive functioning than the normative sample, but better functioning than children with ADHD

Rodrique et al. JPGN 2009;48:341-7
Nydegger et al. J Gastroenterol Hepatol 2008;23:226-30 (n=19)
Impact of Childhood Chronic HCV on Caregiver Quality of Life

• Overall, primary caregivers do not experience decrements in QOL

• HCV-infected mothers had compromised QOL compared with non-infected caregivers

• Caregivers of HCV-infected children reported significantly higher stress and concern over their child’s health, belief that it would deteriorate, and negative impact on the functioning of the family.

Rodrique et al. *JPGN* 2009;48:341-7
Guidelines suggest at least annual clinical and biochemical evaluation for:

- advancing liver disease
- HCC
- selective liver biopsy for treatment guidance if treatment is debated
- education

However... Options for successful treatment are increasing substantially, so that ALL children should be considered for treatment.
HCV Treatment in Children
Chronic HCV in Children: Approved Treatments

- Interferon + Ribavirin
- Pegylated-Interferon a2b + Ribavirin  2008, >3 years
- Pegylated-Interferon a2a + Ribavirin  2011, >5 years

- Sofosbuvir + Ledipasvir for GT1
- Sofosbuvir + Ribavirin for GT 2 and 3

  Approved April 7, 2017  for >12 years or 35 Kg
# Studies of Direct Acting Antivirals in Children

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Genotype (n)</th>
<th>Treatment (weeks)</th>
<th>Age (years)</th>
<th>SVR12 (n, 12-17 year olds)</th>
<th>SVR12 (n, 6-11 year olds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + Ledipasvir</td>
<td>1 (100)</td>
<td>12</td>
<td>3-17</td>
<td>98% $ (98/100, 2 lost to follow-up)</td>
<td>99% * (86/87, 1 relapse)</td>
</tr>
<tr>
<td>Sofosbuvir + Ribavirin</td>
<td>2 (13) 3 (37)</td>
<td>12 24</td>
<td>3-17</td>
<td>100% # 97% (36/37, 1 lost to follow-up)</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir + Velpatasvir</td>
<td>1-6</td>
<td>12</td>
<td>3-17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ombitasvir + Paritaprevir + Ritonavir +/- Dasabuvir +/- Ribavirin</td>
<td>1 4</td>
<td>12 24 (cirrhosis)</td>
<td>3-17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glecaprevir + Pibrentasvir</td>
<td>1-6</td>
<td>8-16</td>
<td>3-17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$ World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition, 2016
# AASLD 2016
* EASL 2017
Viral Hepatitis in Children: Summary

- Both HBV and HCV are Global Health problems for children
- Treatments for both viral infections are improving, although for HBV remains suboptimal
- Continuing to advance research in and for children is imperative
- Providing all children with the best available treatments is necessary and the right thing to do
- The future is bright for children with viral hepatitis
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