Hepatitis B & C: Treatment in Children
(I will cover some diagnosis and prevention too...)

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Faculty Disclosure Information

• In the past 12 months, I have had the following financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial service(s) discussed in this CME activity:
  – Consulting for Dynavax

• I have relationships with these entities for activities unrelated to the content of this presentation:
  – Consulting for AstraZeneca, Seqirus
  – Editorial stipend from Elsevier

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

• Review Hepatitis B treatment strategies in children

• Discuss research opportunities to enhance elimination of HBV

• Review Hepatitis C treatment strategies in children

• Discuss research opportunities to enhance elimination of HCV
Hepatitis B in Children
Prototype case #1

• 12 y.o. female of Asian descent presents for initial evaluation

• Mother has chronic HBV infection and is on therapy

• Child received HepB vaccine/HBIG at birth, full 3-dose vaccine series but still got infected

• Growth, Development and Physical Exam are completely normal

• Normal AST/ALT, HBsAg+, HBeAg+, HBV DNA >10 million IU/ml
Key questions

• Does this child need to be treated now? Or later? Or ever?

• If yes, what is our endpoint?

• What agent(s) is/are best?
Hepatitis B-treatment

• Most children are in what is called the “immune tolerant” phase
  – Very high HBV DNA levels (>10 million) but no symptoms, no immune activity
  – Can achieve some level of suppression of virus, but to what end given possibility of resistance and lack of immune participation
  – Most children do okay if left alone
  – **Untreated, these children could transmit HBV to susceptible individuals**
Hepatitis B-treatment

• Current strategies focus on treatment once patients progress into Immune Clearance phase

  – Occurs as early as teens and as late as 30’s

  – Essentially the immune system “wakes up” to the presence of HBV and begins to target infected hepatocytes

  – Damage leads to increased AST/ALT

  – HBV DNA levels may fluctuate, anti-HBc IgM may reactivate
Hepatitis B-treatment

• Several options:
  – 1st line: **Tenofovir**
    • nucleotide analog with most potency, low rate of resistance thus far
  – Other agents available:
    – Entecavir
    – Adefovir
    – **Interferon-α**
      • Pegylated form is preferred with better PK
    – Lamivudine
Going back to our case #1...

- Plan would be an initial evaluation and baseline risk assessment
  - AFP, liver ultrasound
  - Document Hepatitis A immunity/vaccination

- Annual visits to monitor liver enzymes, HBV DNA, HBeAg, HBeAb

- Intervene with antiviral therapy when liver enzymes >2x normal and/or new symptoms of hepatitis
- OR in the future if/when she becomes pregnant

- Observe decrease in HBV DNA and hope for HBeAb seroconversion (continue min 1 year)
Research Gaps: HBV treatment in Children

• What regulates transition from “Immune Tolerant” to “Immune Active”?

• Can we influence this transition to create treatment opportunities?
  – Somewhat similar to “shock and kill” strategies for HIV cure efforts

• What about alternative treatment strategies?
  – Combination anti-viral agents
  – Novel immunomodulators plus anti-virals
  – A novel gene editing strategy to excise or destroy the cccDNA from infected hepatocytes?
Prototype case #2

• 6 y.o. child presents with several week history of bloody diarrhea and is ultimately diagnosed with Inflammatory Bowel Disease

• Prior to the initiation of anti-TNF therapy, serologic studies demonstrate that this patient has no detectable HBsAb (<10 mIU/ml)

• Patient has a history of prior 3-dose series
• The first 2 doses of a planned 3-dose series are administered, and the patient still has no detectable antibodies

• What do you do now?
Hepatitis B vaccine non-responder options

• A significant minority of patients do not respond to a full repeat 3-dose series
  ⚫ We deal with this often in our GI/Rheum patients and pre-transplant evaluation patients

• My personal recommendations to consider for this group:
  ⚫ Double dose of HBV vaccine (sort of on label)

  ⚫ Combined HAV-HBV vaccine (not FDA approved for children under 18 y.o.; approved in other countries for younger children with an excellent safety profile)

  ⚫ Adjuvanted HBV vaccine (FDA approved for those 18 y.o. and over; some data from adolescents in their pre-clinical studies; still largely untested in children)
Research Gaps: HBV vaccine responses in Children

- More research to define robust antibody responses to HBV vaccine
- Research to define and test for cellular protection against HBV independent of antibody
- Prioritizing and incentivizing research in children with other versions of vaccine
- Funding of pragmatic studies to determine the relative efficacy of current “off-label” approaches I mentioned
- To reach our elimination goal, 90% response is not good enough...we have to keep trying to do better
Hepatitis C in Children
Prototype case #3

• 5 m.o. infant comes to see you in the outpatient clinic

• Recently adopted from southern part of Illinois

• Birth mother was known to have HCV infection and substance abuse

• Adoptive mother asks you about testing and possible treatment
Recommendations for testing infants for HCV

• Prior recommendation was to use HCV Ab testing after 18 months

• This strategy led to 90% infants never getting tested and being lost to follow up

• People wanted to use PCR, but were unsure when to test
  – Our HCV guidance panel recommended 2-6 months as a practical window

• Now we have data to suggest this is a sound recommendation

Kuncio et al, CID 2016; Chappell et al, Pediatrics 2018; Lopata et al Pediatrics 2020
Recommendations for testing infants for HCV

- Group tested 750 infants exposed to HCV using HCV RNA between 2-6 months.

- All of the children tested with HCV RNA who were positive had follow up PCR testing that was positive.

- All of the children who had negative HCV RNA testing who were tested later all had negative HCV RNA.
  - Many never had follow up testing.

Table 1. Diagnostic Performance of HCV-RNA RT-PCR in Perinatally Exposed Infants Age 2-6 Months

<table>
<thead>
<tr>
<th>Point Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity, (%)</td>
<td>100</td>
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<tr>
<td>Specificity, (%)</td>
<td>100</td>
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<tr>
<td>Positive likelihood ratio</td>
<td>—</td>
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<tr>
<td>Negative likelihood ratio</td>
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<tr>
<td>Assume 5.8% prevalence</td>
<td>100</td>
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<tr>
<td>Positive predictive value, (%)</td>
<td>100</td>
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<tr>
<td>Negative predictive value, (%)</td>
<td>100</td>
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</table>

https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa949/5868931
Testing of HCV exposed infants

Current guidance from AASLD/IDSA:

“Testing with an HCV RNA assay can be considered as early as 2 months of age.”

AAP Red Book recommendation is now harmonized with this language.

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HCV in Children

Testing

<table>
<thead>
<tr>
<th>Recommendations for HCV Testing of Perinatally Exposed Children and Siblings of Children With HCV Infection</th>
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</thead>
<tbody>
<tr>
<td>RECOMMENDED</td>
</tr>
<tr>
<td>All children born to HCV-infected women should be tested for HCV infection. Testing is recommended using an antibody-based test at or after 18 months of age.</td>
</tr>
<tr>
<td>Testing with an HCV-RNA assay can be considered in the first year of life, but the optimal timing of such testing is unknown.</td>
</tr>
<tr>
<td>Testing with an HCV-RNA assay can be considered as early as 2 months of age.</td>
</tr>
</tbody>
</table>

www.hcvguidelines.org/unique-populations/children
Going back to our case #3

- You send HCV RNA at this visit and it shows 100,000 copies
- Adoptive mom asks you about treatment for this infection
- What are your options? How young can you start treatment?
Basic principles for treating children with HCV

• We do not treat anyone younger than 3 y.o.
  – Those younger still have a window for spontaneous clearance, even with high-level viremia

• Rationale for treatment is less about avoiding worst liver outcomes
  – Studies do show that treatment of children is cost-effective

• Ability of curing infection, eliminating future transmission events and avoiding stigma at school are all powerful reasons

Greenaway et al, J Peds 2021; Nguyen et al, J Peds 2019
Hepatitis C-Treatment

• As of June 2021, both pan-genotype regimens now approved for children as young as 3 y.o.
  - Sofosbuvir/Velpatasvir (Epclusa®-Gilead)
  - Glecaprevir/Pibrentasvir (Mayret®-Abbvie)

• Once daily, all oral regimens with nearly 100% cure rate make treatment pretty easy now
  - no liver biopsy needed
  - Microcapsule formulation for children can be mixed with thicker foods to administer (Nutella good, apple sauce bad!)

• www.HCVguidelines.org is a great resource
  - Specific page for children under “unique populations”
Research Gaps-HCV in infants and children-1

- Paucity of data on serial testing with current HCV RNA real-time assay to precisely define optimal testing window

- No studies with other testing methods (combined Ag/Ab assay) in infants and children

- Studies to demonstrate how HCV testing can be integrated with mother’s care
  - Co-opting model that is so successful for HIV
Research Gaps-HCV in infants and children-2

• Poor understanding of the transition from acute infection to chronic infection in infants

• Research to ensure that health systems/insurers around the country can provide medication to children when prescribed
Prototype case #4

- 16 y.o. male is admitted to the hospital after a recent drug overdose
- He has sought outpatient treatment for his drug use without much progress
- In the hospital, he tests positive for HCV Ab and his HCV RNA is 350,000 copies
- He states that he has been using for about 1.5 years, seen a few doctors along the way, including his PMD and his substance use specialist
- He was never previously screened for HCV....
Hepatitis C - Epidemiology

- Driven by widespread opioid use, HCV has transitioned from an infection primarily in Baby Boomers to one seen in young adults
  - Prior age-based screening only captured right half of peak
  - Many young adult cases were being missed
  - Adolescent cases are not zero!

https://www.cdc.gov/mmwr/volumes/69/wr/mm6914a2.htm?s_cid=mm6914a2_w
Universal Screening for HCV in adults

- All adults should be tested for HCV at least once
- Per CDC, pregnant women should be tested with each pregnancy
- Adolescents not included in these recommendations except based on risk...

Box 1. Persons recommended for hepatitis C testing

- Universal hepatitis C screening:
  - Hepatitis C screening at least once in a lifetime for all adults aged ≥18 years, except in settings where the prevalence of HCV infection (HCV RNA-positivity) is <0.1%
  - Hepatitis C screening for all pregnant women during each pregnancy, except in settings where the prevalence of HCV infection (HCV RNA-positivity) is <0.1%

- One-time hepatitis C testing regardless of age or setting prevalence among persons with recognized risk factors or exposures:
  - Children born to mothers with HCV infection
Increasing Prevalence of Hepatitis C among Hospitalized Children Is Associated with an Increase in Substance Abuse

A. Sidney Barritt, IV, MD, MSCR¹, Brian Lee, MPH, PhD², Thomas Runge, MD, MPH¹, Monica Schmidt, MPH, PhD³, and Ravi Jhaveri, MD¹

Objective To evaluate the impact of substance abuse on pediatric hepatitis C virus (HCV) prevalence, we examined geographic and demographic data on inpatient hospitalizations in children with HCV.

Study design We examined hospitalizations in children using the Kids’ Inpatient Database, a part of the Healthcare Cost and Utilization Project. We identified cases using the International Classification of Diseases, 9th edition, codes for HCV infection during 2006, 2009, and 2012. Nonparametric tests for trend were used to calculate trend statistics.
<table>
<thead>
<tr>
<th>Predictors of substance abuse in inpatient pediatric patients</th>
<th>OR</th>
<th>Lower CL</th>
<th>Upper CL</th>
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<td>3 1.01</td>
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<td>0.71</td>
<td>1.64</td>
<td>.713</td>
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</tbody>
</table>

Bold indicates subgroup with significant difference in statistical analysis.
Including 15 y.o in screening is cost-effective
Including 15 y.o in screening is cost-effective
Elimination goals

• If we truly want to eliminate HCV in the US, we need to include adolescents 15-18 y.o. in our universal screening recommendations

• Need to study innovative ways to reach this population:
  – Fingerstick when they get their driver’s license
  – Fingerstick when they present for their HS sports physicals
  – Other ways?
Thank you for your attention.

Questions? Comments?