Hepatitis C Virus

- Nucleic Acid: 9.6 kb ssRNA
- Classification: *Flaviviridae*, *Hepadnavirus*
- 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
The Scope of The Problem
US Prevalence: 1.8% are chronically infected with Hepatitis C virus (HCV)

Hepatitis C is Underdiagnosed in US

HIV=human immunodeficiency virus; HBV=hepatitis B virus; HCV=hepatitis C virus

Annual Age-adjusted Mortality Rates from HBV, HCV, and HIV

Hepatitis C-Related Cirrhosis Is Projected to Peak Over Next 10 Years

25% of patients with HCV currently have cirrhosis

37% of patients with HCV are projected to develop cirrhosis by 2020, peaking at 1 million
Indications for OLT over 12 years: HCV still most common indication for OLT

SRTR Annual report 2011 (http://srtr.transplant.hrsa.gov)

Estimated 29,700 estimated cases of acute hepatitis C: 2013

Prevalence by age of Hepatitis C in US

- Chronic HCV prevalence, US (all persons per CDC)
  - 1.3% (3.2 million)
- 65.6% of all infected persons in the U.S. were born between 1945-1964
  - Overall prevalence, 4.3%
  - Men 6.2%
  - Black Americans, 9.4%
  - Black American men, 13.6%
  - Higher incidence in Hispanics too

Liver-Related Death Top Cause of Non-AIDS Deaths – 1999-2008

Risk Factors for Acute Hepatitis C

- Injection Drug Use 43.0%
- Other High Risk* 30.0%
- Unknown 1.0%
- Household 3.0%
- Occupational 4.0%
- Transfusion** 4.0%
- Sexual (MSM and Multiple Partners) 15.0%

*Other High Risk
- 16% drug related
- 11% previous drug use not within last 6 months
- 5% intranasal cocaine use
- 4% history of STDs
- 1% prison
- 5% lower socio-economic status (fewer years of education)

Diagnostic Tests Hepatitis C

- ELISA: detects hepatitis C antibodies
- HCV RNA by RT-PCR detects virus in the bloodstream
- Liver Biopsy: determines the extent of liver injury but cannot alone establish a diagnosis
Importance of Confirming Viremia

Anti-HCV Antibody
Positive | HCV RNA | Positive | HCV Genotype
No Further Testing

No Active Disease

Who Should Be Tested For HCV?

- One-time HCV testing is recommended for persons born between 1945 and 1965*, without prior ascertainment of risk.
  
  Rating: Class I, Level B

- Other persons should be screened for risk factors for HCV infection, and 1-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection.
  
  Rating: Class I, Level B

<table>
<thead>
<tr>
<th>Risk Behaviors</th>
<th>Exposures</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection-drug use (current or ever, including those who injected once)</td>
<td>Long-term hemodialysis (ever)</td>
<td>HIV infection</td>
</tr>
<tr>
<td>Intranasal illicit drug use</td>
<td>Getting a tattoo in an unregulated setting</td>
<td>Unexplained chronic liver disease and chronic hepatitis including elevated alanine aminotransferase levels</td>
</tr>
<tr>
<td></td>
<td>Health care, emergency medical, and public safety workers after needlesticks, sharps, or mucosal exposures to HCV-infected blood</td>
<td>Solid organ donors (deceased and living)</td>
</tr>
<tr>
<td></td>
<td>Children born to HCV-infected women</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prior recipients of transfusions or organ transplants, including persons who:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>† Were notified that they received blood from a donor who later tested positive for HCV infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>‡ Received a transfusion of blood or blood components, or underwent an organ transplant before July 1992</td>
<td></td>
</tr>
<tr>
<td></td>
<td>† Received clotting factor concentrates produced before 1987</td>
<td></td>
</tr>
<tr>
<td></td>
<td>† Persons who were ever incarcerated</td>
<td></td>
</tr>
</tbody>
</table>

Rating: Class I, Level B

*Regardless of country of birth

2013 USPSTF HCV Screening Recommendations

1. Those at high risk for HCV infection
2. Those born from 1945 to 1965
   – Grade B recommendation – high certainty that the net benefit is moderate to substantial

• The Affordable Care Act
   – Requires insurance plans to provide Grade A or B recommendations without cost sharing

USPSTF = United States Preventive Services Task Force

Moyer VA - on behalf of the USPSTF. Ann Intern Med 2013;159:349-357

HCV Genotypes and Subtypes

Developed countries

South Africa

Middle East North Africa

IVDU

Americas + Western Europe

Asia

Simmonds P, Journal of Hepatology, 1999
**Chronic HCV Infection**

![Graph showing the natural history of HCV infection](image)

**Natural History of Hepatitis C**

1. **Acute Hepatitis C**
2. **Chronic Hepatitis C**
   - **75%–85%**
3. **Cirrhosis**
   - **20%**
4. ** Decompensation**
   - **6%**
5. **HCC**
   - **4%**
6. **Death**
   - **~4%**

Immune-Mediated Clearance in Hepatitis C

Infected Hepatocyte → Clearance of Infected Hepatocytes

TNF α, IFN γ, CD8, CTL

Liver Inflammation due to HCV
Histologic Staging

- Stage 0: No Fibrosis
- Stage 1: Portal Fibrosis
- Stage 2: Few septa
- Stage 3: Numerous septa
- Stage 4: Cirrhosis

Stages of Fibrosis In Chronic Hepatitis

1. Portal
2. Penportal
3. Septal
4. Cirrhosis
Why Do We Treat Chronic HCV?

Disease Progression in HCV is Not Linear: Importance of Early Treatment


**Risk Factors Associated with Faster Fibrosis Progression in Chronic HCV**

**Disease state factors**
- Fibrosis stage
- HCV onset after 40 years of age
- Persistently elevated ALT

**Host factors**
- Male gender
- Age >45 years
- Obesity/steatosis
- Diabetes
- HIV, HBV co-infection
- Immune system compromise
- Iron overload
- Life style (ETOH, smoking)

**Viral factors**
- Genotype 3


ALT=alanine transaminase

**“Sustained Responders” Fibrosis scores**

Hepatitis C is curable: SVR = Cure

SVR Decreases but Does Not Eliminate Risk for Liver Related Complications in those with hepatitis C


Be Careful Using Fibrosis as the Only Indication for Therapy: REVEAL C

HCV Infection Associated with Significantly Higher Prevalence of Comorbidities

<table>
<thead>
<tr>
<th>Incidence of Comorbidities (%)</th>
<th>Employees w/ HCV (n=1329)</th>
<th>Employees w/out HCV (n=26,580)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasm</td>
<td>19*</td>
<td>13</td>
</tr>
<tr>
<td>Metabolic abnormality (eg, diabetes)</td>
<td>34*</td>
<td>27</td>
</tr>
<tr>
<td>Mental disorder</td>
<td>20*</td>
<td>10</td>
</tr>
<tr>
<td>Nervous</td>
<td>31*</td>
<td>24</td>
</tr>
<tr>
<td>Circulatory</td>
<td>36*</td>
<td>28</td>
</tr>
<tr>
<td>Digestive</td>
<td>42*</td>
<td>18</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>35*</td>
<td>28</td>
</tr>
</tbody>
</table>

*P<0.0001 vs. employees without HCV infection

- Significantly higher prevalence of comorbidities in the HCV-infected vs. non-infected cohort


Benefits of Diagnosis

Prevent Transmission
- Avoid sharing objects with blood
- Stop illicit drugs or sharing needles
- Discuss risk of sexual transmission with “unsafe sex”

Other Recommendations
- Avoid alcohol consumption
- Discuss available treatments
- Vaccinate for hepatitis A and B
- Test for HBV, HIV
- Consider family member screening
HCV Epidemiology Screening and Natural History - Summary

- Most HCV patients remain undiagnosed
- 75% of them were born from 1945-1965
- 33% of them have advanced fibrosis
  - “ticking time bombs” waiting to explode (bleed) on a Friday at midnight when you are on call
- Therapy is more effective and safer
- It’s time to incorporate screening into your practice!