VIRAL AND AUTOIMMUNE HEPATITIS

Arthur M. Magun, M.D.
Clinical Professor of Medicine

WHAT IS HEPATITIS?
• Inflammation of the liver
• Almost always, inflammation implies elevation in liver enzymes
• AST and ALT are the key liver enzymes
• Other Liver Function Tests (LFTs) which can be abnormal in hepatitis include:
  • Bilirubin, albumin, alkaline phosphatase, gamma glutamyl transpeptidase

CAUSES OF ACUTE HEPATITIS
• Viral hepatitis
• Other infectious etiologies e.g. CMV, EBV, TB
• Alcoholic hepatitis
• Drug hepatitis
• Ischemic hepatitis
• Choledocholithiasis

OTHER INFECTIOUS ETIOLOGIES OF ACUTE HEPATITIS
• CMV - cytomegalovirus; immunocompromised host
• EPSTEIN-BARR – mononucleosis; lymphadenopathy; splenomegaly
• TB and M. avium intracellulare (MAI)

SYMPTOMS OF ACUTE VIRAL HEPATITIS
• Fatigue, nausea, anorexia
• Jaundice
• Low-grade fever, abdominal pain
• Arthralgia, myalgia, headache
SIGNS OF ACUTE VIRAL HEPATITIS

- Jaundice
- Hepatomegaly with RUQ tenderness
- Fever – low grade
- Splenomegaly – infrequent

LIVER BLOOD TEST
ABNORMALITIES IN ACUTE VIRAL HEPATITIS

- AST AND ALT - 1000-5000 IU
- Bilirubin – generally elevated – both conjugated and unconjugated
- Alkaline Phosphatase – minimally elevated
- Bilirubin and urobilinogen increased in urine

OUTCOMES OF VIRAL HEPATITIS

HEPATITIS A

- Oral fecal route of transmission
- Excreted in stool about 2 weeks prior to clinical illness
- 1 month incubation period
- Children often asymptomatic
- Never causes chronic hepatitis
HEPATITIS A
PREVENTION AND TREATMENT

- No treatment of infection available
- Passive immunity with gamma globulin can ameliorate disease in early stages of the infection
- Gamma globulin can prevent disease pre-exposure
- Vaccine available to induce active immunity
Hepatitis B Virus - Replication

- Uncoating
- Nuclear import
- Repair
- Transcription
- Translation
- Removal of pregenome
- Negative strand synthesis
- Encapsidation
- cccDNA
- 3.5 kb RNA
- 2.4/2.1 kb RNA

Hepatitis B Virus: Viral Replication. Pt. 4

- Assembly & budding
- ER
- Positive strand synthesis
- Nuclear import
- HBsAg
- HBsAg

Hepatitis B Virus - Immunopathogenesis

- HBV
- Hepatocytes
- CTL
- Ig
- CD4
- CD8
- Class II
- Class I
- B cell
- NK, NKT cells
- Cytokines
- Nonspecific inflammatory cells
- Direct cytotoxicity?
- Clearance
- Apoptosis

HEPATITIS B VIRUS
NATURAL HISTORY

- Transmission – parenteral, secretions, sexual, mother to child (vertical)
- 6-8 week incubation
- 20% pf patients have serum sickness prodrome
- 4% of patients develop chronic hepatitis
- Treatment and vaccine available
Serological Markers | Clinical Significance
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HBsAg | Acute/Chronic infection
Anti-HBc IgM | Acute infection
HBeAg | High infectivity
Anti-HBe | Low infectivity
Anti-HBs | Immunity
Anti-HBc IgG and HBsAg | Chronic infection
Anti-HBc IgG and anti-HBs | Resolved infection

**Hepatitis C Virus**
- Nucleic Acid: 9.6 kb ssRNA
- Classification: Flaviviridae, Hepacivirus
- Genotypes: 1 to 6
- Enveloped
- In vitro model: primary hepatocyte and T cell cultures; replicon system
- In vivo replication: in cytoplasm, hepatocyte and lymphocyte; human and other primates

**Genome and Gene Products**
- Core (C): Nucleocapsid
- E1 and E2: Envelope proteins, hypervariable region in E2
- p7: Nonstructural, ion channel (?)
- NS 2: NS 2-3 protease
- NS 3: Protease, nucleotide triphosphatase, and RNA helicase
- NS 4: Cofactor for NS 3 protease activity
- NS 4B: Formation of membranous web
- NS 5A: Interferon sensitivity sequence
- NS 5B: RNA-dependent RNA polymerase

**HBV - Diagnosis**
- Acute HBV Infection
- HBV DNA: Structural protein coding region
- HBeAg: Nonstructural protein coding region
- Anti-HBe: Structural protein coding region
- Anti-HBs: Nonstructural protein coding region
- Anti-HBc IgM: Structural protein coding region
- Anti-HBc IgG and HBsAg: Nonstructural protein coding region
- Anti-HBc IgG and anti-HBs: Structural protein coding region

**Hepatitis C Virus - Replication**
- Entry: Lipoproteins
- Gene Products and Functions:
  - Core (C): Nucleocapsid
  - E1 and E2: Envelope proteins, hypervariable region in E2
  - p7: Nonstructural, ion channel (?)
  - NS 2: NS 2-3 protease
  - NS 3: Protease, nucleotide triphosphatase, and RNA helicase
  - NS 4: Cofactor for NS 3 protease activity
  - NS 4B: Formation of membranous web
  - NS 5A: Interferon sensitivity sequence
  - NS 5B: RNA-dependent RNA polymerase
Hepatitis C Virus: Viral Replication, pt. 2

- Uncoating
- Translation
- NS4B
- E1-E2
- NS2
- NS3/4A
- NS5B
- NS5A
- Chaperones
- Nucleus
- ER

Hepatitis C Virus: Viral Replication, pt. 3

- Export
- Progeny genome
- Assembly
- E1-E2
- NS4B
- NS3/4A
- Golgi
- NS2
- NS5B
- NS5A
- Chaperones
- Nucleus
- ER

Hepatitis C Virus: Viral Replication, pt. 4

- Replication
- Progeny genome
- Assembly
- E1-E2
- NS4B
- NS3/4A
- Golgi
- NS2
- NS5B
- NS5A
- Chaperones
- Nucleus
- ER

Hepatitis C Virus: Immune Responses and Pathogenesis, pt. 1

- Antigen presenting cells
- Ig
- Cytokines
- CD4 Class II
- CD8 Class I
- B cell
- TH

Hepatitis C Virus: Immune Responses and Pathogenesis, pt. 2

- CTL
- Cytokines
- CD4 Class II
- CD8 Class I

Hepatitis C Virus: Immune Responses and Pathogenesis, pt. 3

- Cytokines
- Nonspecific inflammatory cells
- CTL
HEPATITIS C CLINICAL
- Most common cause of chronic hepatitis in USA
- 1.5% of population in USA carries the virus
- Parenteral transmission – blood, sexual
- 6-8 week incubation period
- Acute infection generally mild
- 80% of acute develop chronic disease
- No vaccine available
- Treatment – 40-80% cure rate

HEPATITIS D AND E
- HEPATITIS D
  - Also known as delta agent
  - Uses the HBsAg protein coat
  - Hepatitis B must be present – coinfection or preexist
- HEPATITIS E
  - Water borne virus resembling hepatitis A
  - Rarely seen in USA
**CHRONIC HEPATITIS**

- Elevated liver enzymes (AST and/or ALT) for greater than 6 months with characteristic pathologic findings
- Many different diseases can cause chronic hepatitis
- Liver biopsy is frequently performed for definitive diagnosis

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**PATHOLOGY OF CHRONIC HEPATITIS**

- Portal tracts, peri-portal regions and lobules are involved
- Liver biopsy shows chronic inflammation manifested as increased inflammatory cells - mainly plasma cells and lymphocytes
- The inflammation may result in fibrosis which can lead to cirrhosis

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**ETIOLOGY OF CHRONIC LIVER ENZYME ELEVATIONS**

- Viral – B and C
- Autoimmune
- Drugs
- Metabolic – Wilson’s
- Fatty liver - Steatohepatitis
- Alcohol
- Others – CHF, hemochromatosis, ulcerative colitis, celiac disease, and others.
Dynamics of the different phases of chronic hepatitis B virus (HBV) infection

Serologic events in HBV infection

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<th>Anti-HBs</th>
<th>Anti-HBc IgG</th>
<th>Anti-HBc IgM</th>
<th>Anti-HBe</th>
<th>HBV DNA</th>
<th>ALT</th>
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<td>Exposure with Immunity</td>
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<td>Chronic HBV (Wild Type)</td>
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<td>Chronic HBV (Precore Mutant)</td>
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<td>Inactive Carrier</td>
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AUTOIMMUNE HEPATITIS

- Genetically predisposed host exposed to an environmental agent triggering an autoimmune response directed at liver antigens leading to a necroinflammatory response
- Associated with other autoimmune diseases - thyroid disease, colitis, hemolytic anemia, ITP, diabetes, celiac disease, polymyositis, pericarditis, SLE, MCTD

AUTOIMMUNE HEPATITIS

- Clinical presentation – generally female, fatigue, jaundice, hypergammaglobulinemia, elevated AST and ALT
- Lab - presence of associated autoantibodies – ANA, thyroid antibodies, LKM, smooth muscle
- Diagnostic liver biopsy – interface hepatitis and plasma cell infiltration
- Treatment - steroids and immunosuppressants

END