Hepatitis B

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Hepatitis B (HBV) – Basics

- HBV is a DNA virus - member of the Hepadnaviridae family
- Virus structure has several components
  - Surface protein – surface antigen
  - Lipid layer
  - Inner protein core – core antigen
  - Viral polymerase – needed to replicate viral genetic material
  - Viral genome
    - Partially double stranded DNA
- Virus attaches to liver cells and viral genetic material enters the infected cell
- Viral genome is converted to tightly coiled covalently closed circular DNA (cccDNA)
  - Incorporated into the host cell genome
  - Serves as the template for creating new viral particles
  - Unusually stable and able to avoid immune clearance

Hepatitis B (HBV) – Genotypes

- Ten genotypes have been identified – A to J
- Prevalence varies geographically
  - US – types A (35%), B (22%), C (31%) are most common
  - Asia – types B and C
  - Southern Europe, Middle East, Africa and India – type D
  - West Africa – type E
  - Central and South America – types F and H
- Genotype A responds better to interferon therapy
- Genotype C has generally worse outcomes
  - Higher tendency to chronicity
  - Higher level of viral DNA and rate of positivity of e antigen
  - Higher risk of cirrhosis or cancer

Hepatitis B – Epidemiology

- Estimated 2 billion individuals have been infected worldwide
  - 254 million chronically infected in 2022
  - 10-30 million new infections per year
  - 1.1 million deaths in 2022
  - Risk of chronic infection varies by geographic area
    - Sub-Sahara Africa – 8.83%
    - Western Pacific region – 5.26%
    - Eastern Mediterranean region – 3.01%
    - Europe – 2.06%
    - Southeast Asia – 1.90%
    - Americas – 0.81%
- Majority of infections in endemic areas occur in the perinatal period or early in childhood

Hepatitis B – Epidemiology

- Estimated 12 million individuals have been infected in the US
  - 880,000 to 1.89 million chronically infected (0.3%-0.7% of population)
  - 13,800 new acute infections,16,729 new chronic infections reported in 2022
  - 1,797 deaths reported in 2021
- Foreign born individuals account for 70% of the cases in the US
  - Majority of those chronically infected are of Asian/Pacific Island descent
- Highest incidence rate (new infections) is in those aged 30-59
- Rate of acute hepatitis B has decreased 88.5% since advent of universal vaccination

Hepatitis B – Infectivity and Transmission

- Hepatitis B is extremely infectious with easy transmission
- Virus can survive on inanimate surfaces for up to 7 days
- Modes of transmission
  - Parenteral
    - IV drug use
    - Exposure to blood through medical procedures (needle stick, surgery, dialysis etc.)
  - Non-medical contact with blood
    - Dental procedure, tattooing, sharing razors
  - Sexual contact
    - Heterosexual
    - MSM contact
  - Contact with body fluids
    - Peripartum
    - Daycare centers
    - Household contacts
    - Developmentally disabled (group homes etc.)

Hepatitis B – Prevention

- Vaccine is available and highly effective
  - Leads to the development of HBsAb without the HBcAb
- Universal vaccination of children is recommended
  - First dose at birth
- Children born to HBsAg mothers receive special therapy - 95% effective
  - Vaccination and hepatitis B immune globulin (HBIG) at birth
  - Mothers with high HBV DNA load (> 200,000 IU/ml) are also treated with tenofovir beginning at 28-32 weeks gestation until 1 to 3 months post partum
- As of 2022 vaccination is recommended for all adults less than age 60 in the US
- Vaccination is recommended for high-risk adults including:
  - Health care workers
  - IV drug users
  - Individuals with high-risk sex behaviors
  - Household contacts of infected individuals
  - Workers in chronic care facilities
  - Travelers to high-risk areas

Hepatitis B – Serology

- Hepatitis B surface antigen (HBsAg)
  - Protein from the viral coat
  - Indicates active infection and potential infectivity
  - Often produced in excess of the number of actual viral particles
  - High levels may cause immune fatigue or tolerance in the host

- Antibody to the core protein of the virus particle (HBcAb)
  - Found only in those with a prior hepatitis B infection
  - All of those infected will develop this antibody
  - Two types
    - IgM – only found associated with recent acute infection
    - IgG – found associated with recent or remote infections, may persist for life
    - Latter may be the only marker for a prior acute infection

Hepatitis B – Serology

- Hepatitis B surface antibody (HBsAb)
  - Develops with recovery from acute infection or after vaccination
    - Presence of a positive HBcAb indicates prior infection
    - Presence of the HBsAb alone indicates vaccination
  - Only 80% of those who recover from an acute infection develop the HBsAb
  - Conveys immunity from reinfection with the virus
  - Does *NOT* indicate cure or freedom from potential reactivation of the virus in those that have been infected

- Hepatitis B e antigen (HBeAg)
  - Protein that is an indicator of active viral replication
  - Important prognostic marker
  - Individuals with a Pre-Core mutation do not develop the e antigen
    - Viral DNA level determines degree of viral replication and infectivity in these cases

Hepatitis B – Serology

- Antibody to the hepatitis B e antigen (HbeAb)
  - Indicates seroconversion or cessation of active viral replication
  - Appearance is a good prognostic marker and goal of initial therapy

- Viral DNA (HBV DNA)
  - Gold standard for presence of the virus in the blood, viral replication & infectivity
  - Level represents a measure of active replication even if e antigen not present
  - Level has prognostic value

Hepatitis B – Serology –Tests to Predict Outcomes and Response to Rx

- Quantification of surface antigen (HBsAg) levels
  - Higher in HBeAg positive individuals
    - Level usually > 1000 IU/ml
  - Lower in HBeAg negative individuals

- HBV RNA
  - Marker for cccDNA transcription
  - Help in assessing response to newer therapies

Hepatitis B – Sequence of Events in a Resolved Infection

- Incubation period to onset of clinical illness is approximately 45 to 160 days
- Viral DNA is detected first (10 – 20 days before the surface antigen)
  - Usually disappears some time after e antigen becomes undetectable
- HBsAg appears 1 – 9 weeks after infection (average 4 weeks)
  - Persists for several months
- HbeAg is detectable shortly thereafter and persists for 3 to 6 weeks
- HbcAb appears shortly before the onset of clinical illness
  - IgM version persists for several months, then disappears
  - IgG version continues indefinitely
- HBeAb appears shortly after the e antigen disappears
- HBsAb appears after the surface antigen is no longer detectable
  - May be a gap when the surface antigen and surface antibody are both negative
  - Infection detected by IgM core antibody or presence of viral DNA

Hepatitis B – Serologic Screening (HBsAg and/or HBcAb)

- Individuals from a country with a prevalence ≥ 2%
- US born, not vaccinated, with parents from an area with prevalence ≥ 8%
- History of high-risk sexual activities
- Those being treated for a sexually transmitted disease
- History of IV drug use
- Unexplained ALT elevation
- All pregnant women
- Persons needing immunosuppressive or chemotherapy or dialysis
- Persons with other chronic liver disease
- Persons with HIV disease or hepatitis C infection
- Household contacts of someone who is chronically infected
- Health care or other workers regularly in contact with bodily fluids
- Blood, organ or sperm donors

Key Point to Remember

- Hepatitis B virus is NOT cytopathic
  - Virus does not injure liver cells directly
- Damage is done by the immune response to the infection
- Elevated liver function tests, especially ALT reflect the injury and, indirectly, viral activity

Hepatitis B – Acute Disease

- Clinical findings depend on host factors
  - Infants, children under age 5 and immunosuppressed individuals are usually asymptomatic
  - Older children and adults – symptomatic in 30%-50% of cases
- Symptoms include jaundice, anorexia, nausea, vomiting, hepatomegaly, fever
- Fulminant hepatitis is possible but uncommon
- Mortality rate from acute hepatitis B is < 1.5%
  - Primarily in adults > age 55
- Loss of the surface antigen and development of the surface antibody indicates clinical resolution, immunity from reinfection and *functional* cure
- However, viral ccc DNA remains in the nucleus of the infected cells for life
  - May become reactivated with immune suppression or cancer chemotherapy

Hepatitis B – Chronic Disease

- Defined as persistence of HBsAg beyond 6 months post infection
- Probability of chronic infection depends on the age of onset of disease
  - Perinatal infection – 90%
  - Infection in childhood (before age 5) 30%-50%
  - Adult - < 5%
- A significant number of chronically infected individuals will die prematurely
  - 25% of those infected during childhood
  - 15% of those developing chronic disease after childhood
- Major causes of death
  - Hepatocellular cancer (HCC) – second most common cause of cancer death worldwide
    - Develops in 30% of those with cirrhosis
    - Approximately 10% of cases occur in individuals without cirrhosis
  - Cirrhosis of the liver
    - Develops in up to 40% of untreated patients

Chronic Disease – Different Phases

- Immune tolerant phase
  - Primarily occurs with infection at birth
  - More common with genotype C
  - Associated with a positive e antigen
  - Seroconversion to e antibody may or may not occur and timing varies with genotype
  - HBV DNA $\geq$ 200,000 IU/ml, often in the millions
  - ALT normal
  - No or minimal inflammation or fibrosis on biopsy

Chronic Disease – Different Phases

- Immune active phase
  - Phase of active virus clearance
  - Most often occurs between ages 20 and 40 in those infected perinatally
  - ALT levels are usually elevated and reflect immune damage to the hepatocytes
  - HBV DNA usually ≥ 20,000 IU/ml
  - High risk of cirrhosis and HCC
  - Seroconversion from e antigen to e antibody may occur
    - 10% to 40% revert to e antigen positive, often with a flare of hepatitis (may be asymptomatic)
      - Risk of HCC is greater the later seroconversion to e antibody occurs (after age 40)
    - 20% remain in immune active phase
    - Remainder go to Inactive Phase

Chronic Disease – Different Phases

- Inactive phase
  - E antigen negative
  - ALT normal
  - HBV DNA < 2,000 IU/ml, often undetectable
  - Liver inflammation improves over time
  - Fibrosis may revert over time
    - May only slowly change on biopsy
  - 5% may revert to immune active phase with recurrent liver damage
    - Remain at risk for cirrhosis and HCC
  - About 1%-2% per year (10%-25% overall) will clear the surface antigen
    - Clearance is variable and unpredictable
    - May or may not develop the surface antibody
  - Prognosis is generally good, especially if no significant liver damage
    - Risk of progression, HCC and cirrhosis are low

Hepatitis B – Mutations that Affect Prognosis

- Basal Core Promoter (BCP)
  - Associated with increased risk of HCC and cirrhosis
  - Relative risk 1.7-3.2 for HCC
  - RR – 1.9 for cirrhosis

- Pre-Core (PC)
  - Prevents the production of the e antigen
  - Common in the Mediterranean region
  - Does not occur with genotype A
  - Tip off is the presence of high viral DNA level with absent e antigen
    - In this scenario prognosis is driven by the viral load
  - More common in individuals with active liver inflammation
  - Some variants may be associated with an increased risk of HCC
  - Risk of cirrhosis appears to be lower

Risk Factors for Developing Cirrrhosis or HCC

- E antigen positive
- Higher HBV DNA/viral load
- Elevated ALT level, especially higher values
- Genotypes C and F
- Basal core promoter (BCP) mutation
- Co-infection with other viruses (hepatitis C, D or HIV)
- Male sex (3 to 4:1 risk)
  - Higher for HCC than cirrhosis
- Age – increases significantly after 40
- Family history of cirrhosis or HCC
- Moderate to heavy alcohol use
- Smoking
- Coffee intake decreases risk

Hepatitis B – Indicators for Fibrosis or Cirrhosis

- Higher levels of ALT and/or AST
- AST:ALT ratio > 1
- AST to Platelet Ratio Index (APRI) score
  - Higher levels are more suggestive of fibrosis or cirrhosis
    - Score < 0.5 low risk of fibrosis, score > 1.5 more suggestive of cirrhosis
- Fibrosis-4 (FIB-4) Index
  - Uses age, AST level, ALT level and platelet count to assess risk for liver fibrosis
  - Scores correlate with risk for advance fibrosis
    - Low risk - < 1.30, Intermediate risk – 1.30-2.67, High risk or cirrhosis - > 2.67
- FibroTest/FibroSURE
  - Uses age, AST level, ALT level and platelet count to assess risk for liver fibrosis
  - < 0.31 – minimal to none, 0.31-0.58 – moderate, 0.58-0.74 – advanced, > 0.74 – severe fibrosis or cirrhosis
- Liver elastography (Fibroscan) - scores
  - Moderate fibrosis – 8 to 9 kPa, severe fibrosis – 9 to 11 kPa, cirrhosis – 12 kPa up

Hepatitis B – Goals of Therapy

- Suppression of inflammation
- Reduction or prevention of liver fibrosis
- Avoidance of cirrhosis
- Prevention of hepatocellular cancer
- For those who achieve goals about 1% to at most 2% become HBsAg negative per year
- Loss of HBsAg = “Functional Cure”

Hepatitis B – When to Treat

- Most treatment occurs in immune active phase
  - ALT elevation, generally more than 2x normal (levels may be variable) *plus*
  - E antigen positive with HBV DNA levels > 20,000 IU/ml *or*
  - E antibody positive with HBV DNA levels > 2,000 IU/ml *or*
  - Liver biopsy or noninvasive tests showing moderate to severe inflammation and/or fibrosis

- Clear reactivation after seroconversion also treated
  - Return to positive HBeAg and/or increased HBV DNA levels
  - Rebound of ALT elevations

Hepatitis B – When to Treat

- Immune tolerance phase generally not treated
  - High viral load (> 20,000 IU/ml), e antigen positive, normal ALT
  - Viral clearance only 10% with therapy
  - Exceptions based on liver biopsy or non-invasive testing results:
    - Moderate to severe inflammation (A2, A3) and/or
    - Moderate or greater fibrosis (≥ F2)
  - May be most useful in those > age 40

- No evidence of benefit in the truly inactive carrier phase
  - E antigen negative, e antibody positive
  - HBV DNA < 2000 IU/ml or undetectable
  - Persistently normal ALT levels
  - No biopsy or noninvasive evidence for significant inflammation or fibrosis
  - Exceptions to non-treatment
    - Individuals with moderate or more fibrosis
    - Elevated HBsAg levels > 1000 IU/ml

Hepatitis B – 2 Major Types of Treatment

- Interferon alfa (peg-interferon)

- Nucleos(t)ide analogs
  - Entecavir (Baraclude)
  - Tenofovir disoproxil fumarate (Viread)
  - Tenofovir alafenamide (Vemlidy)
  - Lamivudine (Epivir)
  - Adefovir (Hepsera)

Hepatitis B – Interferon Therapy

- Advantages
  - Limited duration of therapy (up to 12 months)
  - No viral resistance
  - Immunomodulatory and modest antiviral effects
  - Greater chance of clearing hepatitis B surface antigen

- Disadvantages
  - Requires subcutaneous injection
  - Can induce hepatitis flares
  - Can’t be used in decompensated cirrhosis, pregnancy, autoimmune illnesses or depression
  - Frequent side effects – often difficult to tolerate

Hepatitis B – Nucleos(t)ide analogs

- Advantages
  - Oral use
  - Strong antiviral activity
  - Side effects are infrequent (lowest with tenofovir alafenamide or Vemlidy)
  - Can use in compensated and de-compensated cirrhosis

- Disadvantages
  - Drug resistance can occur, affects other drugs in the class
    - Especially lamivudine (Epivir) and adefovir (Hepsera)
    - Entecavir and tenofovir are the drugs of first choice because of low resistance
  - Needs to be used for an extended period of time- often lifetime
    - Compliance and side effects may become an issue
  - Consideration for stopping drugs in those who do not achieve HBsAg loss
    - After 1 year in those with HBeAg loss
    - After 3 years in those who were HBeAg negative at time of therapy
  - Relapses may occur after drug is stopped

Hepatitis B – Indicators for Success of Therapy

- Decrease of HBV DNA values to undetectable levels
- Seroconversion of HBeAg to HBeAb
- Normalization of serum ALT readings
- For those who achieve goals about 1% to 2% become HBsAg negative per year
- Loss of HBsAg = “Functional Cure”

Hepatitis B – "Functional" Cure

- Clearance of surface antigen
  - With or without development of the surface antibody
- Viral DNA undetectable without ongoing treatment using conventional assays
- However, risk of occult hepatitis B infection remains

Hepatitis B – Occult HBV Infection

- Condition where viral cccDNA is incorporated into hepatocytes with low levels of viral replication
- More common in individuals with risk factors for hepatitis B (IV drug users, dialysis patients, co-infection HCV or HIV)
- Surface antigen (HBsAg) is either consistently or intermittently negative
- Hepatitis B core antibody (HBcAb) positive with or without detection of surface antibody (HBsAb)
- HBV DNA is detectable in the liver
  - Viral DNA at very low levels in the blood without ongoing treatment but usually undetectable using conventional assays
- Felt to be due to suppression by the host immune system
- Individuals remain capable of transmitting infection through transfusion or transplantation
- Immunosuppression can lead to reactivation of infection with significant adverse consequences
  - Progression of chronic liver disease from any of several causes (hepatitis B, fatty liver disease, hepatitis C, alcohol related disease etc.) to cirrhosis
  - Ongoing risk for developing hepatocellular cancer – similar to overt hepatitis B infections
- All individuals who are going to receive immunosuppressive or chemotherapy should be checked for a prior HBV infection
  - Treatment may cause reactivation of the virus – in up to 40% of patients
  - Prophylactic therapy with nucleos(t)ide analogs during and up to 12 months after completion of therapy is recommended

Hepatitis B – New Therapies in Development

- Drugs that reduce HBsAg levels
  - Fight immune fatigue
- Entry inhibitors
  - Impair viral entry into cells
- Capsid inhibitors
  - Impair viral particle assembly
- Viral RNA inhibitors – small interfering RNA, antisense oligonucleotides
  - Impair viral RNA products (interfere with transcription, increase degradation)
  - Effectively silence viral genome
- Elimination of cccDNA in the hepatocyte
  - Gene editing (CRISPR/Cas9)
  - Epigenetic modification – silence transcription
  - Accelerated degradation
- Enhancement of host immune response
  - Augment usual immune response
  - Block inhibition of immune response

Hepatitis B – "True" Cure

- Involves elimination of the cccDNA
- Will likely require combination therapy
- Similar to approach with HIV disease
- At present effective, reliable therapy to achieve it is not available

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