Hepatitis C virus
Some HCV History

- 1970s: many cases reported – called non-A, non-B hepatitis
- 1988: hepatitis C virus identified
- 1990: antibody screening tests available
- 1992: better tests to insure safety of blood supply
- 1948: blood samples stored since 1948 contain HCV antibodies, earliest known
• Flaviviridae, genus Hepacivirus (HCV and GBV-C).

• Enveloped, 37-60 nm.

• + ss RNA genome
  - 9.4 kb
  - over 98% contains protein coding sequence.
  - a single large ORF
Hepatitis C Virus

capsid
Envelope protein

c22

Protease/helicase

RNA-dependent RNA polymerase

c 33
C-100

core E1 E2 NS2 NS3 NS4 NS5

Hypervariable region
• The genome codes for nine proteins; 3 structural and 6 nonstructural.

• The structural proteins are; core protein (C22), E1(gp76), and E2 (gp35).

• The nonstructural proteins are; NS2, NS3, NS4A, NS4B, NS5A, and NS5B.

• HCV has circumvented the cap requirement by evolving an Internal Ribosome Entry Site (IRES) at its 5′ end.
Genetic heterogeneity

• Marked genetic heterogeneity due to hypervariable region (Major neutralization epitope of HCV).

• Six major genotypes (1-6)

• It mutates under immunologic pressure

• Genotype dictates length of therapy and predicts therapeutic response
  – Genotype 1 requires longer therapy and has lower response
Pathogenesis and Pathology

• HCV used to cause about 90% of transfusion associated hepatitis.

• The percutaneous route is the most efficient in transmission.

• Risk groups are recipients of blood or blood products, IV drug users, renal dialysis and needle stick victims.

• Sexual and transplacental spread may take place.
• 70-80% of HCV infections results in chronicity.

• Chronic HCV is commonly associated with

- The appearance of lymphoid follicles and/or aggregates within portal tracts

- Large droplet fat vacuoles in the cytoplasm of infected hepatocytes (steatosis)

- Activation of lobular sinusoidal inflammatory cells.
• There might be bile duct damage.

• The level of necrosis, scarring and fibrosis can vary widely.

• Cirrhosis is seen in about 20% of cases and is commonly followed by PHCC within a period of 30 years.
Clinical Features

- Incubation of 40-120 days
- Commonly asymptomatic
- 25% of cases are icteric but milder than HAV or HBV
- Fatigue is the most common symptom but weakness, wasting, edema and ascites also occur
• Extrahepatic Manifestations

- Mixed cryoglobulinemia (vasculitis)

- Membranoproliferative glomerulonephritis

- Porphyria cutana tarda
  - photosensitivity
  - increased skin fragility
  - hypopigmentation
  - sclerodermoid plaques.
Conditions Linked to HCV

- Arthritis
- Autoimmune hepatitis
- Sjogrens Syndrome
- Cryoglobulinemia
- Kidney disease
- Liver Cancer
Serologic Pattern of Acute HCV Infection with Recovery

- Time after Exposure
- Titer
- Anti-HCV
- Symptoms +/−
- HCV RNA
- ALT
- Normal

Months
Years

0 1 2 3 4 5 6 1 2 3 4
Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection

- **Titer**
- **Symptoms +/-**
- **HCV RNA**
- **anti-HCV**
- **ALT**

Time after Exposure

<table>
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<tr>
<th>Months</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
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Normal
Symptoms, or Lack of, in Chronic HCV Infection

Symptomatic 37%
Cirrhosis 7%
56% Asymptomatic

Fatigue
80

Patients (%)
ALT Elevations Are Not Indicative of Chronic HCV Infection

Patients* With HCV infection (%)

Persistently Normal ALT: 42%
Intermittently Elevated ALT: 43%
Persistently Elevated ALT: 15%
Chronic Hepatitis C
Factors Promoting Progression or Severity

- Increased alcohol intake
- Age > 40 years at time of infection
- HIV co-infection
- Others
  - Male gender
  - Chronic HBV co-infection
Laboratory Diagnosis

- **HCV antibody** - generally used to diagnose hepatitis C infection. Not useful in the acute phase as it takes at least 4 weeks after infection before antibody appears.

- **HCV-RNA** - various techniques are available e.g. PCR and branched DNA. May be used to diagnose HCV infection in the acute phase. However, its main use is in monitoring the response to antiviral therapy.

- **HCV-antigen** - an EIA for HCV antigen is available. It is used in the same capacity as HCV-RNA tests but is much easier to carry out.
## Diagnostic Tests for HCV Infection

<table>
<thead>
<tr>
<th>Specifications</th>
<th>Serologic</th>
<th>Virologic</th>
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<tr>
<td>Mode of detection</td>
<td>Antibodies</td>
<td>Virus</td>
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<tr>
<td>Sensitivity</td>
<td>&gt; 95%</td>
<td>&gt; 98%</td>
</tr>
<tr>
<td>Specificity</td>
<td>Variable</td>
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<tr>
<td>Detection postexposure</td>
<td>2-6 mos</td>
<td>2-6 wks</td>
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<tr>
<td>Use</td>
<td>Screening</td>
<td>Confirmation</td>
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</tbody>
</table>

*Prevalence of HCV Infection Among Blood Donors*

Anti-HCV Prevalence

- **Red**: >5% - High
- **Yellow**: 1.1%-5% - Intermediate
- **Green**: 0.2%-1% - Low
- **Orange**: ≤0.1% - Very Low
- **White**: Unknown

*Anti-HCV prevalence by EIA-1 or EIA-2 with supplemental testing; based on data available in January, 1995.*
Epidemiology

• The high incidence of chronic asymptomatic infection and the inadequacy of screening procedures promoted the spread of the virus via blood supply.

• Viremia can be detected within 3 weeks of infection and lasts for 4-6 months in acute infection and for up to 10 years or longer in chronic infections.
• Antibody is detected within 7-31 weeks of infection and its detection forms the basis for diagnosis but is not always present in viremic individuals.

• Detection of viral RNA is a better determinant of disease.

• It is estimated that nearly 200 million people are chronically infected with HCV worldwide.
• During HCV replication, hypervariable regions within the envelope genes are constantly undergoing mutation.

• Thus an infected individual carries not one unique virus but rather a whole population of related quasi-species.

• Such properties may allow these viruses to escape immune mediated clearance.
Risk Factors Associated with Transmission of HCV

- Transfusion or transplant from infected donor
- Injecting drug use
- Hemodialysis (yrs on treatment)
- Accidental injuries with needles/sharps
- Sexual/household exposure to anti-HCV-positive contact
- Multiple sex partners
- Birth to HCV-infected mother
HCV CANNOT BE SPREAD BY

- BREAST FEEDING
- SNEEZING
- COUGHING
- HUGGING
- FOOD OR WATER
- SHARING EATING UTENSILS OR DRINKING GLASSES
- CASUAL CONTACT
Occupational Transmission of HCV

• Inefficient by occupational exposures
• Average incidence 1.8% following needle stick from HCV-positive source
  – Associated with hollow-bore needles
• Case reports of transmission from blood splash to eye; one from exposure to non-intact skin
• Prevalence 1-2% among health care workers
  – Lower than adults in the general population
  – 10 times lower than for HBV infection
Perinatal Transmission of HCV

- Transmission only from women HCV-RNA positive at delivery
  - Average rate of infection 6%
  - Higher (17%) if woman co-infected with HIV
  - Role of viral titer unclear
- No association with
  - Delivery method
  - Breastfeeding
- Infected infants do well
  - Severe hepatitis is rare
HEPATITIS C : Treatment

• Pegylated interferon alfa plus ribavirin

• Treatment for 24-48 weeks

• Overall success rates of 50%; Decreased by genotype 1, HIV+, old age

• Can try longer treatments – 48 weeks

• Follow by serum HCV viral load, liver biopsy
Clinical Significance of HCV Genotypes

- Great genetic diversity: 6 genotypes (1 through 6)
  - Multiple subtypes: a, b, c, etc
- Genotype is best pretreatment predictor of response
  - Genotype 1: least responsive to therapy
- Determines dose and duration of therapy
  - Genotype 1: 48 weeks of peg-IFN alfa + RBV 1000-1200 mg
  - Genotype 2/3: 24 weeks of peg-IFN alfa + RBV 800 mg
- All patients should have genotype determined prior to initiating therapy
Influence of Genotype on Treatment Response

Type 1

Type 2, 3
Telaprevir (Incivek)

Approval
- FDA Approved May 23, 2011

Indications
- In combination with Peginterferon-alfa and Ribavirin (PR)
- Chronic HCV genotype 1 infection
- Adults (≥ 18 years of age) with compensated liver disease, including cirrhosis
- Treatment-naïve or prior interferon-based treatment

Dosing
- 750 mg (two 375-mg tablets) three times daily with food
- Treat with PR for 12 weeks (followed by additional 12 or 36 weeks PR)

Adverse Effects
- Rash, anemia, nausea, fatigue, headache, diarrhea, pruritus, and anal or rectal irritation and pain
Prevention of Hepatitis C

- Screening of blood, organ, tissue donors
- High-risk behavior modification
- Blood and body fluid precautions
• Vaccine development has been hampered by at least 2 properties:

- The presence of multiple genotypes and numerous subtypes
- Sequence diversity of envelope glycoproteins.

• Consistent with this is the fact that patients who appear to have cleared an HCV infection have no protective immunity to future infections.
Hepatitis GB Virus

• Three types of the virus; A, B and C.

• The genome is ss RNA of positive polarity. It is related to HCV virus and is enveloped.

• It is transmitted by the parenteral route and it is present in 1-2% of eligible blood donors.

• There has been a large difference between exposure rates (80-90%) and active infection (15-20%)
• 10-20% of HCV infected individuals are coinfectected with HGBV.

• There is no clear association with disease but it is believed that it causes both acute and chronic infections.

• Best diagnosed by PCR detection of the RNA genome as anti-E2 is a recovery phase antibody that is detectable only when HGBV-RNA has been cleared.
Hepatitis E Virus

- Recognized as a distinct disease in 1980. Classified as a Calicivirus

- Virion is 32-34 nm in diameter, nonenveloped, icosahedral

- Genome is +ss RNA 7.5kb in length.

- It encodes 3 proteins, a structural one; a nonstructural one and a third of unknown nature.
Hepatitis E Virus
• One serotype exists with many strains.

• The pathogenesis of HEV is poorly understood.

• Infection is acquired by the fecal oral route of transmission or by person-to-person contact.

• Primary site of replication is believed to be the GI tract and the liver is then invaded probably via the portal vein.

• Virus is released to bile and blood after replication in hepatocytes.
• The incubation period is 10-40 days.

• Pathologically, there is focal necrosis with minimal infiltration and no localization to a particular zone of the lobule.

• Cholestatic hepatitis is often present characterized by ballooning hepatocytes.

• Clinical manifestations are similar to those of hepatitis A but with higher mortality (1% Vs 0.1%).
• HEV infection is particularly severe among pregnant women and mortality increases with gestational age to reach up to 20% in the 3rd trimester (fluminant hepatitis).

• Water borne outbreaks especially in the developing countries.

• Epidemics of HEV were first reported in 1980 from the Indian subcontinent but outbreaks involving tens of thousands cases have also been documented in the previous USSR, Southeast Asia, Northern Africa and Mexico.
Hepatitis E Virus Infection

Typical Serologic Course

Symptoms

Virus in stool

ALT

IgG anti-HEV

IgM anti-HEV

Titer

Weeks after Exposure
Geographic Distribution of Hepatitis E

Outbreaks or Confirmed Infection in >25% of Sporadic Non-ABC Hepatitis