Learning Objectives (HBV)

- Differentiate the various stages of HBV infection
- Review diagnostic tests
- Discuss treatment
  - Choice of agents
  - Treatment endpoints and long-term data
  - Resistance

Schematic Representation of HBV

DNA polymerase

Inner protein core (HBcAg)

Outer lipid envelope containing HB surface antigen

HBV DNA

HBsAg

HBeAg

Spectrum of Disease

Acute HBV infection

~2%

Fulminant hepatic failure

90–95% neonatal infection

50% childhood infection

5–10% adult infection

15–40%

Liver failure

Chronic HBV infection

Cirrhosis

Liver Cancer

Decompensated cirrhosis

Transplant/Death
Natural History of Chronic HBV Infection

- **Replacive Phase**: HBeAg(+) Anti-HBe(+)
- **Non-replacive Phase**: HBeAg(-) Anti-HBe(-)
- Time (Years) From Onset of Infection:
  - 0 to 10: Seroconversion
  - 10 to 20: Reactivation

Risk Factors for Development of Liver Cancer
- Demographic factors:
  - Male gender
  - Age > 45 years
  - Ethnicity (Asian)
  - Perinatal transmission: sAg carrier: 0.4%/yr
- Acquired later in life: <0.1%/yr
- Family history of HCC
- Cirrhosis
- Detectable HBV DNA

AASLD Hepatitis B Treatment Guidelines

<table>
<thead>
<tr>
<th>HBeAg</th>
<th>HBV DNA &gt; 10^5 copies/mL</th>
<th>ALT</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td></td>
<td>≤ 2 x ULN</td>
<td>Follow</td>
</tr>
<tr>
<td>+</td>
<td></td>
<td>&gt; 2 x ULN</td>
<td>Treat</td>
</tr>
<tr>
<td>-</td>
<td></td>
<td>&gt; 2 x ULN</td>
<td>Treat</td>
</tr>
<tr>
<td>-/-</td>
<td></td>
<td>≤ 2 x ULN</td>
<td>Follow</td>
</tr>
<tr>
<td>*</td>
<td></td>
<td>Cirrhosis</td>
<td>Comp: Treat</td>
</tr>
<tr>
<td>+/-</td>
<td></td>
<td>Cirrhosis</td>
<td>Decomp: Refer for Liver Tx</td>
</tr>
</tbody>
</table>

Anti-HBV Active Compounds

- **Nucleoside analogues**
  - Lamivudine
  - Entecavir
  - Elovurabine
  - Adefovir
  - Emtricitabine
  - Telbivudine
  - Tenofovir
  - Tenofovir

- **Nucleotide analogues**
  - Adefovir dipivoxil
  - Tenofovir
  - Telbivudine
  - Emtricitabine

- **Cytokines**
  - Interferon alfa
  - Peginterferon alfa-2a

*Currently approved for HIV
**Phase 3 in South Korea
Treatment Endpoints in Chronic Hepatitis B

- **HBeAg Loss**
- **Normal ALT**
- **Histological Improvement**
- **Undetectable Serum HBV DNA**
- **HBeAg Seroconversion**

**HBV DNA Levels Over Time**

- **PEGASYS® + placebo**
  - HBeAg seroconversion: EOT = 27%, EOF = 32%

- **PEGASYS® + lamivudine**
  - HBeAg seroconversion: EOT = 24%, EOF = 27%

- **lamivudine**
  - HBeAg seroconversion: EOT = 20%, EOF = 19%

*all numbers shown are log_{10} reduction from baseline

*HBeAg Seroconversion Increases With Duration of LAM Therapy*

- **HBeAg Seroconversion, %**
  - 0% 22% 29% 40%
  - Duration of Therapy, years 0 1 2 3

*Cumulative Lamivudine Genotypic Resistance Rates*

- YMDD mutation detectable, %
  - 0 24 42 53 70
  - Baseline Year 1 Year 2 Year 3 Year 4

Lau et al. AASLD 2004


HBeAg Seroconversion Rates Increase With Prolonged Adefovir

Kaplan-Meier estimates of time to confirmed event


Adefovir Resistance

a. Cumulative probabilities calculated by Life-Table analysis

Borroto-Esoda K., EASL 2006, Abstract 483

rtN236T and/or rtA181V mutations

Entecavir for HBeAg-Positive Patients: Up to 96 Weeks

- Response in nucleoside-naive patients receiving up to 96 weeks entecavir
  - Cumulative HBV DNA suppression < 300 copies/mL during 96 weeks
    - Entecavir, 80% — Lamivudine, 39%
  - Cumulative HBeAg seroconversion during 96 weeks
    - Entecavir, 31% — Lamivudine, 26%
- No evidence of entecavir resistance through Week 96


Managing Resistance

- Better than no treatment in some patients?
- Risk of disease reactivation and worsening
- Risk of liver enzyme flare during transition
- Consider risk of cross-resistance
- May be more effective
- Consider risk of cross-resistance
**Learning Objectives (HCV)**

- Virology
- Epidemiology
- Transmission
- Natural History
- Management
  - ? Newer drugs

**Hepatitis C Genome**

*Specific HCV enzymes*

**HCV Polyprotein**

- NS3 Protease domain
- NS3 Helicase domain
- NS3 Bifunctional protease / helicase
- NS5B RNA-dependent RNA polymerase

**HCV: Virology**

- Genotype distribution in the U.S.
  - Genotype 1a/b ~75%
  - Genotype 2 ~10%
  - Genotype 3 ~10%
  - Genotype 4-6 ~<5%
  - Mixed genotypes ~<5%

**HCV: Epidemiology**

- ~1.8% (approximately 4 million people) in the U.S. are estimated to be afflicted with HCV
- ~4 times the prevalence of chronic HBV
- ~4 times the prevalence of HIV
Estimated Incidence of Acute HCV Infection
United States, 1960-1999

New Infections/100,000
Year

0 20 40 60 80 100 120 140

Decline in transfusion recipients
Decline in injection drug users

Adapted from CDC Hepatitis Slide Kit http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/accessed 01/18/03


Prevalence of HCV Infection
United States, 1988-1994

<table>
<thead>
<tr>
<th>Group</th>
<th>Percent Anti-HCV Positive</th>
<th>Est. Infections Millions (95% CI)</th>
<th>Percent of Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1.8</td>
<td>3.9 (3.1-4.8)</td>
<td>100</td>
</tr>
<tr>
<td>White</td>
<td>1.6</td>
<td>2.4 (1.8-3.1)</td>
<td>61</td>
</tr>
<tr>
<td>Black</td>
<td>3.2</td>
<td>0.8 (0.6-1.0)</td>
<td>20</td>
</tr>
<tr>
<td>Mex American</td>
<td>2.1</td>
<td>0.3 (0.2-0.3)</td>
<td>7</td>
</tr>
<tr>
<td>Other</td>
<td>2.9</td>
<td>0.5 (0.3-1.0)</td>
<td>13</td>
</tr>
</tbody>
</table>

Adapted from CDC Hepatitis Slide Kit http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/accessed 01/18/03

Transmission of HCV

- Injecting drug use (may be remote)
- Blood transfusion prior to 1990
- Dialysis
- Nosocomial
- Maternal fetal
- Sexual
- Occupational
- Intranasal drug use
- Other

Adapted from Hepatitis Slide Kit http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/. Accessed 01/18/03.□

HCV: Epidemiology

- Currently the leading indication for liver transplantation in the U.S. (33%-50%)
- Number of patients with HCV seeking liver transplantation in the next 10-15 years is expected to increase dramatically

Adapted from CDC Hepatitis Slide Kit http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/accessed 01/18/03


HCV: Transmission

- Blood transfusion
- Dialysis
- Intranasal drug use
- Intravenous drug use
- Sexual contact
- Maternal-fetal transmission
- Occupational exposure
- Intranasal drug use
- Other exposures
Injecting Drug Use and HCV Transmission

- Highly efficient among injection drug users
- Rapidly acquired after initiation
- Four times more common than HIV
- Prevalence 60-90% after 5 years

Post-transfusion Hepatitis C

- % of Recipients Infected
- Year

- All volunteer donors
- Donor Screening for HIV Risk Factors
- Improved HCV Tests

HCV: Transmission

- HCV not spread by kissing, hugging, sneezing, coughing, food or water, sharing eating utensils or drinking glasses, or casual contact
- Do not exclude from work, school, play, child-care or other settings based on HCV infection status

HCV: Transmission

- Sexual transmission is thought to be quite uncommon. However, it is recommended that spouses of afflicted patients be checked for HCV
- CDC does NOT currently recommend changing sexual practices when one member of a monogamous couple has HCV
**HCV: Transmission**

- Maternal-fetal transmission is quite uncommon, but it does occur (~2%).
- When it occurs, it is usually in the setting of high viral titers.
- Women should be informed of the slight risk of vertical transmission but not discouraged from having children.

**Preventing HCV Transmission to Others**

- Avoid direct exposure to blood.
- Do not donate blood, body organs, other tissue or semen.
- Do not share items that might have blood on them.
  - Personal care (e.g., razor, toothbrush).
  - Home therapy (e.g., needles).
- Cover cuts and sores on the skin.

**HCV Testing Routinely Recommended**

Based on increased risk for infection:
- Ever injected illegal drugs.
- Received clotting factors made before 1987.
- Received blood/organ before July 1992.
- Ever on chronic hemodialysis.
- Evidence of liver disease.

Based on need for exposure management:
- Healthcare, emergency, public safety workers after needle stick/mucosal exposures to HCV-positive blood.
- Children born to HCV-positive women.

**Disease Progression of HCV**

*Adapted from Brown RS. Epidemiology and Natural History of Hepatitis C. Presented at an ACG Clinical Implications meeting April 6, 2000 in Dallas, TX.*

HCV: Natural History
- Liver enzyme (blood tests) elevations do NOT accurately represent liver damage from HCV. They are very poor surrogate markers for scar tissue in the liver.
- Liver biopsy is the only way to determine the stage of disease.

HCV: Therapy
- Interferon alpha 2a, 2b, consensus interferon, pegylated IFN alpha 2a and 2b are approved as single agents for therapy of HCV
- IFN alpha 2b + ribavirin, pegylated IFN alpha 2a + ribavirin and pegylated IFN alpha 2b + ribavirin are approved as combination regimens for HCV
- Interferon products are administered by subcutaneous injection and ribavirin orally

Patient Management
- As soon as chronic hepatitis C is diagnosed:
  - Immunize against hepatitis A and hepatitis B
  - Avoid alcohol consumption
  - Review all medications, including vitamins, OTC, and herbal medications

HCV: Therapy
- Sustained viral response (SVR) indicates that the virus is not detectable in the blood six months after the antiviral medications have been discontinued.
- It is controversial whether or not an SVR is a “cure”
- HCV RNA (blood virus test) is followed throughout therapy and follow-up to determine if an SVR is achieved
The Problem

- Pegylated interferon alfa + ribavirin yield SVR of 54%-56%
- Relapsers and NR comprise ~45% of the treated HCV population
- Efficacy: Certain groups respond poorly (ie African Americans, HIV/HCV co-infection, renal failure, cirrhosis with decompensation)
- Toxicity: Side effects limit usage in other groups (ie, patients with autoimmune and psychiatric diseases)

New Therapeutic Approaches

- Enhance Current Therapies
  - New interferons
  - Ribavirin-like Molecules
  - Immunomodulators
  - HCV Replication Enzyme Inhibitors
  - Other HCV-Specific Approaches
  - Anti-fibrotics
New Interferons
- Albumin-interferon
  - Fusion of albumin and interferon alfa
- Interferon omega
- Oral interferon inducers
  - resiquimod

Ribavirin-like Molecules
- Ribavirin prodrug
  - Viramidine
- IMPDH inhibitor
  - Merimepob (VX-497)

Immunomodulators
- Histamine
- Thymosin
- Isatoribine
  - Toll-like receptor (TLR) 7 agonist
- CpG oligonucleotides
  - TLR 9 agonist

Specific HCV Replication Enzymes
HCV Polyprotein
- NS3 Protease domain
- NS3 Helicase domain
- NS3 Bifunctional protease / helicase
- NS5B RNA-dependent RNA polymerase

© 2002 JG McHutchison, DUMC
HCV Replication Enzyme Inhibitors
- Protease inhibitors
  - BILN 2061
  - VX 950
- Polymerase inhibitors
  - Nucleoside (NM 283)
  - Non-nucleoside (JTK-003)
- Helicase inhibitors
  - In development

Other Approaches
- Anti-sense oligonucleotides
- Pancaspase (apoptosis) inhibitors
- Ribozymes
- Small interfering RNAs

Anti-Fibrotic Approaches
- Interferon gamma
  - Ineffective in a 48 week placebo-controlled trial in reducing hepatic fibrosis
- Other compounds are in pre-clinical development

Conclusion
- Multiple treatments available for Hepatitis B
- Long term resistance concerning combination therapy
- Response rates for HCV depend on genotype (1=40-50%, 2/3=80-90%)
- New drugs for HCV actively being investigated
  - 5-10 years away from being available