Hepatitis C and E

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Section A

Background and Overview
Cloning of HCV, Production of High-Titer Concentrates

Collect units of chronic-phase plasma at ALT peaks (assumes virus is cytopathic)

Chimp
Inoc. FVIII (HCV)

ALT
Year

Plasma Units

3,200 ml Pool

ALTM
Day

Pool
≥10⁶ CID/ml

Dilute aliquots 4-6x in TENB, pH 8.0 buffer and pellet virus (assumes HCV has S20, w ≥ 150S and is most stable at alkaline pH)

Pelleted Virus
Resuspend

Extract TOTAL RNA (assumes virus has no 3’-polyA tail); Prepare cDNA, insert into λgt₁₁: screen
Molecular Cloning and Characterization

HCV Agent → RNA → cDNA → EcoR1 → Phage GT-11 → E. coli → Agar → HCV Patient Serum → Locate Clone and Express

Microwell ELISA for HCV Antibody
Conserved and HV Domains of HCV Genome

HCV-FVIII (US): 9,379 nt; 3011 aa ORF
HCV-Japan: 9,416 nt; 3010 aa ORF

Homology ~ 85% (aa)
The Flaviviridae Family

Diagram showing the relationships between Hepatitis C Virus, Flavivirus, and Pestivirus.
Flaviviruses and Pestiviruses

- **Flaviviruses**
  - Yellow fever virus
  - Dengue viruses
  - St. Louis encephalitis virus
  - Japanese B encephalitis virus

- **Pestiviruses**
  - Bovine viral diarrhea
  - Hog cholera virus
  - Border disease virus of sheep
## Features of Hepatitis C Virus Infection

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incubation period</td>
<td>Average: 6–7 weeks</td>
</tr>
<tr>
<td></td>
<td>Range: 2–26 weeks</td>
</tr>
<tr>
<td>Acute illness (jaundice)</td>
<td>Mild (20% or less)</td>
</tr>
<tr>
<td>Case fatality rate</td>
<td>Low</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>75–85%</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>70% (most asymptomatic)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>10–20%</td>
</tr>
<tr>
<td>Mortality from CLD</td>
<td>1–5%</td>
</tr>
</tbody>
</table>
Natural History of HCV Infection

- Exposure (Acute Phase)
  - Resolved 15% (15)
  - Chronic 85% (85)
    - Stable 80% (68)
    - Cirrhosis 20% (17)
      - Slowly Progressive 75% (13)
      - HCC Transplant Death 25% (4)

HIV and Alcohol
Serologic Pattern of Acute HCV Infection with Recovery

Adapted by CTLT from CDC.
Serologic Pattern: Progression to Chronic Infection

Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection

- ALT
- Anti-HCV

Symptoms +/-

HCV RNA

Time After Exposure

0 1 2 3 4 5 6 1 2 3 4

Years

Months

Normal

Adapted by CTLT from CDC.
Chronic Hepatitis C

- Factors promoting progression or severity
  - Increased alcohol intake
  - Age >40 years at time of infection
  - HIV co-infection
  - Possible other
    - Male gender
    - Other co-infections (e.g., HBV)
Fibrosis: Gender, Age at Biopsy, Duration of Infection

- **Age at Biopsy (Years):**
  - Women: n = 2231
  - Men: n = 1156

- **Duration of Infection (Years):**
  - Women: n = 2231
  - Men: n = 1156
Fibrosis: Age at Infection, Duration of Infection

- Mean Fibrosis Stage vs. Duration of Infection (Years)
- Two lines represent groups:
  - < 40 Years at Infection (green)
  - ≥ 40 Years at Infection (orange)

- Data points for each duration category:
  - ≤5
  - 6-10
  - 11-15
  - 16-20
  - >20

- Sample size: n = 1157
Fibrosis: Alcohol, Age at Biopsy, Duration of Infection

- For patients consuming 0-49g Alcohol Daily:
  - Age at Biopsy (Years):
    - <30: 1.0
    - 31-40: 1.5
    - 41-50: 2.0
    - 51-60: 2.5
    - >60: 3.0
    - Total: 1574 patients

- For patients consuming >50g Alcohol Daily:
  - Duration of Infection (Years):
    - ≤10: 1.0
    - 11-20: 1.5
    - 21-30: 2.0
    - 31-40: 2.5
    - >40: 3.0
    - Total: 1039 patients
HCV and HIV: Liver-Related Mortality

- Liver deaths
  - HIV- up 16.7-fold
  - HIV+ up 94.4-fold
- Risk up after 10 years

Interaction of HIV and Hepatitis C Virus Infection

1. Both are spread parenterally, so injection drug users and other risk populations (hemophiliacs) are often co-infected
2. HIV infection increases HCV viral load (0.5–1.0 log)
3. Effect of HCV on HIV viral load inconsistent
4. HIV accelerates development of liver fibrosis from HCV
5. Effect of HCV on HIV progression unclear (Swiss cohort = accelerated HIV)
6. Response to interferon/ribaviran therapy poorer in HIV-infected subjects
7. Drug interactions: ribaviran and AZT or d4T, ribaviran and DDI
8. HIV infection increases sexual and perinatal transmission of HCV
9. T cell immune responses to HCV decreased in HIV co-infected subjects (both CD8+ CTL and CD4+ proliferative responses)
10. T cell responses to HIV may be increased in HCV co-infected subjects
Studies of Cellular Immune Responses
Co-Infection and Perinatal HCV and HIV Transmission

Effect of Coinfection on Perinatal HCV and HIV Transmission

- **HCV Transmission**
  - HIV+ n = 22
  - HIV- n = 94
  - HCV+ n = 161
  - HCV- n = 326

Genetic Diversity of Full Length HCV and HIV Isolates
HCV Diversity vs. Time

HCV Diversity vs. Time

Number and Frequency of Clonotypes

Months After HCV Seroconversion

Colors represent different clonotypes.
## Hepatitis C Virus Infection, United States

<table>
<thead>
<tr>
<th>New infections (cases) per year</th>
<th>242,000 (42,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985–1989</td>
<td>40,000 (6,500)</td>
</tr>
<tr>
<td>1998</td>
<td></td>
</tr>
</tbody>
</table>

| Deaths from acute liver failure | Rare             |

| Persons ever infected (1.8%)    | 3.9 million (3.1–4.8)* |

| Persons with chronic infection  | 2.7 million (2.4–3.0)* |

| Of chronic liver disease—HCV-related | 40–60% |

| Deaths from chronic disease per year | 8,000–10,000 |

*95% confidence interval
<table>
<thead>
<tr>
<th>Group</th>
<th>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>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.5%</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>Mexican 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>

Section B

Transmission of HCV
Transmission of HCV

- Percutaneous
  - Injecting drug use
  - Clotting factors before viral inactivation
  - Transfusion, transplant from infected donor
  - Therapeutic (contaminated equipment, unsafe injection practices)
  - Occupational (needlestick)

- Permucosal
  - Perinatal
  - Sexual
Injecting Drug Use and HCV Infection

- Highly efficient mode of transmission
- Rapidly acquired after initiation
- Four times more common than HIV
- Prevalence of 50–90% after five years
- Predominant risk factor in low-prevalence countries
HCV Prevalence by Selected Groups, United States

Adapted by CTLT from CDC.
Sources of Infection for Persons with Hepatitis C

- Injecting Drug Use: 60%
- Sexual: 15%
- Transfusion (Before Screening): 10%
- Health-Care Work Perinatal: 5%
- Unknown: 10%

Adapted by CTLT from CDC.
Seroprevalence of Infectious Diseases among IDUs

Seroprevalence of Infectious Diseases Among IDUs
Baltimore, ALIVE

Percent Seropositive

HCV | HBV | HIV | HEV | HDV | Syphilis | HTLV IVI
Relationship of Duration of Injecting Drug Use With the Prevalence of Bloodborne Viruses

Reported Acute Cases by Selected Risk Factors

Reported Cases of Acute Hepatitis C by Selected Risk Factors, United States, 1983-1998

- Injecting Drug Use
- Transfusion
- Sexual
- Health Related Work

Adapted by CTLT from CDC Sentinel Counties Study.
Posttransfusion Hepatitis C, United States

Adapted by CTLT from CDC and HJ Alter; Tobler and Busch, Clin Chem 1997.
Estimated Incidence of Acute HCV Infection, U.S.

Estimated Incidence of Acute HCV Infection,
United States, 1960-1999

New Infections per 100,000

Year

'60 '65 '70 '75 '80 '85 '89 '95 '99

Decline in Injection Drug Users

Decline in Transfusion Recipients

Adapted by CTLT from Hepatology 2000;31:777-82;
Hepatology 1997;26:625-655.
Nosocomial Transmission of HCV

- Recognized primarily in context of outbreaks
- Contaminated equipment
  - Hemodialysis*
  - Endoscopy
- Unsafe injection practices
  - Plasmapheresis,* phlebotomy
  - Multiple-dose medication vials
  - Therapeutic injections

*Reported in the U.S.
Occupational Transmission of HCV

- Inefficiently transmitted 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
  - No reports of transmission from skin exposures to blood
- Prevalence 1–2% among health care workers
  - Lower than adults in the general population
  - 10 times lower than for HBV infection
- Presence of recognized risk factor does not necessarily equate with “increased risk”
HCW-to-Patient Transmission of HCV

- Rare
  - In the U.S., none related to performing invasive procedures
- Most appear related to HCW substance abuse
  - Reuse of needles or sharing narcotics used for self-injection
  - Reported mechanism for transmission of other bloodborne pathogens from some HCWs
- No restrictions routinely recommended for HCV-infected HCWs
Perinatal Transmission of HCV

- Transmission only from women HCV-RNA positive at delivery
  - Average rate of infection is 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
Sexual Transmission of HCV

- Occurs, but efficiency is low
  - Rare between long-term steady partners
  - Factors that facilitate transmission between partners unknown

- Accounts for 15–20% of acute and chronic infections in the United States
  - Sex is a common behavior
  - Large chronic reservoir provides multiple opportunities for exposure to potentially infectious partners
Geographic and Temporal Differences

- Geographic and Temporal differences in the epidemiology of HCV infection
  - HCV infection is endemic in most parts of the world
  - Substantial differences in endemicity of HCV infection
    ▶ Related to frequency and extent to which various risk factors contributed to transmission
Prevalence of HCV Infection Among Blood Donors

Anti-HCV Prevalence

- Unknown
- Very Low (≤0.1%)
- Low (0.2%-1%)
- Intermediate (1.1%-5%)
- High (>5%)

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

Adapted by CTLT from CDC.
Distributions of Hepatitis C Genotypes
Geographic Patterns of Age-Specific Prevalence of HCV

Geographic Patterns of Age-Specific Prevalence of HCV Infection

- Egypt
- Japan, Italy
- U.S., Australia

Adapted by CTLT from CDC.
HCV Infection Related to Therapeutic Injections, Egypt

- HCV infection related to therapeutic injections for schistosomiasis, Egypt

<table>
<thead>
<tr>
<th>Blood donors</th>
<th>HCV-positive</th>
<th>HCV-negative</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection therapy</td>
<td>36%</td>
<td>7%</td>
<td>8.9 (2.4–33.5)</td>
</tr>
<tr>
<td>Village population</td>
<td>Inject</td>
<td>No inject</td>
<td>PR (95% CI)</td>
</tr>
<tr>
<td>HCV-positive</td>
<td>63%</td>
<td>23%</td>
<td>2.8 (2.5–3.2)</td>
</tr>
</tbody>
</table>

Health Care Related HCV Transmission

- Blood transfusion from unscreened donors
  - Including plasma-derived products not inactivated
- Unsafe injection practices
  - Inadequate sterilization of reusable needles and syringes
  - Sharing of disposable needles and syringes
- Contaminated equipment
  - Inadequate cleaning and disinfection
    - In health care settings
    - Alternative medicine practices, rituals
## Unsafe Injections and HCV Infection

- **Moderate endemic countries**

<table>
<thead>
<tr>
<th>Country</th>
<th>HCV-positive (%)</th>
<th>HCV-negative (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>63%</td>
<td>31%</td>
<td>3.8 (2.7, 5.3)</td>
</tr>
<tr>
<td></td>
<td>89%</td>
<td>53%</td>
<td>7.0 (4.4, 11.2)</td>
</tr>
<tr>
<td></td>
<td>76%</td>
<td>72%</td>
<td>1.2 (0.6, 2.5)</td>
</tr>
<tr>
<td>Taiwan</td>
<td>26%</td>
<td>8%</td>
<td>4.2 (1.2, 14.5)</td>
</tr>
<tr>
<td>Pakistan (≥5 per year)</td>
<td>36%</td>
<td>6%</td>
<td>8.2 (1.9, 41.4)</td>
</tr>
</tbody>
</table>

Percent history reused needles/syringes
HCV Infections Attributable to Unsafe Injections

- Proportion of HCV infections attributable to unsafe injections, case-control studies

<table>
<thead>
<tr>
<th>Country (author)</th>
<th>Year</th>
<th>Age</th>
<th>Pop. attrib. fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taiwan</td>
<td>1993</td>
<td>Children</td>
<td>84%*</td>
</tr>
<tr>
<td>(Ho)</td>
<td>1990–1994</td>
<td>Adults</td>
<td>20%*</td>
</tr>
<tr>
<td>(Chen)</td>
<td>1990</td>
<td>Adults</td>
<td>57%</td>
</tr>
<tr>
<td>(Sun)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pakistan (Luby)</td>
<td>1994–1995</td>
<td>All</td>
<td>51%*</td>
</tr>
<tr>
<td>Egypt (El Sakka)</td>
<td>1996–1997</td>
<td>All</td>
<td>88%*</td>
</tr>
</tbody>
</table>

*Calculated from data provided by authors

Source: Hutin, Yvan. WHO.
## Alternative Medicine and HCV Infection

<table>
<thead>
<tr>
<th>Country</th>
<th>HCV-positive</th>
<th>HCV-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional Japan</td>
<td>62%* 20%</td>
<td>26% 17%</td>
</tr>
<tr>
<td>Case-control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>U.S.A.</td>
<td>0%</td>
<td>1%</td>
</tr>
</tbody>
</table>

*P < .05, performed by unlicensed therapists
## Health Care Procedures and HCV Infection

### Low/moderate endemic countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Surgery</th>
<th>Dental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>U.S.A.</td>
<td>HCV-positive: 10%</td>
<td>HCV-negative: 12%</td>
</tr>
<tr>
<td></td>
<td>HCV-positive: 24%</td>
<td>HCV-negative: 24%</td>
</tr>
<tr>
<td>Italy</td>
<td>HCV-positive: 17%*</td>
<td>HCV-negative: 2%</td>
</tr>
<tr>
<td></td>
<td>HCV-positive: 24%</td>
<td>HCV-negative: 11%</td>
</tr>
<tr>
<td>Cross-sectional</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>HCV-positive: 56%*</td>
<td>HCV-negative: 36%</td>
</tr>
<tr>
<td></td>
<td>HCV-positive: 91%*</td>
<td>HCV-negative: 80%</td>
</tr>
<tr>
<td>Taiwan</td>
<td>HCV-positive: 77%</td>
<td>HCV-negative: 57%</td>
</tr>
<tr>
<td></td>
<td>HCV-positive: 90%</td>
<td>HCV-negative: 90%</td>
</tr>
<tr>
<td>Pakistan</td>
<td>HCV-positive: 13%</td>
<td>HCV-negative: 3%</td>
</tr>
<tr>
<td></td>
<td>HCV-positive: 24%</td>
<td>HCV-negative: 28%</td>
</tr>
<tr>
<td>Japan</td>
<td>HCV-positive: No data</td>
<td>HCV-negative: 33%</td>
</tr>
<tr>
<td></td>
<td>HCV-positive: No data</td>
<td>HCV-negative: 39%</td>
</tr>
<tr>
<td></td>
<td>HCV-positive: No data</td>
<td>HCV-negative: No data</td>
</tr>
</tbody>
</table>

*P < .05, independent of other risk factors
<table>
<thead>
<tr>
<th>Country</th>
<th>Tattooing</th>
<th></th>
<th>Body piercing</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCV-positive</td>
<td>HCV-negative</td>
<td>HCV-positive</td>
<td>HCV-negative</td>
</tr>
<tr>
<td>Cross-sectional</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>1%</td>
<td>0%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pakistan</td>
<td>3%</td>
<td>0%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>7%</td>
<td>0%</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td>Case-control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>U.S.A.</td>
<td>1%</td>
<td>1%</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>
### Geographic Differences in HCV Transmission Patterns

#### Importance of exposure by HCV endemicity

<table>
<thead>
<tr>
<th>Exposures among prevalent infections</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injecting drug use</td>
<td>++++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Transfusions</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Health care related</td>
<td>+/-</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Unsafe injections</td>
<td>+/-</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Folk medicine</td>
<td>–</td>
<td>++</td>
<td>No data</td>
</tr>
</tbody>
</table>
Posttreatment Rebound and Relapse

Posttreatment Rebound and Relapse - ALT Patterns

Rebound

IFNα-2b
3MIU, TIW

Relapse

IFNα-2b
3MIU, TIW

Weeks

Weeks

Davis G. NHDTNP Consensus Conference, Santa Monica, CA, September, 1990.
IFN Regimens: End-of-Treatment, Sustained Response Rates

Changes in the End-of-Treatment and Sustained Response Rates with Different Interferon Treatment Regimens.

Percent Sustained Virologic Response

- End-of-Treatment Response
- Sustained Response

<table>
<thead>
<tr>
<th>Regimen</th>
<th>End-of-Treatment</th>
<th>Sustained Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN 6m</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td>IFN 12m</td>
<td>13%</td>
<td>24%</td>
</tr>
<tr>
<td>IFN/R 6m</td>
<td>33%</td>
<td>53%</td>
</tr>
<tr>
<td>IFN/R 12m</td>
<td>41%</td>
<td>50%</td>
</tr>
<tr>
<td>PEG/R 12m</td>
<td>54%</td>
<td>62%</td>
</tr>
</tbody>
</table>
Genotype and Response to Interferon-Based Treatment

Impact of Viral Genotype on Sustained Virologic Response to Interferon-Based Treatment

- **Genotype 2 or 3**
- **Genotype 1**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Genotype 2 or 3</th>
<th>Genotype 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN 6m</td>
<td>2%</td>
<td>15%</td>
</tr>
<tr>
<td>IFN 12m</td>
<td>9%</td>
<td>31%</td>
</tr>
<tr>
<td>IFN/R 6m</td>
<td>17%</td>
<td>66%</td>
</tr>
<tr>
<td>IFN/R 12m</td>
<td>29%</td>
<td>65%</td>
</tr>
<tr>
<td>PEG/R 12m</td>
<td>42%</td>
<td>82%</td>
</tr>
</tbody>
</table>
Impact of Degree of Fibrosis on Liver Biopsy on Sustained Virologic Response to Interferon-Based Treatment

- Bridging or Cirrhosis
- No Fibrosis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No Fibrosis</th>
<th>Bridging or Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN 6m</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>IFN 12m</td>
<td>12%</td>
<td>18%</td>
</tr>
<tr>
<td>IFN/R 6m</td>
<td>23%</td>
<td>36%</td>
</tr>
<tr>
<td>IFN/R 12m</td>
<td>36%</td>
<td>43%</td>
</tr>
<tr>
<td>PEG/R 12m</td>
<td>44%</td>
<td>57%</td>
</tr>
</tbody>
</table>
Peak Concentrations of HCV Viraemia Among Previously Infected and Initially Uninfected Individuals

- **Developed Persistent Infection**
- **Cleared**
- **Median**
Will it be possible to develop a preventive vaccine for HCV? pro (yes)

- 30% of persons clear the virus spontaneously
- The genome of HCV is not integrated into the host genome
- After HCV infection, CD-8 CTL responses and antibodies appear, but the “protective immune response” or critical epitopes are not known
- Persons who clear HCV and become re-infected have low viral loads and more likely to clear HCV
Will it be possible to develop a preventive vaccine for HCV? con (no)

- After clearance, persons are not immune to reinfection (chimps can be reinfected with the same virus)
- Great genetic diversity of HCV makes decision on prototype vaccine virus very difficult
- Immune response drives HCV diversity
Hepatitis E Virus: Historical Overview

- 1900: Infectious hepatitis reported with high mortality rates in women
- 1955: A common-source outbreak of infectious hepatitis observed in India
  - Longer incubation period than previously observed (40 days)
  - Mean age was older (27 years)
  - High mortality in pregnant women (20% CFR)
- 1980: Reports of large outbreaks in India and Kashmir
  - Seronegative for hepatitis A and B
  - Increased secondary attack rate in household contacts
**Virus Characteristics**

- HEV is a spherical, non-enveloped, single-stranded RNA virus
- Approximately 27–34 nm in diameter
- Presently unclassified
- May be unstable in external environment/labile

Photo source: Department of Epidemiology, Johns Hopkins School of Hygiene and Public Health.
Hepatitis E virus (HEV) is the principal cause of enterically transmitted non-A, non-B hepatitis
Causes epidemic and sporadic disease in many developing countries
Identified as a distinct virus in 1980
  – Khuroo et al. and Wong et al.
Cloned and partially sequenced in 1990
  – Reyes et al.
First complete nucleotide sequence in 1991
  – Tam et al.
Background

- Clinical hepatitis E disease normally seen in adults 15–40 years old (unlike HAV)
- Low seroprevalence in pediatric populations
- Infection rate is 2–4 times higher than disease rate
- Minimal secondary person-to-person transmission observed (illness and/or serology) 2%
- No treatment or vaccine available
- Median cost of infection = $37 (wages/productivity), 35 days lost
  - Clarke et al. (1999).
Hepatitis E: Epidemiologic Features

- Most outbreaks associated with fecally contaminated drinking water
- Minimal person-to-person transmission
- U.S. cases usually have history of travel to HEV-endemic areas
### Hepatitis E: Clinical Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incubation period</td>
<td>Average: 40 days</td>
</tr>
<tr>
<td></td>
<td>Range: 15–60 days</td>
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<tr>
<td>Case-fatality rate</td>
<td>Overall: 1–3%</td>
</tr>
<tr>
<td></td>
<td>Pregnant women: 15–25%</td>
</tr>
<tr>
<td>Illness severity</td>
<td>Increased with age</td>
</tr>
<tr>
<td>Chronic sequelae</td>
<td>None identified</td>
</tr>
</tbody>
</table>
HEV Infection: Typical Serologic Course

Hepatitis E Virus Infection - Typical Serologic Course

- ALT
- IgM Anti-HEV
- IgG Anti-HEV

Titer

Week After Exposure

Symptoms

Virus in Stool

Adapted by CTLT from CDC.
Geographic Distribution of Hepatitis E

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

Adapted by CTLT from CDC.
Jaundice at Ayurved Hospital (Nepal) and Rainfall

Outpatient Cases with Jaundice at Ayurved Hospital, Nepal (April 1980 - August 1982) and Rainfall from 1981 - 1982