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

<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>Picorniridae hepatovirus</td>
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<tr>
<td></td>
<td>positive sense, single stranded, linear</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>DNA</td>
<td>3.2</td>
<td>+</td>
<td>Hepadnaviridae</td>
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<tr>
<td></td>
<td>partially double stranded, circular</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>RNA</td>
<td>9.6</td>
<td>+</td>
<td>Flaviviridae hepacivirus</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>HDV</td>
<td>RNA</td>
<td>1.7</td>
<td>+</td>
<td>Unclassified (viroid), delta virus</td>
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<tr>
<td></td>
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<tr>
<td>HEV</td>
<td>RNA</td>
<td>7.5</td>
<td>-</td>
<td>Unclassified, togavirus and alpha virus-like</td>
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<tr>
<td></td>
<td>positive sense, single stranded, linear</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
OTHER INFECTIOUS ETIOLOGIES OF ACUTE HEPATITIS

• CMV - cytomegalovirus; immunocompromised host
• EPSTEIN-BARR – mononucleosis; 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

• 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

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

27 nm
Global Prevalence of Hepatitis A Infection

HAV Prevalence
- High
- Intermediate
- Low
- Very Low

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

HAV

Fecal HAV

IgM anti-HAV

Total anti-HAV

Symptoms

ALT

Months after exposure

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

Nucleus
Hepatitis B Virus - Replication

Viral entry

Uncoating

Nuclear import

Repair

Transcription

cccDNA

5' 3.5 kb RNA

3'

5' 2.4/2.1 kb RNA

3'

Hepatitis B Virus - Replication

Viral entry

Uncoating

Nuclear import

cccDNA

5' 3.5 kb RNA

3'

5' 2.4/2.1 kb RNA

3'
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**

<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>

**HBV - Diagnosis**

**Acute HBV Infection**

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

0  2  4  6  0  2  4  6  Months  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**

- Structural protein coding region
- Nonstructural protein coding region

- Core
- Envelope
- Protease
- Protease Cofactor
- Serine protease
- Helicase
- RNA polymerase

- *C E1 E2 NS2 NS3 A NS4 B NS5A NS5B*
**Hepatitis C Virus**

**Gene Products and Functions**

<table>
<thead>
<tr>
<th>Gene Product</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core (C)</td>
<td>Nucleocapsid</td>
</tr>
<tr>
<td>E1 and E2</td>
<td>Envelope proteins &lt;br&gt;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**

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

Hepatitis C Virus - Immunopathogenesis

Antigen presenting cells

Ig

CD4

Cl II

HCV

Cytokines

TH

Class I

CD8

B cell

Hepatocytes

Hepatitis C Virus - Immunopathogenesis

Antigen presenting cells

Ig

CD4

Cl II

HCV

Cytokines

TH

Class I

CD8

B cell

Hepatocytes

Cytokines

Nonspecific inflammatory 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

HCV - Diagnosis

Acute HCV Infection

Hoofnagle JH, Hepatology 1997; 26:155
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

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
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.

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 (though some patients have normal liver enzymes)
  – positive serology
  – positive DNA or RNA in blood
  – diagnostic liver biopsy
• Treatment available with varying success rates
Chronic HBV Infection

- HBV DNA
- HBeAg
- Anti-HBe
- HBsAg
- Anti-HBc IgG
- Anti-HBc IgM

Months
Years

Acute HBV Infection

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

0 2 4 6
Months
Years
Dynamics of the different phases of chronic hepatitis B virus (HBV) infection

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>
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<tr>
<td>Acute HBV Infection</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</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>
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<tr>
<td>Exposure with Immunity</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Normal</td>
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<tr>
<td>Chronic HBV (Wild Type)</td>
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<td>-</td>
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<td>↑/N</td>
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<tr>
<td>Chronic HBV (Precore Mutant)</td>
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<td>-</td>
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<td>+</td>
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<td>-</td>
<td>+</td>
<td>↑/N</td>
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<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
- **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