Hepatitis A and Hepatitis C Viruses
A Clinical Overview

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Blood Moon
# Overview of Hepatitis A and Hepatitis C Viruses

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hepatitis A virus</th>
<th>Hepatitis C virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>Stool</td>
<td>Blood</td>
</tr>
<tr>
<td>Transmission</td>
<td>Enteric</td>
<td>Percutaneous/Permucosal</td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Acute infections (x10^5 persons/year), USA</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Fulminant hepatitis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fulminant deaths/year, US</td>
<td>100</td>
<td>?</td>
</tr>
<tr>
<td>Risk for chronic hepatitis and hepatocellular carcinoma</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Available therapy</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Available vaccine</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Hepatitis A Virus: Overview

- Has existed for centuries
- One of the most common causes of infectious jaundice worldwide
- Usually associated with self-limiting hepatitis
- ~1,500,000 cases annually worldwide
- 1,398 reported cases of acute HAV in the U.S. in 2011
- Estimated cases ~2,800 in 2011
- Etiological agent of ~50% of all reported cases of acute viral hepatitis in the U.S
Hepatitis A: Global Prevalence

Jacobsen KH et al. *Vaccine* 2010;28:6653-6657
Hepatitis A: Epidemiology

- Highly endemic regions: most infections occur in children
- Intermediate areas of endemicity areas: most infections occur in adolescents and adults
- Low and very low areas of endemicity: most infections occur in adolescents and adults at high risk (IDU and travelers) and during outbreaks
Hepatitis A virus
Genomic Organization

5’ UTR

Structural Protein Coding Region

P1

Nonstructural Protein Coding Region

P2

P3

3’ UTR

1A 1B 1C 1D 2A 2B 2C 3A 3B 3C 3D

Capsid Proteins

RNA Helicase

Protease

RNA Polymerase
Hepatitis A: Genotypes and Serotypes

- 4 genotypes affect humans (I, II, III & VII)
- Only one serotype
Hepatitis A: Transmission

- Fecal-oral route (Most common)
  - Person-person spread
  - Intrafamilial
  - Intrainstitutional
- Percutaneous (rare)
- Sexual (rare)
Hepatitis A: Clinical Features

- Incubation period averages 28 days (range, 15–50 days)
- Clinical manifestations include fever, malaise, anorexia, nausea, and abdominal discomfort, followed within a few days by jaundice.
- Severity of illness increases with age
Hepatitis A: Clinical Course

- HAV RNA
- Fecal HAV
- Jaundice
- ALT
- Total anti-HAV
- IgM anti-HAV

Months after exposure

0 1 2 3 4 5 6 12 24

Normal
Hepatitis A: 5 Clinical Patterns

- Asymptomatic
- Symptomatic with jaundice self-limited to <8 weeks
- Cholestatic with prolonged duration of jaundice >10 weeks
- Relapsing, consisting of two or more bouts of acute HAV infection occurring over a 6-10 week period (10% of cases)
- Fulminant hepatitis (1-5% of cases)
Hepatitis A: Outcome

- Recovery is the rule
- Chronic infection does not occur
Hepatitis A: Treatment

- None Required
- Supportive Care
Hepatitis A: Prevention

- Serum immunoglobulin
- Vaccines
  - Havrix
  - Vaqta
Hepatitis A: Declining Incidence in the U.S Following Mandatory Vaccination

![Graph showing declining hepatitis A incidence](image)

- Vaccination recommended: 1996 rate 11.7%
- 2010 rate 0.5%
Hepatitis A: Declining Incidence by County in the U.S.
Hepatitis A: Who Should Be Vaccinated

- Children between ages of 2 and 18 years in existing programs
- International travelers
- Persons who anticipate close contact with an international adoptee
- Men who have sex with men
- Illicit drug users
- Persons with chronic liver disease
- Persons receiving clotting factor concentrates
- Persons who work with HAV-infected primates or with HAV in research settings
- Anyone who wants to obtain immunity
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Chronic Hepatitis C

- Estimated 170-200 million person with chronic infection
- A major cause of chronic liver disease, cirrhosis, end-stage liver disease and hepatocellular carcinoma
- Leading indication for adult liver transplants in the U.S. ~50%
- Death from HCV now exceeds that of HIV
- No vaccine or specific prevention available
- Therapy is problematic and effective only in a proportion of patients
Hepatitis C Virus: Global Distribution of Infection

Prevalence of infection:
- > 10%
- 2.5% to 10.0%
- 1.0% to 2.5%
- NA

Hepatitis C Virus: Genome Organization

Structural proteins
- Core
- Envelope
- NS2
- Helicase
- NS3
- NS4B

Non-structural proteins
- NS2-3 Protease
- Protease cofactor
- Serine protease
- RNA-dependent RNA polymerase
- NS4A
- NS5A
- NS5B

5’ UTR
- C
- E1
- E2
- P7

3’ UTR
Global Distribution of HCV Genotypes

Negro F et. al. Liver Int:2011; S2:1-3
Attributable Fraction of Cirrhosis And HCC Due To HCV Infection

Perz JF et. Al J Hepatol 2006; 45:529-538
Global Mortality of HCV

Lancet 2012;380:2095-128
The Changing Face of HCV in the US

Ever HCV infected
All chronic HCV
Acute HCV infection
Cirrhosis

Peak incidence
Peak cirrhosis

Davis GL, et al, Gastroenterology 2010
Annual age-adjusted mortality rates from HBV and HCV and HIV infections in the United States between 1999 and 2010

Ly, KN et al Ann Intern Med; 156:271-8
Sources of Infection: Globally

- Blood transfusions from unscreened donors
- Injection drug use
- Unsafe therapeutic injections
- Other healthcare-related procedures
Routes of Transmission Vary Depending on Prevalence of Infection

- Household
- Nosocomial
- Transfusion
- Perinatal
- Occupational
- Sexual
- IDU

High
Low
Sources of Infection in Persons with Acute Hepatitis C in the U.S.

- Injection drug use: 54%
- Sexual: 24%
- Transfusion: 1%
- HD*: 1%
- Unknown: 12%
- Nosocomial: 8%

Source: MMWR April 2007
Hepatitis C: Clinical Features

- Incubation period averages 8 weeks (range, 2-26 weeks)
- Clinical manifestations include malaise, anorexia, nausea, and abdominal discomfort, followed within a few days by jaundice.
Hepatitis C: Clinical Course

- HCV RNA
- Jaundice
- ALT
- Normal
- anti-HCV

Time after Exposure:
- Months 0, 1, 2, 3, 4, 5
- Years 0, 1, 2, 3, 4

ALT levels rise sharply after exposure, peak around 6 months, and return to normal over 2-3 years. HCV RNA levels increase rapidly and peak around 6 months, then decrease. Jaundice typically occurs 1-3 years after exposure. Anti-HCV antibodies begin to appear around 1 year after exposure and remain positive for life.
Hepatitis C: 3 Clinical Patterns

- Asymptomatic (majority of cases)
- Symptomatic with jaundice (~20% of cases)
- Fulminant hepatitis (1-3% of cases)
Hepatitis C: Extrahepatic Manifestations

Immune-complex-mediated
- Essential mixed cryoglobulinemia
- Membrano-proliferative glomerulonephritis
- B-cell lymphoma
- MGUS

Non-Immune-complex-mediated
- Sjogren’s
- Lichen planus
- Porphyria cutanea tarda
- Diabetes
Natural History of HCV Infection

Acute HCV

Resolution 25%-45%

Chronicity 55%-75%

~25-30 Yrs

Cirrhosis 20%-30%

Hepatic Decompensation 3%-5%/Yr

Hepatocellular Carcinoma 1%-4%/Yr
Factors Affecting Outcome of Chronic Hepatitis C

• Older age at infection
• Longer duration of infection
• Male gender (worse for male)
• Alcohol use
• Obesity
• Diabetes / insulin resistance
• Steatosis / steatohepatitis
• Co-infection with HIV or HBV
• IL28B Genotype CC
• Higher ALT elevation
Screening
HCV Screening Is the First Step on the Road to a Cure

Screening

Counseling

Testing

Assessment

Treatment

Cure
Who Should Be Screened

• 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
  – 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 blood
• Current sexual partners of HCV-infected persons
• Adults born between 1945-1965
## Screening Criteria for HCV in The General Population

<table>
<thead>
<tr>
<th>Screening Criteria</th>
<th>Participants with Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Persons age 20-50</strong></td>
<td>General population</td>
</tr>
<tr>
<td><strong>Risk factor history</strong></td>
<td>HCV RNA positive population</td>
</tr>
<tr>
<td>IDU</td>
<td>1.9 46.6</td>
</tr>
<tr>
<td>IDU or transfusion before 1992</td>
<td>7.3 53.1</td>
</tr>
<tr>
<td>IDU or transfusion before 1992 or &gt;20 lifetime sex partners</td>
<td>21 76.1</td>
</tr>
<tr>
<td><strong>Any illicit drug use or transfusion before 1992 or &gt;20 lifetime sex partners</strong></td>
<td>33.2 89.7</td>
</tr>
<tr>
<td><strong>Risk Factor history and ALT Level</strong></td>
<td></td>
</tr>
<tr>
<td>Abnormal ALT level</td>
<td>12 62.6</td>
</tr>
<tr>
<td>Abnormal ALT level or IDU</td>
<td>13.3 82.8</td>
</tr>
<tr>
<td>Abnormal ALT level or IDU or transfusion before 1992</td>
<td>18.1 85.1</td>
</tr>
<tr>
<td>Abnormal ALT level or IDU or transfusion before 1992 or &gt;20 lifetime sex partners</td>
<td>30 93.5</td>
</tr>
<tr>
<td>Abnormal ALT level or IDU or transfusion before 1992 or &gt;20 lifetime sex partners</td>
<td>40.7 98.6</td>
</tr>
<tr>
<td><strong>Persons Age &gt;60 years</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Risk factor history</strong></td>
<td></td>
</tr>
<tr>
<td>Transfusion before 1992</td>
<td>17.2 60.1</td>
</tr>
<tr>
<td><strong>Risk factor history and ALT level</strong></td>
<td></td>
</tr>
<tr>
<td>Abnormal ALT level</td>
<td>5.1 56.7</td>
</tr>
<tr>
<td>Abnormal ALT level or transfusion before 1992</td>
<td>21.1 87.4</td>
</tr>
</tbody>
</table>
Proportion of Subjects With CHC Who Remain Undiagnosed

France  | U.S.  | UK    | N. Spain | Germany | Poland |
------- | ----- | ----- | -------- | ------- | ------ |
0%      | 50%   | 70%   | 80%      | 90%     | 100%   |
**Birth Cohort Screening**

**Rationale:**
- Limited effectiveness of risk-based screening
- HCV morbidity and mortality is increasing
- Treatment is improving

**Recommendation by CDC:**
- Screen all persons born between 1945-1965
  - Prevalence of anti-HCV 3.25%
  - Accounts for >three fourths of total anti-HCV prevalence in the U.S.
Hepatitis C: Goals of Therapy

• Prevent the development of complications:
  – Cirrhosis
  – End-stage liver disease
  – Hepatocellular carcinoma
  – Liver-related death

• Surrogate endpoint is the sustained virological response 12 weeks after stopping therapy \( SVR_{12} \)
Outcomes of Therapy for CHC

HCV RNA (log_{10} IU/mL) vs Weeks

- PegIFN/RBV
- Null response
- Partial response
- Breakthrough
- 2 log decline
- Limit of detection
- SVR

Par%al response
0 1 2 3 4 5 6 7 8
0 4 12 18 24 30 36 42 48 54 60 66 72 78
SVR Equivalent to Virological Cure

- Nearly 100% of patients who achieve SVR remain undetectable during long-term follow-up[1-4]

SVR Associated with Improved Outcomes in Patients with HCV and Advanced Fibrosis

Morgan et al. Hepatology 2010;52: 833
SVR Is Associated With Improved Survival

530 patients with chronic HCV infection with advanced fibrosis or cirrhosis (Ishak 4-5) who received an interferon-based treatment regimen between 1990 and 2003, followed for a median of 8.4 years for all cause mortality and liver-related mortality.

Van der Meer et al JAMA 2012;308:2584-93
Optimal Therapy of Hepatitis C Genotype 1: 2014

- **Peginterferon (by injection)**
  - alfa-2a 180 µg weekly
  - alfa-2b 1.5 µg/kg weekly
- **Ribavirin (by mouth)**
  - 1,000-1,200 mg in two divided doses daily
  Combined with either:
- **Sofosbuvir (Nucleoside analogue) (by mouth)**
  - 400 mg once per day
  - For 12 weeks
- **Simeprevir (Protease inhibitor) (by mouth)**
  - 150 mg once per day
  - For 12 weeks (total duration 24 weeks)
Sofosbuvir & Ledipasvir ± RBV in Treatment-Naïve or -Experienced GT1 HCV

ION-1*: GT1 treatment-naïve pts (16% cirrhotic): SOF/LDV FDC ± RBV for 12 wks

ION-3: GT1 treatment-naïve pts: SOF/LDV FDC ± RBV for 8 or 12 wks

ION-2: GT1 treatment-experienced pts (20% cirrhotic): SOF/LDV FDC ± RBV for 12 or 24 wks

Gilead Press release Dec 18th, 2013

*24-wk arms not yet reported.
ABT-450/RTV & ABT-267 & ABT 333 & RBV in Treatment-Naïve or - Experienced GT 1 HCV

**SAPPHIRE-1:** GT1 treatment-naïve noncirrhotic patients:
ABT-450/RTV/ABT-267 FDC + ABT-333 + RBV for 12 wks

- Overall: 96%
- GT1a: 95%
- GT1b: 98%

**SAPPHIRE-2:** GT1 treatment-experienced noncirrhotic patients (49% null responders):
ABT-450/RTV/ABT-267 FDC + ABT-333 + RBV for 12 wks

- Overall: 96%
- GT1a: 96%
- GT1b: 97%

Abbvie Press release Nov 18th 2013; Dec 10th 2013
ABT-450/RTV & ABT-267 & ABT 333 & RBV in Treatment-Naïve or -Experienced GT 1 HCV with Cirrhosis

Overall 12 weeks: 92%
Overall 24 weeks: 96%

Abbvie Press release Nov 18th 2013; Dec 10th 2013
Optimal Therapy of Hepatitis C
Genotypes 2 & 3 : 2014

Sofosbuvir (by mouth)
• 400 mg daily

Ribavirin (by mouth)
• 1,000 to 1,200 mg in two divided doses daily

For 12 weeks (Genotype 2)
For 24 weeks (Genotype 3)
FISSION: Sofosbuvir/RBV vs PegIFN/RBV in Treatment-Naive GT 2/3 HCV Patients

- Randomized, controlled, phase III noninferiority trial
  - 20% to 21% had cirrhosis; 72% had GT 3 HCV

Treatment-naive patients with GT 2/3 HCV (N = 499)

- Sofosbuvir 400 mg QD + RBV 1000-1200 mg/day (n = 256)
- PegIFN alfa-2a 180 µg/wk + RBV 800 mg/day (n = 243)

FISSION: Sofosbuvir/RBV Noninferior to P/R in Tx-Naive GT 2/3 HCV Patients

FISSION: SOF/RBV x 12 Wks: SVR12 By Genotype and Fibrosis Level

Valence: Sofosbuvir + RBV for 12 or 24 Wks in Tx-Experienced GT 2/3 HCV Patients

- Initially randomized, placebo controlled study of sofosbuvir & ribavirin for 12 weeks. Amended to open-label trial of sofosbuvir & ribavirin for 12 weeks in GT 2 and 24 weeks in GT3 patients
  - 62% to 64% had GT 3 HCV, 33% to 35% had cirrhosis, 75% to 76% were previous relapsers

Valance GT 3: SOF&RBV X 24 Weeks

Zeuzem S et al. AASLD 2013 Abstract 1085
Advantages of Future Therapies

- Once-daily dosing
- High potency
- Shorter duration of therapy
- Simpler regimens—no lead-in or response guided therapy
- Fewer adverse events
- IFN and perhaps ribavirin free regimens
Progress in Therapy of Hepatitis C

- **1991**: Standard IFN (6% response)
- **1995**: Ribavirin added (16% response)
- **1998**: Peginterferon (34% response)
- **2001**: Peginterferon 12m (39% response)
- **2002**: Peg/R 12m (54% response)
- **2011**: TVR/BOC (90-100% response)
- **2014**: DAA (66-75% response)
- **2021**: DAA (90-100% response)

**Percent Sustained Response**