Objectives

- Compare and contrast the major types of hepatitis viruses and explain the disease transmission and progression processes in viral hepatitis cases
- Describe how the clinical laboratory may be used to diagnose and monitor the course of infectious hepatitis
- Compare and contrast the current methods for the treatment and prevention of infectious hepatitis

Hepatitis

- General term for inflammation of the liver
- Can be due to non-infectious causes such as:
  - Autoimmune disorders
  - Alcohol abuse
  - Chemical agents
  - Obstruction
Viral Hepatitis

- Can be caused by a number of viruses
  - Referral as **Infectious Hepatitis**
  - **Primary hepatitis viruses** – are those whose main clinical effects are on the liver
  - **Secondary hepatitis viruses** – are those that produce liver inflammation secondary to other disease processes

Primary Hepatitis Viruses

- Hepatitis A Virus (HAV)
- Hepatitis B Virus (HBV)
- Hepatitis C Virus (HCV)
- Hepatitis D Virus (HDV)
- Hepatitis E Virus (HEV)

Primary Hepatitis Viruses

- Two main routes of transmission:
  - **Fecal-oral route** – contaminated food or water
    - Hepatitis A virus
    - Hepatitis E virus
  - **Parenteral route** – contact with blood or body fluids
    - Hepatitis B virus
    - Hepatitis C virus
    - Hepatitis D virus
Clinical Forms of Hepatitis

- **Acute hepatitis**
  - The typical form
  - Includes associated jaundice
  - Includes 4 phases of illness:
    - **Incubation phase** – liver enzymes rise
    - **Preicteric phase** – symptoms occur
    - **Icteric phase** – jaundice occurs
    - **Convalescence** – recovery

- **Fulminant hepatitis**
  - Rare form associated with hepatic failure

- **Subclinical hepatitis**
  - Light or no symptoms

- **Chronic hepatitis**
  - Hepatic inflammation and necrosis that lasts for at least 6 months

---

**Acute Hepatitis**

- All primary hepatitis viruses produce similar clinical syndromes
  - **Symptomology**
    - Flu-like symptoms
    - Loss of appetite
    - Nausea & vomiting
    - Right upper quadrant pain
Acute Hepatitis

- **Progression of disease**
  - Hepatomegaly
  - Jaundice
  - Dark urine
  - Light stools

Acute Hepatitis

- **Laboratory results:**
  - ALT & AST rise quickly due to necrosis of liver cells
    - These are the most useful tests for detecting hepatic cell damage
    - ALT is most specific since highest levels are in the liver
    - ALT levels may increase to 100 times normal
  - Bilirubin levels rise as disease progresses

Hepatitis A Virus

- **HAV** is an RNA virus
- Transmitted by fecal-oral route
  - And possibly by close person-to-person contact
- Incubation period of 28 days
- Most infected adults develop **acute hepatitis**
- Most infections in children remain **subclinical**
Acute Hepatitis A

- Symptoms have an abrupt onset and last 1 to 8 weeks
- Infections do not progress to a chronic state
- Liver enzymes usually return to normal within 6 months

Hepatitis A – Lab Diagnosis

- Presence of IgM antibodies to HAV indicate active disease
  - IgM antibodies peak during the first month of infection, and become undetectable within 6 to 12 months
- Presence of IgG antibodies indicates immunity to HAV
  - IgG antibodies are produced either due to an infection or due to immunization

Course of HAV Infection
**Hepatitis A Treatment & Prevention**

- No specific treatment other than supportive therapy
- **Preventive measures include:**
  - Immunization
  - Food safety
  - Proper sanitation
  - Proper handwashing and hygiene

**Hepatitis E**

- HEV is an RNA virus
- **Transmitted by fecal oral route**
  - Usually from contaminated drinking water in developing nations
  - Infection in U.S. is usually associated with travel to endemic regions
- Presents as acute hepatitis and **does not** progress to a chronic state

**Hepatitis E – Lab Diagnosis**

- IgM antibodies are present during **acute infection** but decline rapidly
- IgG antibodies persist long-term and provide some immunity
Course of HEV Infection

Hepatitis E Virus Infection
Typical Serologic Course

- No specific treatment other than supportive therapy
- Preventive measures include:
  - Food & water safety
  - Proper sanitation
  - Proper handwashing and hygiene

Hepatitis B

- HBV is a DNA virus
- Transmitted by the parenterl route
  - Transmission has been associated with:
    - Sexual contact, blood transfusions, sharing of needles, tattooing, & occupational needle-stick injury
    - May also be transmitted from mother to infant during delivery or from breast feeding
Hepatitis B Infection

- Incubation period of 60 to 90 days
- Clinical course is highly variable
  - Many remain subclinical & asymptomatic
  - 30 to 50% develop symptoms of acute hepatitis which last 1 to 4 weeks

Hepatitis B Infection

- Most HBV-infected adults recover within 6 months and develop immunity
- 1 to 2% develop fulminant disease - High fatality rate
- Chronic HBV infection develops in 5 to 10% of infected adults
  - These have an increased risk of developing cirrhosis or hepatocellular carcinoma

Hepatitis B Epidemiology

- About 300 million people, worldwide, are thought to be chronic carriers of the virus
- It is estimated that HBV causes about 1,000,000 deaths per year, worldwide
**HBV Structure**

- **Nucleocapsid core surrounded by an outer envelope of lipoprotein**

- **Viral core contains:**
  - Circular, double-stranded DNA
  - DNA polymerase
  - Hepatitis B core antigen (HBCAg)
  - Hepatitis Be antigen (HBeAg)

---

**HBV Structure**

- **Hepatitis B surface antigen (HBsAg)** is a protein found in the outer envelope of the virus

- **HBsAg** is also found in particles that float freely in the blood of infected individuals

---

**HBV Structure**

- Diagram showing HBsAg, HBCAg, DNA polymerase, and HBeAg.
**HBV – Serologic Markers**

- Viral proteins, or the antibodies directed against them, are used to:
  - Diagnose HBV infection
  - Monitor the course of infection
  - Assess immunity to the virus
  - Screen blood products

**Hepatitis B Surface Antigen (HBsAg)**

- The **first marker to appear** in HBV infection
- Becomes detectable 2 to 12 weeks after exposure
- Levels peak during acute stage of infection, then decline as the patient develops antibodies to the antigen

**Hepatitis B Surface Antigen (HBsAg)**

- **HBsAg is an indicator of an active infection**
- **Acute infections**
  - Levels become undetectable by 12 to 20 weeks after onset of symptoms
- **Chronic infections**
  - Levels remain elevated
Hepatitis Be Antigen (HBeAg)

- Appears shortly after HBsAg appears
- Disappears shortly before HBsAg disappears
- Present during periods of active replication
  - Indicates a high degree of infectivity when present
  - May be elevated during chronic infection

Hepatitis B Core Antibody (Anti-HBc)

- The HBeAg is not detectable in serum because the viral envelope masks it
- But as the host develops an immune response, antibodies to HBe appear
- IgM anti-HBe is the first to appear
  - IgM anti-HBe is an indicator of a current or recent acute infection

Anti-HBe IgM

- Usually appears 2 weeks after HBsAg in an acute infection
- May be detected for up to 6 months
- Useful for detecting infection during the "core window"
  - "Core window" is the period of time between the disappearance of HBsAg and the appearance of anti-HBsAg
  - This makes it useful for screening donor blood
Anti-HBc IgG
- Appears before IgM anti-HBc disappears
- Persists for the lifetime of the individual
- May be used to detect a past infection

Hepatitis Be Antibody (Anti-HBe)
- Appears shortly after the disappearance of HBeAg
- Indicates that the patient is recovering from HBV

Hepatitis B Surface Antibody (Anti-HBs)
- Appears during the recovery period of acute HBV
- Appears weeks to months after the disappearance of HBsAg
- Provides protective immunity
- Not produced during chronic HBV infection – immunity fails
**Anti-HBs**

- Produced after immunization with the HBV vaccine
- The vaccine consists of recombinant HBSAg produced from genetically engineered yeast
- Used to test for immunity

**HBV Infection**

[Diagram showing HBV infection process]
Acute Hepatitis B

- Acute cases are typically self-limiting and only require supportive therapy

Chronic Hepatitis B

- Chronic cases are treated with antiviral therapies such as interferon and other antiviral agents such as Ribavirin

HBV Treatment

- Molecular methods such as PCR can be used to measure viral DNA to monitor antiviral therapy
HBV Prevention

- **Primary preventive measures:**
  - **Vaccination is #1**
  - Hand hygiene
  - Safe handling and disposal of sharps and biological waste
  - Safe cleaning of equipment
  - Testing of donated blood
  - Training of health personal
  - Safe sex practices

Hepatitis D

- **Transmitted through parenteral route**

- **Can only occur in the presence of HBV**

- Because HDV incorporates the HBsAg into its outer protein coat which it requires to replicate & infect host cells

Hepatitis D

- Presence of HDV in people infected with HBV results in a greater risk of fulminant hepatitis or chronic liver disease

- Indicated by the presence of anti-HDV in the patient’s serum
Hepatitis D Virus

Hepatitis D (Delta) Virus

Hepatitis D Antibody (Anti-HDV)

- IgM anti-HDV appears 6 to 7 weeks after exposure
- Remains elevated through acute phase of illness, then declines
- IgG anti-HDV is produced during convalescence & declines to undetectable levels if infection resolves
- Both IgM & IgG remain elevated in chronic infections

Course of HDV
Course of HDV

Hepatitis D Treatment & Prevention

• Treatment and prevention is the same as for Hepatitis B due to its dependence on HBV

Hepatitis C

• Transmitted through the parenteral route
• Average incubation time of 7 to 8 weeks
• Produces symptoms of acute hepatitis in 20% of individuals
• Majority of infections are subclinical & asymptomatic
Hepatitis C

• But 85% develop a chronic infection which may slowly develop into cirrhosis

• HCV accounts for 1/3 of liver transplants
  – Antiviral therapy following liver transplant is essential to prevent or slow the rate of reinfection

Hepatitis C

• HCV is an RNA virus

• 6 different genotypes and 50 subtypes have been discovered

• A high mutation rate allows it to escape the immune response and persist in the patient

Hepatitis C Testing

• HCV is diagnosed by detecting HCV antibodies

• With current assays, antibodies can usually be detected at the time symptoms appear (7 to 8 weeks after exposure)

• Current tests do not distinguish between acute or chronic infection
Hepatitis C Testing

- Molecular testing such as PCR may also be used to confirm positive results
- PCR may be done as a qualitative or quantitative test
- Quantitative PCR can be used to monitor the viral load
- HCV RNA appears in serum in as little as 1 week

Acute Hepatitis C

Chronic Hepatitis C
Hepatitis C Treatment

• Currently the standard treatment is combination therapy consisting of:
  – Interferon
  – Ribavirin

• Interferon is poorly tolerated in some patients
  – However, combination therapy can be potentially life-saving

• There is no vaccine available

Hepatitis C Prevention

• Primary preventive measures:
  – Hand hygiene
  – Safe handling and disposal of sharps and waste
  – Safe cleaning of equipment
  – Testing of donated blood
  – Training of health personal
  – Safe sex practices

References

• Turgeon, M.L. 2009. Immunology and Serology in Laboratory Medicine, 4th ed. Mosby, St. Louis.
Contact Information

Steven Edwards, MS(MLS)
Assistant Professor of Medical Lab Science
Lincoln Memorial University
6965 Cumberland Gap Pkwy
Harrogate, TN 37752
Office: 423-869-6232
Email: steven.edwards@LMUnet.edu