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

Human Hepatitis Viruses

<table>
<thead>
<tr>
<th>Virus</th>
<th>Genome</th>
<th>Genome size (kb)</th>
<th>Envelope</th>
<th>Family / genus</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAV</td>
<td>RNA</td>
<td>7.5</td>
<td>-</td>
<td>Picornaviridae, hepatovirus</td>
</tr>
<tr>
<td>HBV</td>
<td>DNA</td>
<td>3.2</td>
<td>+</td>
<td>Hepadnaviridae</td>
</tr>
<tr>
<td>HCV</td>
<td>RNA</td>
<td>9.6</td>
<td>+</td>
<td>Flaviviridae, hepacivirus</td>
</tr>
<tr>
<td>HDV</td>
<td>RNA</td>
<td>1.7</td>
<td>+</td>
<td>Unclassified, (viroid), delta virus</td>
</tr>
<tr>
<td>HEV</td>
<td>RNA</td>
<td>7.5</td>
<td>-</td>
<td>Unclassified, togavirus and alpha virus-like</td>
</tr>
</tbody>
</table>
OTHER INFECTIOUS ETIOLOGIES OF ACUTE HEPATITIS

- CMV - cytomegalovirus; immunocompromised host
- EPSTEIN-BARR – mononucleosisis; lymphadenopathy; splenomegaly
- TB and M. avium intracellurare (MAI)

SYMPTOMS OF ACUTE VIRAL HEPATITIS

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

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

ACUTE ILLNESS

CHRONIC HEPATITIS  CURE  FULMINANT HEPATITIS

Hepatitis A Virus

- Nucleic Acid: 7.5 kb ssRNA
- Classification: *Picornaviridae*, *Hepatovirus*
- One serotype and multiple genotypes
- Nonenveloped, acid and heat stable
- In vitro model: monkey and human cell cultures
- In vivo replication: in cytoplasm of hepatocyte; human and other higher primates
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
Typical Serologic Course of Acute Hepatitis A Virus Infection

Fecal HAV

ALT

Symptoms

IgM anti-HAV

Total anti-HAV

HAV

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

- Nucleic Acid: 3.2 kb DNA
- Classification: *Hepadnaviridae*
- Multiple serotypes and genotypes A-F
- Enveloped
- In vitro model: primary hepatocyte culture and transfection of cloned HBV DNA
- In vivo replication: in cytoplasm, cccDNA in nucleus; hepatocyte and other tissues, human and other primates
Hepatitis B Virus - Replication

Viral entry

Uncoating

Nuclear import

cccDNA

5' 3.5 kb RNA

5' 2.4/2.1 kb RNA

3'

Repair

Transcription

Positive strand synthesis

Removal of pregenome

Negative strand synthesis

Encapsidation

Translation
Hepatitis B Virus: Viral Replication

Viral entry → Uncoating → Nuclear import → Repair → Transcription → Translation → Assembly & budding → ER → Positive strand synthesis → Removal of pregenome → Negative strand synthesis → Encapsidation

cccDNA → 3.5 kb RNA → 5' 2.4/2.1 kb RNA → 3'

Hepatitis B Virus: Immunopathogenesis

HBV → Hepatocytes
Hepatitis B Virus - Immunopathogenesis

Cytokines

Apoptosis

Antigen presenting cells

Direct cytotoxicity?

CD4 Class II

CD8 Class I

Nonspecific inflammatory cells

Ig

B cell

Hepatocytes

NK, NKT cells

Hepatitis B Virus: Immune Responses and Pathogenesis, pt. 4

HEPATITIS B CLINICAL

- 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

<table>
<thead>
<tr>
<th>Marker</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Acute/Chronic infection</td>
</tr>
<tr>
<td>Anti-HBc IgM</td>
<td>Acute infection</td>
</tr>
<tr>
<td>HBeAg</td>
<td>High infectivity</td>
</tr>
<tr>
<td>Anti-HBe</td>
<td>Low infectivity</td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Immunity</td>
</tr>
<tr>
<td>Anti-HBc IgG and HBsAg</td>
<td>Chronic infection</td>
</tr>
<tr>
<td>Anti-HBc IgG and anti-HBs</td>
<td>Resolved infection</td>
</tr>
</tbody>
</table>

**Acute HBV Infection**

- HBV DNA
- HBeAg
- Anti-HBe
- Anti-HBs
- Anti-HBc
- Anti-HBc IgM

**Timeline**

- 0 Months
- 2 Months
- 4 Months
- 6 Months
- 1 Year
- 2 Years
- 6 Years
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

<table>
<thead>
<tr>
<th>C</th>
<th>E1</th>
<th>E2</th>
<th>NS2</th>
<th>NS3</th>
<th>NS4B</th>
<th>NS5A</th>
<th>NS5B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Structural protein coding region
Nonstructural protein coding region

Core
Protease
Protease Cofactor
Serine protease
Helicase
RNA polymerase

5' UTR
3' UTR

Hepatitis C Virus:  Morphology and Characteristics

Hepatitis C Virus: Genome and Gene Products, pt.2
### Gene Products and Functions

<table>
<thead>
<tr>
<th>Gene Products</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core (C)</td>
<td>Nucleocapsid</td>
</tr>
<tr>
<td>E1 and E2</td>
<td>Envelope proteins, hypervariable region in E2</td>
</tr>
<tr>
<td>p7</td>
<td>Nonstructural, ion channel (?)</td>
</tr>
<tr>
<td>NS 2</td>
<td>NS 2-3 protease</td>
</tr>
<tr>
<td>NS 3</td>
<td>Protease, nucleotide triphosphatase, and RNA helicase</td>
</tr>
<tr>
<td>NS 4</td>
<td>Cofactor for NS 3 protease activity</td>
</tr>
<tr>
<td>NS 4B</td>
<td>Formation of membranous web</td>
</tr>
<tr>
<td>NS 5A</td>
<td>Interferon sensitivity sequence</td>
</tr>
<tr>
<td>NS 5B</td>
<td>RNA-dependent RNA polymerase</td>
</tr>
</tbody>
</table>

**Hepatitis C Virus - Replication**

- **Entry**
- **Lipoproteins**
Hepatitis C Virus: Viral Replication, pt. 2

Entry

Uncoating

Translation

Nucleus

Lipoproteins

E2

ER

E2

ER

Hepatitis C Virus: Viral Replication, pt. 3

Replication

Progeny genome

NS5B

NS3/4A

NS4B

NS3/4A

NS2

NS2

NS5B

NS5A

NS5A

Chaperones

E2

ER

E1-E2

E1-E2

E1-E2
Hepatitis C Virus - Immunopathogenesis

HCV

Antigen presenting cells

CD4 Class II

CD8 Class I

Cytokines

B cell

Hepatocytes

Ig

TH

CTL

Nonspecific inflammatory cells

Cytokines

Hepatitis C Virus - Immunopathogenesis

HCV

Antigen presenting cells

CD4 Class II

CD8 Class I

Cytokines

B cell

Hepatocytes

Ig

TH

CTL

Nonspecific inflammatory cells

Cytokines

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

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

Cytokines

Antigen presenting cells

Nonspecific inflammatory cells

CTL

Ig

HCV

Hepatocytes

CD4 Class II

CD8 Class I

T

B cell

Autoimmunity

Immune modulation

Cryoglobulins

Lympho-proliferative disorders

Lymphoid cells

Apoptosis or cytopathic replication

Viral Clearance

HCV

Nonspecific inflammatory cells

Steatosis

Viral Clearance

HCV

NK, NKT cells
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

• Fatty liver
• Viral – B and C
• Autoimmune
• Drugs
• Alcohol
• Metabolic
• Others – CHF, hemochromatosis, vasculitis, IBD, celiac disease, neoplasia, etc.

CHRONIC HEPATITIS B AND C

• Cirrhosis develops in 20% of patients
• Liver failure and hepatoma develop in about ½ of cirrhotics
• Diagnosis of chronic hepatitis made on basis of:
  – chronic AST and ALT elevations
  – positive serology
  – positive DNA or RNA in blood
  – some patients have normal liver enzymes
• Treatment available with varying success rates
HBV - Diagnosis

Chronic HBV Infection

**HBV DNA**

**HBeAg**

**Anti-HBe**

**HBsAg**

**Anti-HBc IgM**

**Anti-HBc IgG**

**Months**

**Years**

Serologic events in HBV infection

<table>
<thead>
<tr>
<th></th>
<th>HBsAg</th>
<th>anti-HBs</th>
<th>HBeAg</th>
<th>Anti-Hbe</th>
<th>Anti-HBc IgG</th>
<th>anti-HBc IgM</th>
<th>HBV DNA</th>
<th>ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute HBV Infection</td>
<td></td>
<td>-</td>
<td></td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>↑/N</td>
<td></td>
</tr>
<tr>
<td>Vaccine Responder</td>
<td></td>
<td>+</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Exposure with Immunity</td>
<td></td>
<td>+</td>
<td></td>
<td>+/-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Chronic HBV (Wild Type)</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>↑ / N</td>
</tr>
<tr>
<td>Chronic HBV (Precore Mutant)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>↑ / N</td>
<td></td>
</tr>
<tr>
<td>Inactive Carrier</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>- /+</td>
<td>Normal</td>
</tr>
</tbody>
</table>
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
• Presence of associated autoantibodies – ANA, thyroid antibodies, LKM, smooth muscle
• Diagnostic liver biopsy – interface hepatitis and plasma cell infiltration
• Treatment - steroids and immunosuppressants