Hepatitis C: An Overview

EIP Meeting
August 12, 2005
Hepatitis C - Epidemiology

How many people are infected?
Hepatitis C - Prevalence

- **Prevalence**
  - 1988 -1994 NHANES
    - Approximately 4.0 million Americans have been exposed to the hepatitis C virus.
    - Approximately 2.7 million were chronically infected.
  - 1999 – 2002 NHANES
    - Approximately 3.2 million Americans are chronically infected.
Hepatitis C - Incidence

- **Incidence**
  - 1985 – 1989: Number of new hepatitis C infections each year was estimated at 242,000.
  - Since 1989: Sharp decline in the number of new infections.
  - 2001: Estimated 25,000 new infections.
Michigan

- An estimated 182,000 people have been exposed to the virus.
- An estimated 130,000 are chronically infected.
- Approximately 31,500 cases have been reported to the MDCH to date.
- An estimated 730 new cases each year.
Hepatitis C - Demographics

- 1988-1994 NHANES
  - Estimated prevalence
    - 3.2 percent in African Americans
    - 2.9 percent in Hispanic Whites
    - 1.5 percent in non-Hispanic Whites
    - The subgroup with the highest prevalence was African American males aged 40 to 49 with a prevalence of 9.8 percent.
Hepatitis C - Demographics

1999 – 2002 NHANES

- Highest prevalence was among adults ages 39 to 50.
- Men had higher rates of infection than women.
- Within most age groups, prevalence remains highest among African American men.
What is the natural history of infection?
Natural History

- Natural History - Acute Infection
  - **Symptoms**
    - Are uncommon
    - On average, appear 6 to 7 weeks after infection.
  
  - **Testing**
    - 6 to 8 weeks: Average time antibodies can be detected.
    - 1 to 3 weeks: Average time virus can be detected.
    - 4 to 12 weeks: Often elevation in ALTs
  
- 15 to 25 percent of people resolve acute infection.
Serologic Pattern of Acute HCV Infection with Recovery

Symptoms +/-

HCV RNA

ALT

Titer

Time after Exposure

0 1 2 3 4 5 6

Years

0 1 2 3 4

Months

Normal

Anti-HCV
Chronic Infection
- 75 to 85 percent of infected people develop chronic infection.

- Diagnosed by the detection of HCV RNA in the blood for at least six months.

- 60 to 70 percent of people will have persistent or fluctuating ALT elevations.

- Chronic liver disease usually progresses at a slow rate without symptoms.

- The rate of progression is highly variable.
Natural History

- **Chronic Infection**
  - Progression can move from fibrosis to cirrhosis to end-stage liver disease and death.
  - Estimated that 10 to 20 percent of people will develop cirrhosis 20 to 30 years after infection.
  - Some with cirrhosis:
    - Develop HCC – 1 to 4 percent a year
    - Develop decompensated cirrhosis
  - End-stage liver disease necessitates a transplant or will end in death.
Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection

- **Time after Exposure**: 0 to 4 years
- **Titer**
  - anti-HCV
  - Symptoms +/-
  - HCV RNA
  - ALT
- **Normal**

Time after Exposure:
- 0 to 4 years
- Months: 0, 1, 2, 3, 4
- Years: 1, 2, 3, 4
Natural History

- **Factors that Influence Progression**
  - Greater than age 40 at time of infection
  - Male gender
  - Alcohol use
  - Co-infection with HIV or HBV
  - Co-morbid conditions such as obesity or NASH

- **Factors that Don’t Influence Progression**
  - Viral load
  - Genotype
Transmission

How is hepatitis C being transmitted?
Routes of Transmission

- Injecting drug use 60%
- Sexual 15%
- Transfusion 10% (before screening)
- Occupational 4%
- Other 1%*
- Unknown 10%

* Nosocomial; iatrogenic; perinatal

Source: Centers for Disease Control and Prevention
Injecting Drug Use

- Accounts for 60 percent of HCV transmission
- Accounts for two-thirds of new infections
- Highly efficient mode of transmission
- Prevalence in injecting drugs using populations is high
- Rapidly acquired after first injection
### Prevalence of HCV and HIV in IDUs

<table>
<thead>
<tr>
<th>Location</th>
<th>Year</th>
<th>HCV</th>
<th>HIV</th>
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<tbody>
<tr>
<td>Amsterdam</td>
<td>1991</td>
<td>66%</td>
<td>33%</td>
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<tr>
<td>Geneva</td>
<td>1992</td>
<td>80%</td>
<td>32%</td>
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<tr>
<td>Baltimore</td>
<td>1994</td>
<td>90%</td>
<td>25%</td>
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<td>Seattle</td>
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<td>82%</td>
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<td>Rural UK</td>
<td>2000</td>
<td>56%</td>
<td>14%</td>
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<td>S. China</td>
<td>2003</td>
<td>71%</td>
<td>17%</td>
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<tr>
<td>Vancouver</td>
<td>2004</td>
<td>44%</td>
<td>19%</td>
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H. Hagen, 2004 presentation
Transmission

- **Studies of Young or New Injectors**
  - *Baltimore* (Thomas, et. al): Reported 80 percent prevalence in subjects acknowledging two years of injection drug use or less.
  - *Chicago and Suburbs* (Thorpe, et. al):
    - Reported 27 percent prevalence in subjects age 18 to 30
    - Reported 15 percent prevalence in subjects acknowledging two years of injection drug use or less.
Transmission

- **Studies of Young or New Injectors**
  - *Seattle (Hagan et. al):*
    - Reported 41 percent antibody prevalence in subjects acknowledging drug use for two years or less at time of enrollment.
    - Mean time to seroconversion:
      - 0.6 years for those positive at enrollment
      - 5.4 years for those negative at enrollment who later seroconverted
      - 3.4 years weighted average time to seroconversion
Factors Associated with Infection

- Years of injecting
- Frequency of injection
- Being a young/new injecting drug user
- Sharing syringes
- Sharing cotton/cookers
- Backloading
- ????????????
Transmission

Sexual Transmission
- 15 percent of HCV infection
- However, sex is an inefficient mode of transmission

Long-Term Spouses (CDC)
- A low prevalence of HCV infection has been reported by studies of long-term spouses of patients with chronic HCV infection who had no other risk factors for infection.
- Five of these studies have been conducted in the United States, involving 30-85 partners each, in which average prevalence was 1.5% (range: 0% to 4.4%)
Transmission

- Long-Term Prospective Study (Vandelli et. al.)
  - Enrolled anti-HCV negative partners of HCV positive individuals.
  - 776 partners completed a ten-year follow-up.
  - Three spouses acquired HCV during follow-up.
  - All had other risk factors and/or follow-up testing showed genotype/strain discordant with that of spouse.
Transmission

**Sexual Transmission**
- Risk higher among those with multiple partners and history of sexually transmitted disease
- Prevalence found to average 5 percent among STD clinic patients with no history of injection drug use.

- Factors associated with positivity
  - Greater number of sex partners
  - History of STDs
  - Failure to use a condom
Transmission

Transfusion

- **1990**
  - Routine testing of donors was initiated.
  - Risk was approximately 1.5% per recipient or approximately 0.2% per unit transfused.
- **July 1992**
  - More sensitive testing was implemented.
  - Reducing risk for infection to 0.001% per unit transfused.
- **2005**
  - Current risk for transfusion-associated hepatitis C is 1 per 2 million units transfused.
Transmission

- **Blood Clotting Factor**
  - Used to treat individuals with hemophilia.
  - High risk of infection prior to the use of virus inactivation procedures that were introduced in 1985 and 1987.
  - Prevalence is greater than 90 percent in hemophiliacs treated with these products before inactivation.

- **Solid Organ Transplants**
Transmission

- **Occupational**
  - Occupational exposure is inefficient.

  - In one study that evaluated risk factors for infection, a history of unintentional needle-stick injury was the only occupational risk factor independently associated with HCV infection.

  - Average incidence 1.8 percent following needle stick from HCV-positive source.

  - Prevalence among health care workers is 1 to 2 percent.
Nosocomial Transmission

- Rarely reported in the United States, other than in chronic hemodialysis settings.

- Prevalence of anti-HCV positivity among chronic hemodialysis patients averages 10%.

- Studies have documented an association between anti-HCV positivity and increasing years on dialysis.

- Most likely due to incorrect implementation of infection-control practices.
Transmission

- **Perinatal**
  - Five percent of infected mothers transmit the virus to their baby.
  - Average rate of transmission is higher in women also infected with HIV – 17 percent.
  - No difference seen between vaginal and cesarean births.
Transmission

- **Household Transmission**
  - Rare but not absent
  - Could occur through percutaneous/mucosal exposure to blood
    - Contaminated equipment for home therapies
    - Theoretically through the sharing of personal items (i.e., toothbrushes, razors)
Transmission

- **No Known Risk**
  - In 10 percent of cases, no known risk is identified.

- **Exposures in Other Settings (CDC)**
  - No data or insufficient data to show transmission through:
    - Intranasal cocaine use
    - Tattooing
    - Piercing
Prevention

How can transmission be prevented?
Prevention

Injecting Drug Users:
- Stop using and injecting drugs.
- Enter and complete substance abuse treatment.
- If continuing to inject drugs:
  - Never reuse or "share" syringes, needles, water, or drug preparation equipment.
  - If injection equipment has been used by other persons, first clean the equipment with bleach and water.
  - Use only syringes obtained from a reliable source (e.g., pharmacies).
**Prevention**

- **Injection Drug Use**
  - Use a new sterile syringe to prepare and inject drugs; if possible, use sterile water to prepare drugs; otherwise use clean water from a reliable source (such as fresh tap water).
  - Use a new or disinfected container ("cooker") and a new filter ("cotton") to prepare drugs.
  - Clean the injection site prior to injection with a new alcohol swab.
  - Safely dispose of syringes after one use.
  - Get vaccinated against hepatitis A and B.
Prevention

- **Persons At-risk for STDs**
  - Have sex with only one uninfected partner or do not have sex at all.
  - Use latex condoms correctly and every time to protect themselves and their partners from diseases spread through sexual activity.
  - Get vaccinated against hepatitis B, and if appropriate, hepatitis A.
HCV Testing

Who should be tested?
**CDC Testing Recommendations**

- **Testing Routinely Recommended Based on Risk of Infection**

- Person who ever injected illegal drugs

- Persons with selected medical conditions
  - Persons who received clotting factor concentrates produced before 1987
  - Persons who were ever on long-term hemodialysis
  - Persons with persistently abnormal alanine aminotransferase levels (persons with chronic liver disease)
CDC Testing Recommendations

- Testing Routinely Recommended Based on Risk of Infection

- Prior recipients of transfusions or solid organs
  - Persons who were notified that they received blood from a donor who later tested positive for HCV infection
  - Persons who received a transfusion of blood or blood components before July 1992
  - Persons who received an organ transplant before July 1992
CDC Testing Recommendations

- **Testing Routinely Recommended Based on Need for Exposure**

  - Health care, emergency medical, and public safety workers after needlesticks, sharps, or mucosal exposures to HCV positive blood

  - Children born to HCV positive women
HCV Testing

What do test results mean?
HCV Testing

Initial Screening
- Used to determine exposure/detect hepatitis C antibodies.
  - Example: Enzyme immunoassays (EIA)
  - It takes an average of 6 to 8 weeks before antibodies can be detected.
  - Within three months of infection, 97 percent of persons will have sufficient antibodies to be detected with a screening test.
HCV Testing

Initial Screening – Negative Result

- A negative test most likely means that a person is not infected.

- False negatives are uncommon.
  - May occur if a person has been recently infected.
  - May occur in individuals who are immuno-suppressed or on long-term hemodialysis.
HCV Testing

**Initial Screening - Positive Result**
- False positives are uncommon.
  - Most likely to occur in individuals at low-risk for infection.
  - May occur in individuals with autoimmune liver disease.
- A positive test, especially in a person with known risk factors, most likely means that they have been exposed to the virus.
- Screening test results can be verified with a supplemental or confirmatory test.
HCV Testing

- **Confirmatory Testing**
  - To ensure that a positive screening test result is a true positive.
  - To distinguish between a resolved and an active infection.
  - They can be used alone or more than one test can be used.
Supplemental Confirmatory Assay
- Detects antibodies to HCV.

- Recombinant immunoblot assay (RIBA)

- Can be done on the same blood sample as the screening assay.

- Used to determine whether an antibody positive result is a true positive result, especially in low prevalence populations.
Virus Detection Tests

- Nucleic Acid Tests (NATs)
  - Tests that determine presence of the hepatitis C virus in the blood through detection of HCV RNA.
  - Detection of HCV RNA provides definitive proof that an infection exists.
  - There are both qualitative and quantitative virus detection tests.
HCV Testing

**Qualitative Virus Detection Tests**
- Can detect the virus as early as one or two weeks after exposure.

- Can detect the virus at lower levels than quantitative tests.

- Are the preferred test for determining active infection. (AMA guidelines)

- Examples: Reverse Transcriptase-polymerase chain reaction assays (RT-PCR) or Transcription mediated amplification (TMA)
HCV Testing

- Quantitative Virus Detection Tests
  - Can quantify the actual amount of the virus or the viral load.
  - Often used to monitor response to treatment.
  - Examples: Reverse Transcriptase-polymerase chain reaction assays (RT-PCR), Transcription mediated amplification (TMA), or branched chain DNA assays
AMA: Testing Asymptomatic People

AMA Update on the Screening and Management of Hepatitis C. Adapted From CDC Guidelines for Laboratory Testing and Result Reporting of Hepatitis C. (MMWR. 2003; 52:1-13)
S/Co Ratios

- The CDC guidelines allow for the use of screening-test-positive signal-to-cut off ratios (s/co ratios) to determine need for supplemental testing.

- Positive screening tests with high s/co ratios have been demonstrated to predict a supplemental serologic-test-positive 95 percent or greater of the time.

- These tests can be reported as HCV-antibody positive without supplemental testing.
S/Co-Ratios - MDCH

(+ with high s/co ratio) ----> EIA ----> (-) No HCV

(Probable) Prior or Active Infection

(+ with low s/co ratio) ----> RT-PCR or TMA

(Probable) Prior or Active Infection

(+ with high s/co ratio) ----> RIBA

(Probable) Prior HCV Infection with Recovery

False Positive EIA

No Exposure
If a person is chronically infected, what other tests will they do?
Genotyping

- There are at least six different genotypes of HCV.
  - **Genotype 1** - 70 to 75 percent of persons infected in the US.
  - **Genotypes 2 and 3** - 10 to 15 percent of persons infected in the US.

- Genotype testing should be done on all HCV positive people considering treatment.
  - Often determines length of treatment.
  - Is also a predictor of response to treatment.
Liver Enzyme Tests

Liver Enzyme Tests
- Elevated ALT levels are an indirect measure of liver cell inflammation and damage.

- In patients with risk factors and elevated liver enzymes, HCV infection is probable.

- However, the absence of elevation does not rule out significant liver damage.

- One-third to one-half of HCV infected individuals will have a normal ALT level.
Liver Biopsy

- *Liver Biopsy*
  - Most sensitive measure of disease severity.
  - Used to determine stage of fibrosis.
  - Can be used to help predict natural history of disease.
  - Often used to determine the need for treatment.
  - Can also be used to predict response to treatment.
  - May not be indicted for patients with genotypes 2/3.
Quantitative Virus Detection

- **Quantitative Virus Detection Tests**
  - **Genotype 1:**
    - A change in viral level is used to monitor response to hepatitis C treatment.
    - Test before treatment starts
    - Test at 12 weeks
Who should be treated?
NIH Consensus Statement

- Treatment is recommended for patients with increased risk of developing cirrhosis.
  - Detectable HCV RNA
  - A liver biopsy with portal or bridging fibrosis
  - At least moderate inflammation and necrosis
  - (Majority also have persistently elevated ALTs.)

- In some patient populations, the risks and benefits of treatment are less clear and should be determined on an individual basis.
AASLD Practice Guidelines

- Provides guidance under the following three categories:
  - Characteristics of Persons for Whom Therapy is Widely Accepted
  - Characteristics of Persons for Whom Therapy Should be Individualized
  - Characteristics of Person for Whom Therapy is Currently Contraindicated
Treatment

- Psychiatric Illness
  - Individuals with major, uncontrolled depressive illness
    - AASDL: Listed as a characteristic of persons for whom therapy is currently contraindicated.
  - History of depression but condition is well controlled.
    - AASDL: Listed as a characteristic of persons for whom treatment is widely accepted.
Treatment

Active Substance Abuse
- **AASDL**: Listed as characteristic of persons for whom therapy should be individualized
  - Current users of illicit drugs or alcohol but willing to participate in substance abuse program or alcohol support group

- **2002 NIH**:
  - Treatment of active injection drug users should be considered on a case-by-case basis.
  - Continued alcohol use during therapy adversely affects treatment response, and abstinence is strongly recommended before and during HCV treatment.
Treatment

Treatment Goal

- To prevent complications of infection; principally achieved by eradication of the virus.

- HCV is considered to be eradicated when there is a Sustained Viral Response (SVR).

- An SRV is defined as the absence of detectable HCV RNA (virus) six months after treatment ends.

- A qualitative viral detection test is used for this purpose.
Treatment

- **Standard of Care**
  - Treatment with Peginterferon and Ribavirin
  - Peginterferon is administered once a week by subcutaneous injection.
  - Ribavirin is administered orally twice a day.
Treatment

- **Genotype 1**
  - 48-week course of treatment
  - Higher rates of SVR achievement are seen with longer therapy.
  - Test for HCV RNA level at initiation or shortly before starting treatment
  - Start therapy with peginterferon and ribavirin
  - At 12 weeks retest for HCV RNA level.
  - If HCV RNA is negative or there has been greater than a two log drop, it is considered an Early Viral Response (EVR)
  - EVR is highly predictive of achievement of SVR.
Treatment

- **Genotype 1**
  - IF EVR is achieved, continue treatment for 48 weeks.
  - Throughout treatment, monitor symptoms, blood counts, and ALT.
  - Test for HCV RNA at end of treatment.
  - An End-of-Treatment Response (ETR) is defined as a lack of detectable HCV RNA at the end of treatment.
  - If test at end of treatment is negative, test for HCV RNA 24 weeks after completion of therapy.
  - Sustained Viral Response (SVR) is a lack of detectable virus 6 months post treatment.
Treatment

- **Genotype 2 and 3**
  - Start 24-week therapy with peginteron and ribavirin
  - Throughout treatment, monitor symptoms, blood counts, and ALT.
  - Test for HCV RNA at end of treatment to determine if ETR was achieved.
  - IF ETR is achieved test for HCV RNA at 24 weeks to determine if SVR was achieved.
Treatment

Rates of Viral Clearance
- **Genotype 1**
  - SVR – 40 to 45 percent
- **Genotype 2/3**
  - SVR – 70 to 80 percent

Note:
- Key studies were done in naive patients.
- Key studies excluded those with co-morbid conditions and decompensated cirrhosis.
Treatment

- **Strongest Predictor of Response**
  - Genotype

- **Other Predictors of Response**
  - Higher SVR rates seen in patients:
    - With lower pre-treatment viral loads
    - Of younger ages
    - With lower body weights
    - With minimal liver damage
    - Who are women
  - Lower SVR rates seen in African Americans with genotype 1
Other Treatment Terminology

- *Non-Responder* – HCV RNA levels remain stable during treatment.

- *Partial Responder* – HCV RNA levels decline but never become undetectable.

- *Relapser* – HCV RNA levels undetectable during treatment but detected again after treatment ends.
Treatment Side Effects

Common Side Effects of Peginterferon
- Occurring in more than 10 percent of patients
  - Fatigue
  - Muscle aches
  - Headaches
  - Nausea and vomiting
  - Skin irritation on injection site
  - Low-grade fever
  - Weight loss
  - Depression
  - Mild bone marrow suppression
  - Hair loss
Common Side Effects of Ribavirin
- Occurring in more than 20 percent of patients
  - Anemia
  - Fatigue and irritability
  - Itching
  - Rash
  - Nasal stuffiness, sinusitis, and cough

Ribavirin can cause birth defects
Must use strict contraceptive methods during treatment and for six months after. (AASDL)
Treatment Side Effects

- Uncommon Side Effects of Treatment
  - Less than 2 percent of patients
    - Autoimmune disease (especially thyroid disease)
    - Severe bacterial infections
    - Marked thrombocytopenia (decreased platelets)
    - Marked neutropenia (decreased white blood cells)
    - Seizures
    - Depression and suicidal idea or attempts
    - Retinopathy (microhemorrhages)
    - Hearing loss and tinnitus
Treatment Side Effects

- **Rare Side Effects**
  - Acute congestive heart failure
  - Renal failure
  - Vision loss
  - Pulmonary fibrosis
  - Sepsis

Careful monitoring of all patients is needed for early identification and management of side effects.

In some cases, treatment may need to be discontinued.
Treatment

General Management Issues (AASLD)
- Advise HCV infected people of measures that might reduce or prevent further fibrosis
  - Alcohol use
  - Obesity
  - Hepatitis A vaccination
  - Hepatitis B vaccination
HIV/HCV Co-Infection

- 25 percent with HIV have HCV
- 10 percent with HCV may have HIV

Testing (AASDL)
- All HIV infected person should be tested for HCV
- All HCV infected person with HIV risk factors should be tested for HIV
HIV/HCV Co-Infection

- **Treatment**
  - Urgency of treatment may be greater.
  - Likelihood of achieving SRV is lower.
  - There are no FDA approved drugs for the treatment of co-infection. (2004)
  - Most existing studies have treated co-infected people for 48 weeks regardless of genotype.
  - There may be additional safety concerns due to side effects and medication interactions.