Discovery of Hepatitis C and Natural History

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Hepatitis C Virus (HCV)

- Discovered in 1989 as non-A, non-B hepatitis
- Small RNA blood-borne virus with a large reservoir of chronic carriers worldwide
- Major cause of posttransfusion hepatitis prior to 1992
- Major cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma worldwide

NIH Consensus Development Conference Panel Statement Management of Hepatitis C, 2002
Prevalence of HCV

- US population prevalence is 1.8%
- Worldwide Prevalence is 3%
- 1990-2015: estimated 4-fold increase in the number of patients diagnosed with HCV in the United States
HCV Infection: Worldwide Prevalence

Annual age-adjusted hepatitis C mortality rates and 95% confidence intervals by sex, United States, 1995-2004.

Annual hepatitis C mortality rates and 95% confidence for selected age groups, United States, 1995-2004.

Rate per 100,000 PY

HCV Genome Heterogeneity

• HCV RNA dependent RNA polymerase- high mutation rates generates mutant viruses known as quasispecies

• No Vaccine

• Genotypes
  – ≥ 30% difference at nucleotide level
  – 25% - 30% difference at amino acid level

• Subtypes

HCV Infection: Worldwide Genotype Distribution

Genotype and Viral Load in US Patients

- Genotype 1 HVL: 49.5%
- Genotype 1 LVL: 24.5%
- Genotype 2,3 HVL: 7.3%
- Genotype 2,3 LVL: 14.7%
- Genotype 4,5,6 High Viral Load: 2.7%
- Genotype 4,5,6 Low Viral Load: 1.3%

Acute vs. Chronic Hepatitis C
Hepatitis C Virus
Fate of Acute Infection

Chronic 85%
Spontaneous resolution 15%

Hepatitis C Virus

Response to Acute Infection

Illustration by Mitchell L. Shiffman, MD.
Acute Hepatitis C Clinical Presentation and Natural History

- HCV RNA can be detected in blood within 1-3 weeks after exposure
- Average time from exposure to seroconversion is 8-9 weeks
- Average time from exposure to symptoms period 6-7 weeks
- Liver injury (elevations in ALT) with 4-12 weeks
- Symptoms develop in only of 20% of patients
  - Nonspecific 10%-20%
  - Jaundice in only 20%-30%

Hoofnagle JH Hepatology. 1997;26 (suppl 1): 15S-20S
NIH Consensus Development Conference Panel Statement Management of Hepatitis C, 2002
Risk Factors for Acute Hepatitis C

United States, 1991-1995

- Injection Drug Use: 60%
- Household/Occupational/Transfusion: 20%
- Sexual (Multiple Partners): 10%
- Unknown: 10%

Alter MT. Hepatology. 1997;26 (suppl 1): 62S-65S.
### Table 2. Persons for Whom HCV Screening is Recommended

- Persons who have injected illicit drugs in the recent and remote past, including those who injected only once and do not consider themselves to be drug users.

- Persons with conditions associated with a high prevalence of HCV infection including:
  - Persons with HIV infection
  - Persons with hemophilia who received clotting factor concentrates prior to 1987
  - Persons who have ever been on hemodialysis
  - Persons with unexplained abnormal aminotransferase levels

- Prior recipients of transfusions or organ transplants prior to July 1992 including:
  - Persons who were notified that they had received blood from a donor who later tested positive for HCV infection
  - Persons who received a transfusion of blood or blood products
  - Persons who received an organ transplant

- Children born to HCV-infected mothers

- Health care, emergency medical and public safety workers after a needle stick injury or mucosal exposure to HCV-positive blood

- Current sexual partners of HCV-infected persons*
Symptoms of Hepatitis C

- Fatigue
- Depression
- Anorexia
- Nausea
- Abdominal discomfort
- Myalgia
- Arthralgia
- Muscle weakness
- Weight loss
- Pruritus
- Dark urine
- Fluid retention
- Abdominal swelling
- Jaundice
Chronic Hepatitis C

• A leading cause of cirrhosis in the US

• 10,000-20,000 deaths/yr
  – This number expected to triple in the next 10 to 20 years (without therapy)

• Associated with an increased risk of liver cancer

• Most common reason for liver transplantation in the United States

NIH Consensus Development Conference Panel Statement Management of Hepatitis C, 2002
# Chronic HCV Infection

## Normal Serum ALT

<table>
<thead>
<tr>
<th></th>
<th>Normal ALT</th>
<th>Elevated ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• White, %</td>
<td>48</td>
<td>52</td>
</tr>
<tr>
<td>• Black, %</td>
<td>29</td>
<td>71</td>
</tr>
<tr>
<td><strong>Serum ALT, IU/L</strong></td>
<td>46.6 ± 5.2</td>
<td>76.7 ± 6.0</td>
</tr>
<tr>
<td><strong>Log HCV RNA, copies/mL</strong></td>
<td>5.42 ± 0.13</td>
<td>5.50 ± 0.07</td>
</tr>
<tr>
<td><strong>Histology score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Inflammation</td>
<td>4.2 ± 0.1</td>
<td>5.3 ± 0.1</td>
</tr>
<tr>
<td>• Fibrosis</td>
<td>0.7 ± 0.2</td>
<td>1.6 ± 0.2</td>
</tr>
</tbody>
</table>

Chronic HCV Infection

**Normal vs Elevated Serum ALT**

**Normal ALT**
- No fibrosis: 23%
- Mild: 39%
- Portal: 26%
- Bridging: 6%
- Cirrhosis: 6%

**Elevated ALT**
- No fibrosis: 16%
- Mild: 33%
- Portal: 20%
- Bridging: 13%
- Cirrhosis: 18%

Factors Associated With Disease Progression

• Alcohol consumption
  – 30 g/day in men
  – 20 g/day in women

• Disease acquisition at >40 years
• Male gender
• HIV coinfection
• Hepatitis B virus coinfection
• Immunosuppression

Factors Which Might Influence The Outcome Of Hepatitis C

Virus
- Load
- Genotype
- Quasispecies

Environment
- Alcohol
- HBV
- HIV
- Drugs
- Steatosis
- Iron
- NASH

Host
- Sex
- Age
- Race
- Genetics
- Immune response

Alberti, J of Hepatology, 1999
Cirrhosis
Cirrhosis

- Scarring of the liver or advanced fibrosis
Natural History of HCV Cirrhosis

Manifestations of decompensation

- Ascites
- Variceal bleed
- Encephalopathy
- Jaundice
- Multiple complications

Adapted from Fattovich G et al. Gastroenterology. 1997;112:466.
Modeling of Liver Fibrosis in Chronic Hepatitis C

n=1157 patients

Rapid progressors
Intermediate progressors
Slow progressors

Poynard et al, Hepatology 1999
Natural History of HCV Cirrhosis

Cumulative risk of complications (%)

Years after diagnosis

Adapted from Fattovich G et al. Gastroenterology. 1997;112:466-467.
Natural History of HCV Cirrhosis

Adapted from Fattovich G et al. Gastroenterology. 1997;112:466-467.
Cirrhotic Patients With HCV

Goals of antiviral therapy

- Viral clearance
- Delay decompensation
- Prevent HCC
- Prevent HCV recurrence after liver transplantation
Hepatocellular Carcinoma
Hepatocellular Carcinoma

- Hepatitis B - Most common cause
- Hepatitis C
- Alcoholic Cirrhosis
- Hemochromatosis
- Alpha-1 antitrypsin deficiency
- Primary Biliary Cirrhosis
- Non-alcoholic steatohepatitis
- Autoimmune hepatitis
- Aflatoxin
Global Epidemiology of Hepatocellular Carcinoma

- 320,000-400,000 deaths related to HCC/year
- Incidence and mortality rates are almost equal
- Represents ≈5% of all cancer cases
- Great variability according to gender, age, and geographic areas
  - Highest incidence in Subsaharan Africa and China

Cirrhosis and Hepatocellular Carcinoma

Risk Factors for Fibrosis/ Cirrhosis

- Alcohol consumption
- Increased age at infection
- Longer duration of infection
- Male sex
- HIV

Rising Incidence of Hepatocellular Carcinoma

- Represents a 41% increase in mortality rate and a 46% increase in hospitalization

Predicted HCV-Related Mortality

Predictions for 2010-2019

- 193,000 HCV deaths
  - 720,700 million years of advanced liver disease
  - 1.83 million years of life lost

- $11 billion in direct medical care costs

- $21.3 and $54 billion societal costs from premature disability and mortality

Wong Am J Pub Health 2000
HCV Related Illness is Expected to Increase Greatly in the Coming Years

HCC: 81%
Cirrhosis: 82%
 Decompensation: 106%
Liver-related deaths: 181%

Demand for Livers > Supply

- Waiting List
- Additions to List
- Deceased Donors
- Liver Transplants

UNOS 3/15/03: www.optn.org
HCV Infection: Extrahepatic Manifestations

- Hematologic
  - Cryoglobulinemia
  - Aplastic anemia
  - Thrombocytopenia
  - B-cell lymphoma?
- Renal
  - Glomerulonephritis
  - Nephrotic syndrome
- Dermatologic
  - Porphyria cutanea tarda
  - Lichen planus
  - Cutaneous necrotizing vasculitis
HCV Infection: Extrahepatic Manifestations

- **Endocrine**
  - Diabetes mellitus
  - Antithyroid antibodies
- **Salivary**
  - Sialadenitis
- **Ocular**
  - Uveitis
  - Corneal ulcer

HCV and Cryoglobulinemia

Dermatitis

- Occurs in dependent areas
- Deposition of cryoglobulins in small capillaries
- Ulcerations may develop
- Pruritic
<table>
<thead>
<tr>
<th>Immunoglobulin</th>
<th>Classification</th>
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<tbody>
<tr>
<td>I Monoclonal No rheumatoid factor</td>
<td>Primary</td>
</tr>
<tr>
<td>II Polyclonal IgG Monoclonal IgM</td>
<td>Secondary mixed HCV infection</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td></td>
</tr>
<tr>
<td>II I Polyclonal IgG Polyclonal IgM</td>
<td>Secondary mixed Infections</td>
</tr>
<tr>
<td></td>
<td>Autoimmune disorders</td>
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<tr>
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<td>Lymphoproliferative diseases</td>
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Extrahepatic Effects of HCV

Cryoglobulinemia

- Elevated ALT
- Anti-HCV
- HCV RNA

Chronic HCV and Diabetes Mellitus

Case Prevalence

- N = 179 with chronic HCV
- Prevalence of diabetes mellitus and insulin resistance noted
- Compared with expected rate based on NHANES III study after adjusting for
  - Age
  - Sex
  - Race
- Prevalence of DM or insulin resistance higher in those with chronic HCV

Summary

• Chronic Hepatitis C Prevalence is 1.8% in US
• Factors associated with disease progression-alcohol, age at infection, gender, co-infection, steatosis, immunosuppressive medications
• Disease burden is expected to rise.
• Goal: To prevent progression to cirrhosis, advanced liver disease, HCC and liver related mortality