# ENDING THE EPIDEMIC:
## Case Management of Perinatal HBV

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## HEPATITIS B

- Carrier state and chronic infection state
  - A carrier state is a persistent infection with presence of HBsAg, but without biochemical or clinical signs of ongoing hepatic injury.
  - HBV carriers are infectious.



## Hepatitis B – Let's form a foundation....

## HEPATITIS B

- At-risk populations
  - Infants born to HBV-infected women.
  - Infants/children living in community groups with endemic HBV.
  - Immigrants/adopted children from regions of the world with high prevalence of HBV.
  - Household contacts of individuals with chronic HBV.
  - Adolescents engaging in high-risk behaviors.



## HEPATITIS B

- Double-stranded DNA hepatitis B virus (HBV).
- Mode of transmission
  - Vertical (perinatal transmission)
  - Parenteral
  - Sexual
- Incubation period 45 -160 days (average 90 days).



## HEPATITIS B

- Development of chronic disease varies based on the age of acquisition
  - Infants: 90% chance of developing chronic disease.
  - Children 1-5 years: 30% chance.
  - Children > 5 years: 6% chance.

## HEPATITIS B

- Clinical features
  - Perinatal HBV acquisition is usually asymptomatic; however, if mother is HBeAg positive at birth, ~ 6% of infants will develop acute liver failure by 2 – 3 months of age.
  - Traditionally, a rather benign course during childhood/adolescence.
  - However, 3-5% of chronic carriers develop cirrhosis before adulthood.



## HEPATITIS B

- Annual rate of spontaneous clearance (conversion to HBeAg negative and HBeAb positive
  - 0 – 3 years of age < 2%
  - > 3 years of age ~ 5%
- Check HBV DNA (viral load) if considering treatment.
- Check liver histology (biopsy) if considering treatment.



## HEPATITIS B

- Clinical features (continued)
  - Chronic active hepatitis
    - Persistence of HBsAg > 6 months and elevated ALT and AST levels.
  - Of the neonates who become chronic carriers, many develop an immune tolerant phase = normal ALT/AST despite high HBV DNA levels and persistent HBsAg and HBeAg positivity (and negative antibodies).



## HEPATITIS B

- Prevention
  - HBV vaccine:
    - Universally recommended for all infants (series of 3 doses over 6 – 9 months).
    - Catch up immunizations for older, unimmunized children.
    - HBV-exposed family members/close contacts.



## HEPATITIS B

- Diagnosis
  - Confirmed by detection of HBsAg on two separate testings at least 6 months apart, as well as a HBV Quantitative PCR.
  - Laboratories: Liver panel, HBV: sAg, sAb, eAg, eAb
    - Positive HBsAg = active infection
    - Positive HBeAg = high infectivity
    - HBeAg negative & HBeAb positive = seroconversion with clearance of actively replicating virus
    - Positive HBsAb is rare = Protective immunity



## HEPATITIS B

- Prevention (Continued)
  - MUCH OF PREVENTION IS UNDERSTANDING TRANSMISSION !

## Hepatitis B

- Transmission
  - Transmitted through blood or bodily fluids.
  - HBsAg has been detected in:
    - Human milk
    - Saliva
    - Tears
  - But, most potentially infectious in:
    - Blood/serum
    - Semen
    - Vaginal secretions
    - Cerebrospinal, synovial, pleural, peritoneal and amniotic fluids.



## What about Cesarean Delivery?

Is it necessary?

- Well-conducted controlled trials have been unable to show prevention of maternal-infant transmission.
- Therefore, cesarean delivery is not routinely recommended for carrier mothers.



## Hepatitis B

- Perinatal Transmission
  - Highly efficient.
  - Usually occurs from blood exposures during Labor & Delivery.
  - In utero transmission ....represents <2% of all vertically transmitted HBV infections.



## Hepatitis B

- Perinatal Transmission
  - Without post exposure prophylaxis...there is a 70-90% transmission risk for an infant born to an infected mother who is HBsAg and HBeAg positive.
  - But, this drops to 5-20% transmission risk for a HBsAg positive/HBeAg negative mother.



## Hepatitis B

- Perinatal Transmission
  - What about Cesarean Delivery?



## Hepatitis B

- Perinatal Transmission

  Remember …..
  - HBsAg is detectable during acute infection.
  - HBsAg disappears in most patients within a few weeks to several months after infection followed by appearance of HBsAb.

## HEPATITIS B

- Perinatal Transmission
  - The time between HBsAg disappearance and HBsAb appearance = "the window period" of infection.
  - During this window, the only marker of acute infections is IgM HBcAb… highly specific for establishing the diagnosis of acute infection.
  - However, IgM HBcAb is usually not present in infants infected perinatally.



## HEPATITIS B

- Immunoprophylaxis
  - Two types of products are available
    - HBIG – provides short-term protection (3-6 months) and is indicated only in specific post exposure circumstances.
    - Hep B vaccine is used for pre-exposure and post-exposure protection and provides long-term protection.
  - Remember…Pre-exposure immunization with Hep B vaccine is the most effective means to prevent transmission.



## HEPATITIS B

- Perinatal Transmission
  - Both HBsAb and total HBcAb are present in people with resolved infection, where as HBsAb alone is present in people immunized with Hepatitis B vaccine.



## HEPATITIS B

- Hep B vaccine + HBIG
  - Transmission prevention in 95% of infants born to HBsAg-positive mothers.
- Hep B vaccine alone
  - Highly effective for preventing perinatal infections.
  - However, women with HBV DNA>$10^6$ to $10^8$ IU/mL or who are HBeAg positive have higher perinatal transmission (~15-30% risk vs 5% in lower DNA or HBeAg negative).



## HEPATITIS B

- Treatment
  - No specific therapy for acute HBV infection is available.
  - Hepatitis B Immune Globulin (HBIG) and corticosteroids are not effective treatment for acute or chronic disease.
  - However …..



## HEPATITIS B

- Immunoprophylaxis of Perinatal Infection
  - Effectiveness is related directly to the time elapsed between exposure and administration.
  - Most effective if given within 12 hours of birth.
  - HBIG – interval of effectiveness is unlikely to exceed 7 days.

## Hepatitis B

- Serologic testing of all pregnant women for HBsAg during pregnancy is essential to determine which infants will require post-exposure immunoprophlaxis.
- Repeat testing at time of admission for delivery if high risk of HBV infection or in those mothers who have had clinical HBV infection.



## Hepatitis B

- <2000 grams and HBsAg-positive mother
  - Should receive Hep B vaccine and HBIG within 12 hours of birth.
  - However… the birth dose of Hep B vaccine should NOT be counted toward completion of the Hep B vaccine series.
  - 3 additional doses of Hep B vaccine should be given starting at 1 month of age.



## Hepatitis B

- Vaccine
  - Administered intramuscularly
    - Anterolateral thigh (infants)
    - Or Deltoid area (children and adults)
    - Buttocks? Decreased immunogenicity
    - Intradermal? Mixed results/not approved
  - Pregnancy is not a contraindication to immunization of mothers!
  - Lactation is not a contraindication to immunization!



## The Foundation is set…

Let's go through some cases ….



## Hepatitis B

- Pre-term infants weighing <2000g at birth
  - Decreased seroconversion rates after Hepatitis B vaccine administration at birth.
  - However, by chronological age of 1 month, regardless of birthweight or gestational age, these infants are likely to respond to Hep B immunization like term and larger infants.



## Case 1

An unimmunized mother comes into your office during pregnancy.

Should she be immunized while pregnant?

**Yes**

## Case 2

An unimmunized, breastfeeding mother comes into your office.

Should she be immunized while breastfeeding?

**Yes**



## Case 5

- A <2000 gram preterm infant is born to a mother with unknown HBsAg status. Next steps?

1. Obtain mother's Hep BsAg status ASAP.
2. Give Hep B vaccine within 12 hours of birth.
3. Give HBIG if maternal HBsAg status cannot be determined within 12 hours of life –
   Why? Because of the less reliable immune response in preterm infants weighing <2000 grams precludes the option of the 7 day waiting period acceptable for term and larger preterm infants.



## Case 3

- What should a >2000 grams term infant born to a HBsAg-positive mother receive for immunoprophylaxis?

1. Hep B vaccine.
2. HBIG within 12 hours of birth.



## Case 6

- You are in a remote area where the mother's HBsAg status cannot be tested/no lab available – What should the term infant receive?

1. Hep B vaccine within 12 hour of birth & then complete the usual Hep B vaccine series.
2. No mandate for HBIG by definition, due to Hep B vaccine being highly effective for preventing perinatal infection. The possible added value and the cost of HBIG do not warrant its immediate use. However, most experts say give HBIG if status remains unknown as of 7 days post birth.



## Case 4

- What should a <2000 grams term or preterm infant born to a HBsAg-positive mother receive for immunoprophylaxis?

1. Hep B vaccine.
2. HBIG within 12 hours of birth.
3. But… the birth dose of Hep B vaccine should not be counted toward completion of the Hep B vaccine series, and 3 additional doses of Hep B vaccine should be given starting when the infant is 1 month of age.



## Case 7

- If you have a HBsAg-positive mother, the infant regardless of weight should receive what?

1. Initial dose of Hep B vaccine within 12 hours of birth (<2000 grams a total of 4 doses required).
2. HBIG concurrently, but at a different anatomic site.

# Case 8

- A HBsAg-positive mother presents to your office for the 1st time and asks about the risk of transmitting Hep B to her infant while breastfeeding. What is your recommendation?

1. Poses no additional risk of HBV infection acquisition with appropriate administration of Hep B vaccine and HBIG to the infant.



# Summary & Recommendations

Prevention is the KEY!!!



# Case 8 (continued)

2. Although HBV DNA has been detected in the colostrum of HBsAg positive mothers, studies have failed to show a relationship between breastfeeding and subsequent HBV infection.
3. However, mothers who are breastfeeding should exercise care to prevent bleeding from cracked nipples.



Thank You!

# Summary & Recommendations

- Hepatitis B
  - Vertical transmission occurs most commonly during labor and delivery.
  - Neonates rarely show clinical or biochemical signs of disease at or soon after birth.
  - Serologic testing is necessary to make the diagnosis and can guide therapy.
  - No therapy is available for acute infection.
  - Immunoprophylaxis with Hep B vaccine and HBIG are vital tools in preventing long term disease.



## The Hepatitis Viruses: Characteristics and Terminology of Associated Antigens and Antibodies

| MARKER | DEFINITION | SIGNIFICANCE OF MARKER |
|---|---|---|
| Serologic Markers of HAV | | |
| Anti-HAV IgM | Antibody (IgM directed against HAV | Current or recent infection |
| Anti-HAV IgG | Antibody (IgG) directed against HAV | Previous infection/vaccine and protective immunity |
| Serologic Markers of HBV | | |
| HBsAg | Hepatitis B surface antigen; found on surface of intact virus and in serum as free particles | Active HBV infection |
| HBcAg | Hepatitis B core antigen, found within virus core | Detectable in liver tissue |
| HBeAg | Hepatitis B e antigen; soluble antigen produced during self-cleavage of HBcAg | High infectivity |
| HBV DNA | DNA of HBV (PCR test) | Active HBV replication |
| Anti-HBs IgG | Antibody (IgG) to HBsAg | Protective immunity |
| Anti-HBc IgM | Antibody (IgM) to HBcAg | Early infection |
| Anti-HBc IgG | Antibody (IgG) to HBcAg | Indicates infection |
| Anti-HBe | Antibody to HBeAg | Resolution of active viral replication |

## The Hepatitis Viruses: Characteristics and Terminology of Associated Antigens and Antibodies

| MARKER | DEFINITION | SIGNIFICANCE OF MARKER |
|---|---|---|
| Serologic Markers of HCV | | |
| Anti-HCV | Antibody (IgG) to HCV | Exposure to HCV. Not protective |
| HCV RNA | RNA of HCV (PCR test) | Active HCV infection |
| Serologic Markers of HDV | | |
| HDVAg | Hepatitis D antigen | HDV infection |
| Anti-HDV | Antibody (IgM/IgG subclass) to HDV | Exposure to HDV |
| HDV RNA | RNA of HDV (PCR test) | Active HDV replication |
| Serologic Markers of HEV | | |
| HEVAg | Antigen associated with HEV | Stool test; recent infection |
| HEV RNA | RNA of HEV (PCR test) | Early HEV infection |
| Anti-HEV | Antibody (IgM) to HEV | Early HEV infections |
| Anti-HEV | Antibody (IgG) to HEV | Protective immunity |

Adapted from the NASPGHAN Fellows Concise Review of Pediatric Gastroenterology, Hepatology and Nutrition



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11. HAV, hepatitis A virus; HBV, hepatitis B virus, HBcAG, hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus, PCR, polymerase chain reaction.
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