Hepatitis B Overview

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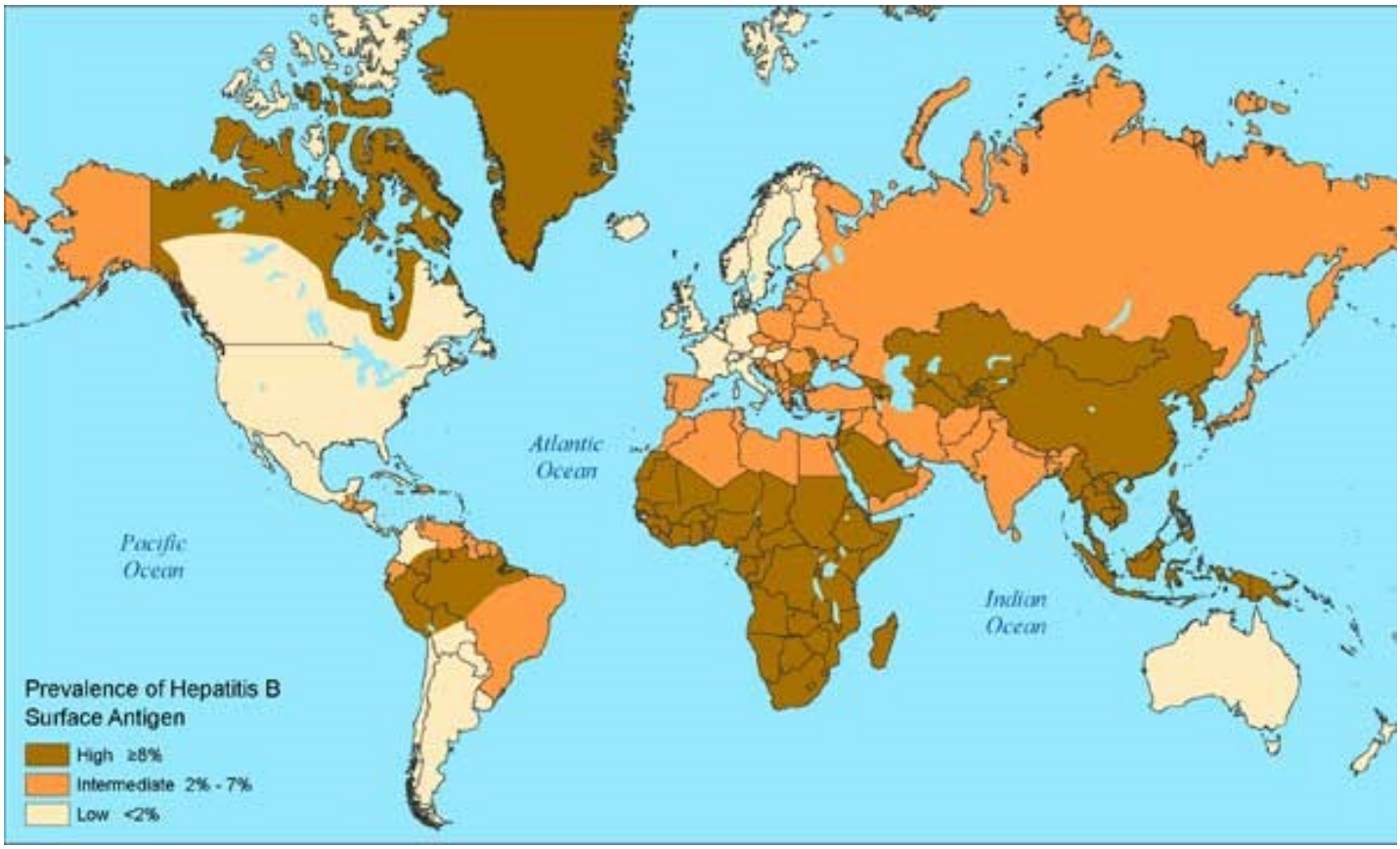
Virology

The hepatitis B virus (HBV) is an enveloped virus of the Hepadnaviridae family, which only includes one other virus (Duck hepatitis B virus).

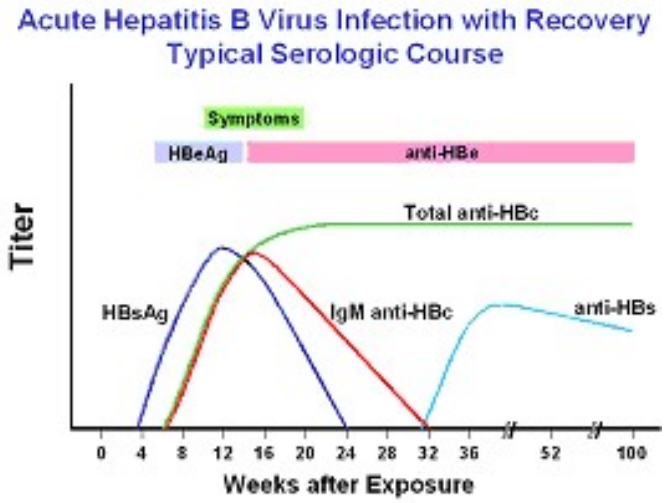
- HBV is composed of 2 components:
  - Inner capsid→composed of hepatitis B core antigen (HBcAg) and hepatitis E antigen (HBeAg)
  - Lipid envelope→contains hepatitis B surface antigen (HBsAg)
    - Produced in excess in comparison to the inner capsid = higher concentration of HBsAg in comparison to HBcAg and HBeAg
- 8 genotypes (A-H) based on variation in nucleotide sequence

Epidemiology

- ~ $^1/_3$ of the world's population show serologic evidence of past or present HBV infection
- 350 million people suffer from chronic HBV infection
- 621,000 people die each year due to HBV
  - Deaths are usually due to the gradual progression of HBV rather than acute illness
  - 69% of deaths occur in adults infected *before* age 5
- Highest concentration of HBV infection is in African and Asian countries
  - Population studies of East Asian countries from the 1970s-1990s:
    - 63-93% of the studied populations showed current or past HBV infection
    - 12-18% showed chronic infection



Serologic Diagnosis of HBV infection



- HBV has an incubation period of 6 weeks-6 months
  - Serologic markers are noted within 4-8 weeks after infection→ normally present with acute symptomatic infection
- HBsAg and IgM anti-HBc
  - First positive markers indicating HBV infection
  - IgM anti-HBc is a *diagnostic* marker of acute infection
- HBeAg
  - Indicator of viral replication extent and viral load
  - Associated with increased risk of hepatocellular carcinoma (HCC)

Resolution of Acute Illness	*Chronic Infection*
HBsAg disappears	HBsAg persists
Anti-HBsAg appears • Can resolve with time	No anti-HBsAg
Both will show persistent IgG anti-HBc	

- "Window Period"
  - Transition point after acute illness where a patient's serologic tests exhibit no HBsAg or anti-HBsAg
  - IgM anti-HBc remains positive

Transmission of HBV

- Vertical transmission
  - Exposure to blood of infected mother during delivery
  - Low risk of transplacental infection
  - 85-90% risk in infants with HBeAg positive mothers versus 32% risk with HBeAg negative mothers
- Percutaneous/permucosal transmission
  - IV drug use, transfusion of infected blood, nosocomial exposure
  - Acupuncture, tattooing, piercing
- Sexual contact
- Horizontal transmission
  - Spread within a family/household
  - Associated with close contact or sharing of blood-exposed products such as toothbrushes or razors
  - Rare cases of spread via saliva

Natural History of HBV infection

- Symptomatic range from:
  - Asymptomatic
  - Acute hepatitis
    - Fever, jaundice, dark urine, abdominal pain, general malaise
  - Fulminant hepatic failure
    - Occurs in <1% of acute HBV infections
- HBV is not cytopathic to the liver
  - Clinical presentation of liver injury is due to the level of immune response to HBV
    - ↑ immune response → ↑ symptoms → ↓ risk of chronic illness
- Chronic HBV infection= virus that remains in spite of immune response
  - Defined by positive HBsAg 6 months after acute illness
  - Risk of progression to chronic infection depends on age
    - Likely due to relative immune responses between age groups
    - Perinatal → >90% risk
    - Age 1-5 → 25-50%
    - Adults → <5-10%

Long-term Sequelae of Chronic HBV Infection

- Hepatic cirrhosis
  - Result of gradual fibrosis with recurrent immune response to infected hepatocytes
- Hepatocellular carcinoma
  - Combination of factors – regenerative hyperplasia, chronic fibrosis, insertional mutagenesis by viral genome
- Polyarteritis nodosa, glomerular nephropathy (Membranous vs Membranoproliferative)
  - Less common but likely secondary to the deposition of circulating immune complexes

Treatment of HBV

- No cure for chronic HBV infection – issue of prevention versus suppression of illness

- HBV Vaccination
  - Prevents perinatal HBV infection in 90-95% of cases
- Hepatitis B Immunoglobulin (HBIG)
  - Provides 3-6 months of protection with high concentrations of anti-HBs
  - Recommended for:
    - Infants with HBsAg-positive mothers
    - Unvaccinated individuals with percutaneous exposure to a person who is HBsAg-positive or at high risk of being positive
    - Unvaccinated individuals with sexual contact of a person who is HBsAg-positive or at high risk of being positive
- Interferon-alpha, Lamivudine, Adefovir, Entecavir, Pegylated interferon
  - Options for suppression of viral replication

Management of Immigrants from a Country with Intermediate to High Rates of HBV Infection

- Immigrants of all ages from countries of intermediate-high HBV infection prevalence are to be screened with HBsAg
  - Individuals with positive HBsAg (chronic infection) do not need vaccination
    - Proper follow-up tests on a new patient with a positive HBsAg
      - Liver function (transaminases, Tbili, PT/INR)
      - Hepatitis B replicative status (HBeAg/HBeAb, HBV DNA)
      - Viral serologies (Hep A, C, D, HIV)
      - Alphafetoprotein
      - Abdominal ultrasound
    - Patients with chronic Hep B should be referred to GI clinic for further management
- It is cost-effective to screen for anti-HBc in adults but NOT children
  - HBsAg →current or chronic infection versus anti-HBc → history of prior infection
  - Identifies an additional subset of individuals who do not need vaccination
- All children should start vaccination series regardless of country of origin
  - Series can be stopped with positive HBsAg
  - Unnecessary to start only with reliable documentation of prior vaccination
- All susceptible adults who live in close contact with a positive HBsAg person should receive the vaccination series
  - Exceptions include documentation of prior vaccination or serologic evidence of current/prior HBV infection
- Post vaccination testing for anti-HBs should be done in the following groups:
  - Infants borns to HBsAg-positive mothers
  - Hemodialysis patients
  - Immunocompromised patients
  - Sex partners and needle-sharing partners of individuals with chronic hepatitis B infection

Key Questions to be answered when treating a patient with HBV

1. Does this patient need surveillance for HCC (periodic alpha fetoprotein labs and/or abdominal ultrasounds)?
   - Consider risk factors for progression of chronic hepatitis B:
     - Age of infection (↑ risk with ↓ age)
     - Patient's current age (↑ risk with time)
     - Male gender
     - Alcohol consumption
     - Smoking
     - Coinfection with HIV, Hep C, Hep D
     - Genotype D has ↑ risk compared to genotype A
     - HBeAg status
     - Viral load
   - Surveillance recommended for: (per American Association for the Study of Liver Diseases)
     - Asian males ≥ 40 years
     - Asian females ≥50 years
     - Hepatitis B carriers with cirrhosis
     - Family history of HCC
     - Africans over age 20
2. Should this patient be receiving suppressive therapy?
   - Chronic Hep B is separated into 5 phases (immune tolerance, immune clearance, inactive HBsAg carrier, reactivation of HBV replication, resolved)
     - Determined by serial monitoring of HBV DNA and serum transaminases
       - Both HBV DNA and serum transaminases can fluctuate from high to normal during chronic infection
     - Suppressive therapy only effective during 2 stages
       - Immune clearance
         a. Flares of transaminase spikes due to immune response towards infected hepatocytes
       - Reactivation of HBV replication
         a. Progression from an inactive state
         b. Fluctuations of transaminase spikes