Disclosures

• Research Support: Centers for Disease Control and Prevention; Cancer Prevention Research Institute of Texas

• Consultant: Novovax
Objectives

• Describe the epidemiology and natural history of Hepatitis B virus (HBV) infection in infants
• Outline the modes of acquisition of perinatal HBV
• Describe currently recommended preventative strategies for perinatal HBV
• Briefly describe therapeutic options for infants infected perinatally
Perinatal HBV: Natural History
Hepatitis B

• Most common form of chronic hepatitis worldwide

• Potentially preventable global health problem

• World Health Organization (WHO) estimates that
  - More than 2 billion individuals have been infected
  - 360 million are chronically infected
    • maternal to child infections (perinatal) account for one third of these
  - 600,000 deaths annually from HBV-related complications
HBV: Structure

- 42-nm double stranded DNA hepadnavirus
- Nucleocapsid core (HBcAg) and a viral envelope (HBsAg)
- Eight genotypes (A-H) and 2 provisional genotypes (I, J) have variable prevalence and differences in severity
HBV Serology: Acute Infection with Recovery

- HBeAg*: Hepatitis B e antigen.
- anti-HBe: Antibody to HBeAg.
- Total anti-HBc$: Antibody to hepatitis B core antigen.
- HBsAg: Hepatitis B surface antigen.
- IgM** anti-HBc: Immunoglobulin M.
- anti-HBs: Antibody to HBsAg.

Titer vs. Postexposure (wks)
Incidence of Acute, Symptomatic Hepatitis B — United States, 1982–2008

1991 Universal vaccination of infants recommended

Source: National Notifiable Diseases Surveillance System (NNDSS)

Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)
Acute HBV: Clinical Features

• Development of symptoms is age dependent:
  - < 1% of infants < 1 year
  - 5-15% of children 1-5 years
  - 30-50% of people > 5 years

• Subacute illness: anorexia, nausea, or malaise

• Clinical hepatitis with jaundice
Acute HBV: Clinical Features during Pregnancy

- Does not increase mortality
- Does not increase rate of teratogenic effects
- Higher rate of low birth weight
- Higher rate of prematurity
- In infected early, 10% rate of perinatal transmission
- Rate of transmission increases according to gestation infected
HBV Serology: Acute Infection with Progression to Chronic Infection

* Hepatitis B e antigen.
† Antibody to HBeAg.
§ Antibody to hepatitis B core antigen.
¶ Hepatitis B surface antigen.
** Immunoglobulin M.
# HBV Serology Interpretation

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>HBsAb</th>
<th>HBcAb</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Neg</td>
<td>Pos</td>
<td>Pos</td>
<td>Immune after natural infection</td>
</tr>
<tr>
<td>Neg</td>
<td>Pos</td>
<td>Neg</td>
<td>Immune after vaccine</td>
</tr>
<tr>
<td>Pos</td>
<td>Pos</td>
<td>Pos (IgM +)</td>
<td>Acute infection</td>
</tr>
<tr>
<td>Pos</td>
<td>Neg</td>
<td>Pos (IgM -)</td>
<td>Chronic infection</td>
</tr>
</tbody>
</table>
| Neg   | Neg   | Pos         | • Resolved infection  
                                      • False-positive  
                                      • “Low level” chronic infection  
                                      • Resolving acute infection     |
Epidemiology of HBV

Geographic Distribution of Chronic HBV Infection

HBsAg Prevalence
- >8% - High
- 2-7% - Intermediate
- <2% - Low
HBV Epidemiology – United States

Table 3.16. Estimated International HBsAg Prevalence

<table>
<thead>
<tr>
<th>Region</th>
<th>Estimated HBsAg Prevalenceb</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>0.1%</td>
</tr>
<tr>
<td>Mexico and Central America</td>
<td>0.3%</td>
</tr>
<tr>
<td>South America</td>
<td>0.7%</td>
</tr>
<tr>
<td>Western Europe</td>
<td>0.7%</td>
</tr>
<tr>
<td>Australia and New Zealand</td>
<td>0.9%</td>
</tr>
<tr>
<td>Caribbean (except Haiti)</td>
<td>1.0%</td>
</tr>
<tr>
<td>Eastern Europe and North Asia</td>
<td>2.8%</td>
</tr>
<tr>
<td>South Asia</td>
<td>2.8%</td>
</tr>
<tr>
<td>Middle East</td>
<td>3.2%</td>
</tr>
<tr>
<td>Haiti</td>
<td>5.6%</td>
</tr>
<tr>
<td>East Asia</td>
<td>7.4%</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>9.1%</td>
</tr>
<tr>
<td>Africa</td>
<td>9.3%</td>
</tr>
<tr>
<td>Pacific Islands</td>
<td>12.0%</td>
</tr>
</tbody>
</table>

HBsAg indicates hepatitis B surface antigen.


bLevel of HBV endemicity defined as high (≥8%), intermediate (2%–7%), and low (<2%).

≈25,000 infants born to HBsAg pregnant women in the U.S annually
• Without intervention up to 90% of infants of HBsAg+ mothers will be infected.
• In infants infected perinatally rate of spontaneous clearance is 0.6% per year during the first decade (1.8% in adolescents and adults).

Figure 213-4 Outcome of hepatitis B virus infection by age of infection.
HBV: Chronic Infection

• Primary determinant of risk for chronic infection
  - Age at the time of acute infection
    • > 90% of infants infected perinatally;
    • 25%-50% of children infected at 1-5 years
    • 2%-6% of acutely infected older children and adults

• Without treatment...
  - Up to 25% will die prematurely from HBV-related hepatocellular carcinoma or cirrhosis...
Perinatal HBV: Chronic Infection

• Immune tolerant
  - HBsAg +, HBeAg +; high HBV DNA
  - Indicates high level of HBV replication
  - Normal/minimal ↑ ALT
  - Minimal inflammation on biopsy
  - 30-50% of patients have stage 0 and remainder stage 1 fibrosis
  - One study showed these biopsy scores unchanged after 5 years
  - Remain in this phase for 10-30 years

Clin Gastroenterol Hepatol 2007; 5:6362
Hepatology 2007;46:395
www.uptodate.com
Perinatal HBV: Chronic Infection

• Immune active
  - Transition occurs in 2\textsuperscript{nd} or 3\textsuperscript{rd} decade
  - HBeAg seroconversion
  - High virema; ALT rises
  - Asymptomatic or episodes of acute hepatitis
  - Liver inflammation, possible fibrosis
  - Exacerbations may be severe; have required transplant
Perinatal HBV: Chronic Infection

• Inactive carrier
  - ALT normal; anti Hbe is present
  - Inflammation and fibrosis generally improve
  - ALT is not a good marker for this phase
  - Classified as such only after monitoring ALT and viral load over a period of 12 months or more

• Extrahepatic manifestations
  - Mediated by circulating immune complexes
HBV: Perinatal Infection

• 6% born to mothers + for HBV early antibody develop acute hepatitis at age 2 months

• 90% chance of chronic infection

• Low rate of spontaneous clearance

• Most infants remain in immune tolerant stage for 1-2 decades

• No licensed treatment in infancy, therefore prevention is the key!
Perinatal HBV: Mode of Acquisition
Mother to Child Transmission

• Pre-embryonic and Assisted Reproduction
  - Detected in sperm, oocytes and embryos
  - Occur in germ cell line?
  - Theoretically possible during assisted reproduction therapy

• Prenatal/Intrauterine
  - Considered to be low
  - Maternal HBeAg + associated with higher viremia
  - HBeAg can pass through placenta; induction of T-cell tolerance *in utero*
  - Higher transmission following amniocentesis when high viremia (very small numbers)

*J Pediatr Infect Dis 2014; 3:S7-12*
Mother to Child Transmission

• Intrapartum is most common
  - Microtransfusion or leaks of maternal blood during contractions
  - Inoculation of mucus membranes or breaks in skin
  - Most studies find no difference by vaginal (assisted or not assisted) versus c-section delivery
  - Viremia in cord blood is not diagnostic of infant infection

• Breastfeeding
  - Markers for infection are detectable in colostrum/breastmilk
  - Rates of infection are similar by mode of feeding
  - Not contraindicated if preventive measures taken

J Pediatr Infect Dis 2014; 3:S7-12
Perinatal HBV: Prevention of Transmission
Prevention: Pregnancy

• Screen all pregnant women for HBsAg at first prenatal visit (including vaccinated or previously tested)

• Vaccinate those negative but who remain at risk

Modes of Transmission of HBV

Includes those with:
• End-stage renal disease
• Chronic liver disease
• Diabetes
• HIV infection
HBV vaccine

• Produced by recombinant DNA technology

• Licensed in the US as single antigen formulations and as components of conjugate vaccines in childhood schedule

• Contains trace or no thimerosal (pediatric)

• 90-95% efficacy for preventing HBV infection
HBV Immunization in Pregnancy

HBV vaccine is:
- Safe
- Immunogenic
- Protects both mother and infant who are at risk: a “2 for 1” strategy

Before birth  
Birth  
Infant immunization schedule starts

Maternal antibody  
Child’s own antibody

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Before birth  
Birth  
Infant immunization schedule starts

Maternal antibody  
Child’s own antibody
Provider recommendation is key

Factors that influence a pregnant woman’s ultimate decision regarding immunization (0=not important; 5=very important)

- Fear of shots
- Cost
- Extra time for visit
- Adequate Information
- Safe for Me
- Safe for Baby

83% said they would receive a vaccine *if their provider recommended it*

*Vaccine 2015; doi.*
Obstetric Provider Strategies

- **Advocate**
  - Talk with patients directly; determine risk status
  - Strongly recommend HBV vaccine

- **Identify**
  - Use paper or E-prompts to remind which patients need HBV vaccine

- **Educate and Vaccinate**
  - Educate clinical and office staff

- **Integrate:** Standing orders, documentation

Prevention: Pregnancy

• Screen/rescreen those who present late or remain at risk

• All HBsAg women should receive evaluation and medical management
  - HBeAg, viremia, LFTs
  - Results guide management and timing of interventions

• Consider anti-viral therapies in the third trimester to decrease maternal viral load
  - Tenofovir or Telbivudine (nucleoside analogues)
  - Lamivudine

*J Pediatr Infect Dis 2014; 3:S7-12*
Pediatric Provider Strategies

- Review records to assess infant status and results of maternal screening
- Talk with parents directly to determine risk for infant
- Identify
  - Use paper or E-prompts to remind all providers which infants need prophylaxis
- Educate and Vaccinate staff
- Integrate: Standing orders, documentation
Prevention: Infant

• Starts at birth
• Skin contamination might increase transmission risk
• Occupational exposure
• Bathe with a mild soap

J Pediatr Infect Dis 2014; 3:S7-12
Postexposure Prophylaxis

• Mainstay of prevention in infants is early passive (Hepatitis B immune globulin [HBIG]) and active (vaccination) immunoprophylaxis.

• Prevents 85-95% of cases of perinatal HBV in infants of HBsAg+ moms.

• HBeAg + mom or mom with viremia of $10^6$ to $10^8$ has a higher risk of transmission than those with HBsAg + alone.

  - 15-30% versus 5%
Infant > 2000g: Mother HBsAg +

- Hepatitis B vaccine (single antigen)/HBIG within 12 hours of birth
- Continue vaccine series at age 1-2 months
- Check HBsAg and anti HBs 1-2 months after completion of vaccine series
  - If HBsAg – and anti HBs >/= 10 IU/mL infant is protected
  - If HBsAg – and anti HBs < 10 IU/mL infant should be reimmunized with a 2nd 3-dose series and retested
  - If HBsAg + referral for appropriate follow-up
Infant < 2000g: Mother HBsAg +

- Hepatitis B vaccine (single antigen)/HBIG within 12 hours of birth
- Restart vaccine series at age 1-2 months (i.e. the birth dose does not count)
  - Decreased immunogenicity of HBV vaccine in preterm infants
- Check HBsAg and anti HBs 1-2 months after completion of vaccine series
  - If HBsAg – and anti HBs >/= 10 IU/mL infant is protected
  - If HBsAg – and anti HBs < 10 IU/mL infant should be reimmunized with a 2nd 3-dose series and retested
  - If HBsAg + referral for appropriate follow-up
Infant > 2000g: HBsAg unknown

- Test mother for HBsAg ASAP
- Hepatitis B vaccine (single antigen) within 12 hours of birth
- Administer HBig within 7 days if mother is +
- Continue vaccine series at age 1-2 months
- Check HBsAg and anti HBs 1-2 months after completion of vaccine series
  - If HBsAg – and anti HBs >/= 10 IU/mL infant is protected
  - If HBsAg – and anti HBs < 10 IU/mL infant should be reimmunized with a 2nd 3-dose series and retested
  - If HBsAg + referral for appropriate follow-up
Infant < 2000g: HBsAg unknown

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  - If HBsAg – and anti HBs >/= 10 IU/mL infant is protected
  - If HBsAg – and anti HBs < 10 IU/mL infant should be reimmunized with a 2nd 3-dose series and retested
  - If HBsAg + referral for appropriate follow-up
Infant > 2000g: Mother HBsAg -

• Hepatitis B vaccine (single antigen) at birth
• Continue vaccine series at age 1-2 months
• Follow-up testing not needed
Infant < 2000g: Mother HBsAg -

• Hepatitis B vaccine at 1 month of age or hospital discharge, whichever is first
• Restart vaccine series at age 1-2 months
• Follow-up testing not needed
Why HBIG?

• Provides a short term increase in antibody that may protect until infant responds to vaccine

• Systematic review found higher efficacy of vaccine and HBIG than with vaccine alone (risk ratio 0.54; 95% confidence intervals 0.41-0.73)

• Most studies included infants of women who were both HBsAg + and HBeAg +

• However, worldwide administration of HBIG may not be feasible (supply, safety, cost)

*J Pediatr Infect Dis 2014; 3:S7-12*
Postexposure Prophylaxis: Factors associated with Failure

• Maternal HbeAg +
• High viral load in mothers
• Delay in infant receipt of HBV vaccine
• Failure of infant to receive HBIG
• Vaccine non-responders
• HBV mutations
• Overall transmission occurs in 5-15% despite PEP
Post Vaccination Testing

• All infants born to HBsAg + mothers
• Optimal timing is 1-2 months after series at age \( \geq 9 \) months
• Testing within 1 month of vaccine might detect HBsAg from vaccine
• Testing at < 9 months might miss infected infants with prolonged incubation due to birth HBIG
• Testing late might result in unnecessary vaccination of infants whose anti HBs has declined to < 10IU/mL
Don’t Forget Contacts!

• Unvaccinated contacts are at risk of infection from infected mother

• Negative mothers and infants may be at risk from contacts with “at risk” behaviors

• Infants are at risk from everyone who may become infected

• The many provider-patient contacts during pregnancy and in the postpartum period offer a unique opportunity to encourage or provide vaccination in contacts
## Prevention: Research Gaps

<table>
<thead>
<tr>
<th>Topic</th>
<th>Knowledge Gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>In utero transmission</td>
<td>Improved understanding; targeted prevention including during assisted reproduction procedures</td>
</tr>
<tr>
<td>Mode of Delivery</td>
<td>Benefit from elective c‐section in selected women?</td>
</tr>
<tr>
<td>Antiviral agents</td>
<td>• Determine safety, efficacy and timing of treatment during pregnancy&lt;br&gt;• Understand effects of infant exposure to antivirals in breast milk</td>
</tr>
<tr>
<td>HBV vaccine (birth)</td>
<td>Quantify protective efficacy by time of vaccination relative to maternal viral load</td>
</tr>
<tr>
<td>Neonatal antivirals</td>
<td>Determine indications, safety and efficacy</td>
</tr>
<tr>
<td>HBig</td>
<td>• Further determination of the benefit for HBeAg- women&lt;br&gt;• Efficacy in preventing fulminant hepatitis&lt;br&gt;• Quantitate increase in HBV incubation period and potential for missing infected infants by early testing</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>Determine optimal level for initiating antiviral therapy</td>
</tr>
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*J Pediatr Infect Dis 2014; 3:S7-12*
Test Question

• You are in the newborn nursery, when you are get called by a frantic OB/Gyn nurse about a full term, 2000 g baby bta a 22 yo mom with no prenatal care and unknown HBV status.

• She asks you whether the baby needs immunization. If so, what would be your recommendations?
Answer

• Test the mom immediately for HBsAg
• HBV vaccine within 12 hours regardless of birth weight
• HBIG if mom’s HBsAg + or remains unknown
  -> 2 kg: HBIG within 7 days
  <- 2 kg: within 12 hours of birth
• Continue vaccine series at 1-2 months
• < 2 kg give 4 vaccine doses (do not count birth dose)
Perinatal HBV: Therapeutic Options for Infants
Let’s Recap

HBV: transmission to neonates

• Usually from blood exposures during labor/delivery
• Overall transmission 5-15%, even with prophylaxis
• Some neonates may already be infected in utero with virus present in cord blood (rare)
• When a mother is acutely infected during pregnancy, risk of transmission to infant increases when later gestation at time of infection
• Risk is increased in mothers with HBsAg + HBeAg positive (70-90%)
• Breast feeding does not increase the risk of transmission
Clinical Illness with Perinatal HBV

- Perinatally infected children are immune tolerant.

- Lasts 10-30 years with a low rate of spontaneous clearance.

- Enters a replicative phase during which immune clearance rates increase.
  - Genotype dependent.

- Exacerbations are generally asymptomatic (M>F).
Treatment of HBV

• No specific therapy for acute infection

• Chronic infection
  - Has not been studied in neonates
  - Treatment not recommended in children with immune tolerant or those without any necroinflammatory changes in the liver
Monitoring of Children with Perinatal HBV Infection

• Evaluate for risk factors for coinfection (HIV, Hepatitis C, Hepatitis D)
  - Some similar risk behaviors
  - Areas of high prevalence of Hepatitis D (Eastern Europe, Mediterranean, Central America)

• Monitor serum ALT, HBV viremia, HBeAg

• Screening for hepatocellular carcinoma?
  - Right upper quadrant ultrasound
  - Serum alphafetoprotein

• Ensure immunized against Hepatitis A
Antiviral Therapy

• Few large scale trials
  - Only short or intermediate term outcomes
• Aim is to reduce progression to hepatocellular carcinoma and cirrhosis
• Treatment is not particularly efficacious
• Risk of developing resistance
Child with chronic hepatitis B (≥1 yr of age; persistent HBsAg+ for > 6 mos)

ALT persistently normal

- HBeAg positive and HBV DNA ≥20,000 IU/mL (Immune Tolerant)
  - Benefit of treatment not established
  - Risk of drug resistance if treated with nucleos(t)ide analogs
  - Continue to monitor regularly

- HBeAg negative and HBV DNA <2,000 IU/mL (Inactive Carrier)
  - No indication for treatment
  - Continue to monitor regularly

ALT persistently >1.5 x lab ULN or >60 IU/L

- HBeAg positive (>6 mos) and HBV DNA ≥2,000 IU/mL (Immune Active)
  - Rule out other causes of liver disease
  - Consider liver biopsy
  - Minimal/mild inflammation and/or fibrosis
  - Benefit of treatment not established
  - Family history of HCC may influence treatment decision

- HBeAg negative (>12 mos) and HBV DNA ≥2,000 IU/mL (Reactivation)
  - Moderate/severe inflammation and/or fibrosis
  - Treatment indicated

Fig. 1. Algorithm for selection of children for HBV antiviral treatment.
Available Antivirals

• Interferon alfa
  - Finite period of treatment (3/week for 16-24 weeks)
  - Not associated with development of resistance
  - Response better with genotypes A and B
  - Better in Western than Asian populations (58% vs 17% response rates)
  - Contraindicated in those < 1 year (risk of spastic diplegia)

• Entacavir
  - Approved age 2 and over
  - Lower rates of resistance
  - Optimal duration is unclear
Available Antivirals

• Tenofovir
  - Licensed age 12 and older
  - Viremia reduced to < 400 copies/ml in 89%
  - Optimal duration of therapy not established

• Lamivudine and adepovir
  - Rarely used due to lack of efficacy and concerns re resistance
  - Lamivudine may be used in situations where only short term therapy is contemplated (eg time-limited immunosuppression)
Conclusions

• Perinatal HBV carries serious consequences for infants, despite relatively benign course in childhood

• As treatment options are limited, prevention of perinatal acquisition is the key

• Effective prevention is dependent on antenatal screening, antiviral therapy of selected cases

• Postexposure prophylaxis effectively prevents the overwhelming majority of perinatal infections