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

- 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.

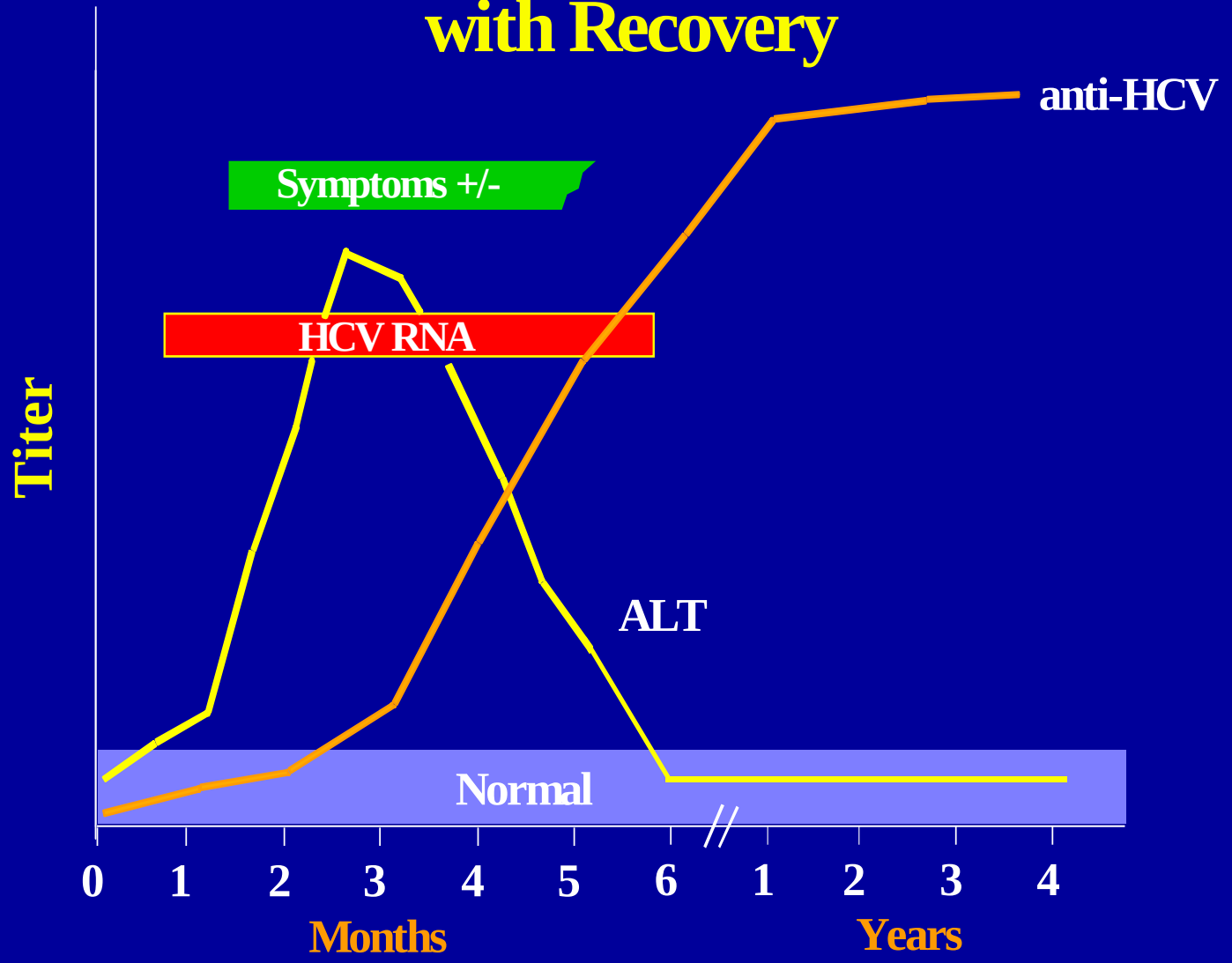
Natural History

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



CDC

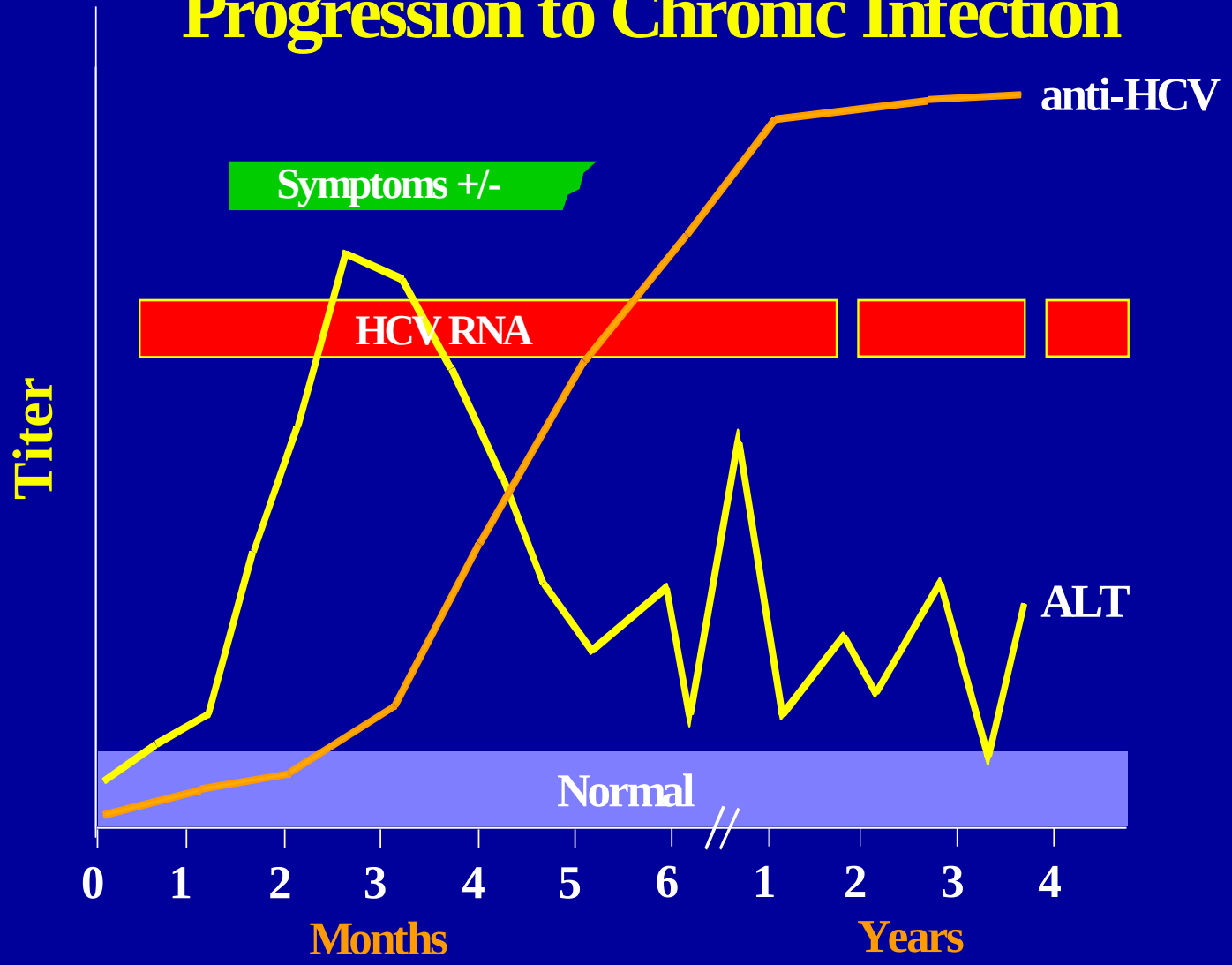
Natural History

- 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



CDC

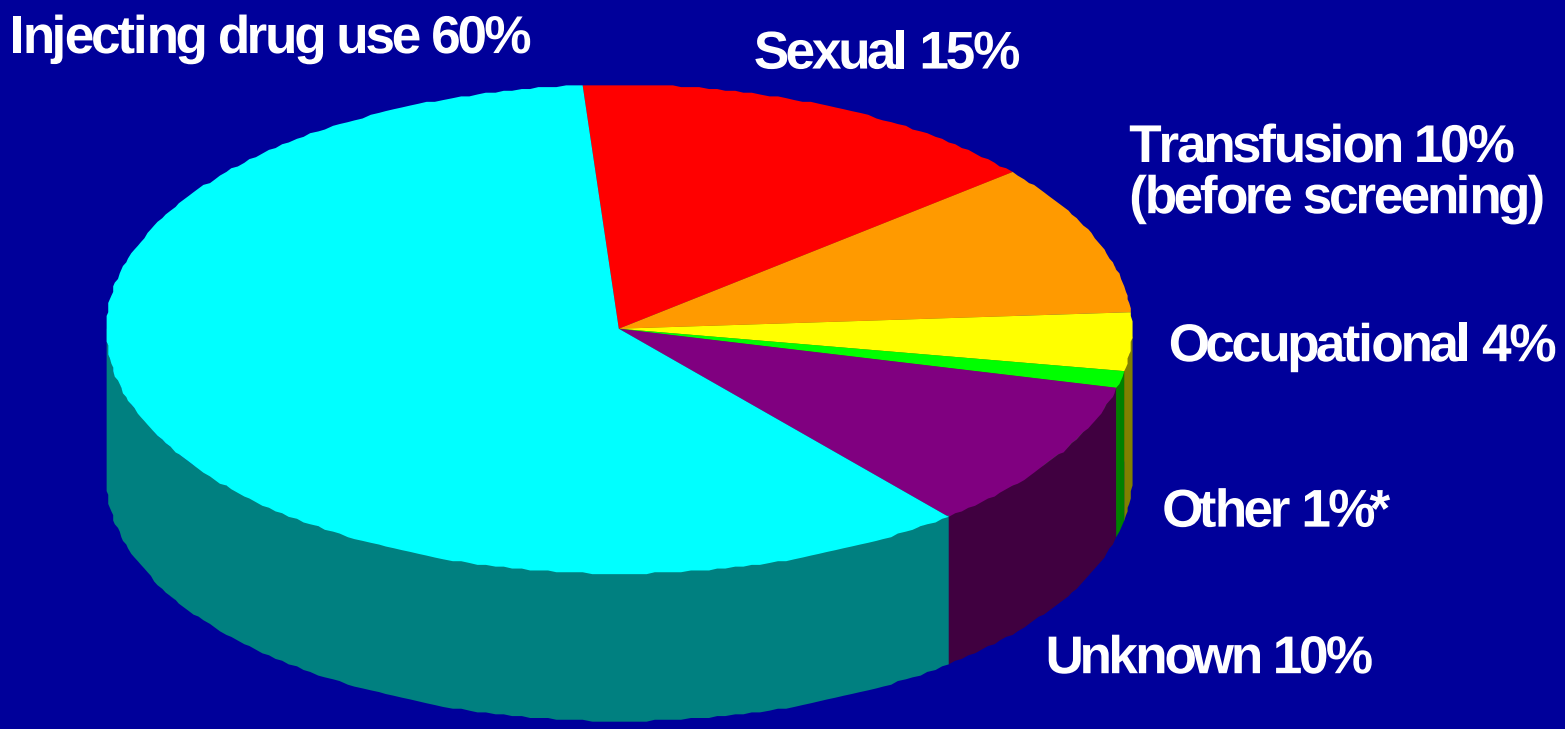
Natural History

- 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



* Nosocomial; iatrogenic; perinatal

Source: Centers for Disease Control and Prevention

Transmission

- 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

Transmission

Prevalence of HCV and HIV in IDUs

Location	Year	HCV	HIV
Amsterdam	1991	66%	33%
Geneva	1992	80%	32%
Baltimore	1994	90%	25%
Seattle	1999	82%	2%
Rural UK	2000	56%	14%
S. China	2003	71%	17%
Vancouver	2004	44%	19%

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

Transmission

- 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.

Transmission

- 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

- **<u>Injecting Drug Users</u>:**
  - 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 aminotransferace 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.

HCV Testing

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

- 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.

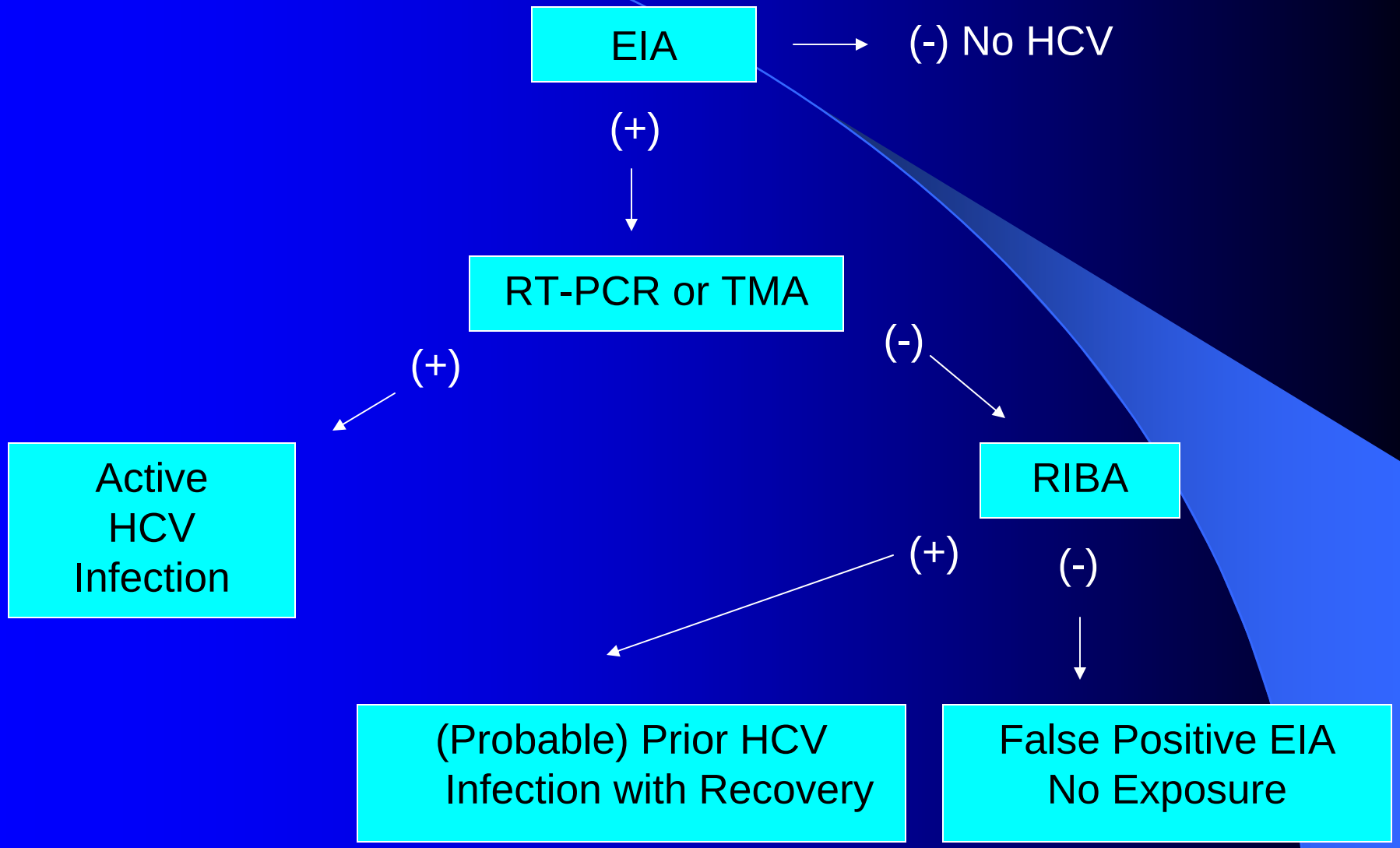
HCV Testing

- 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

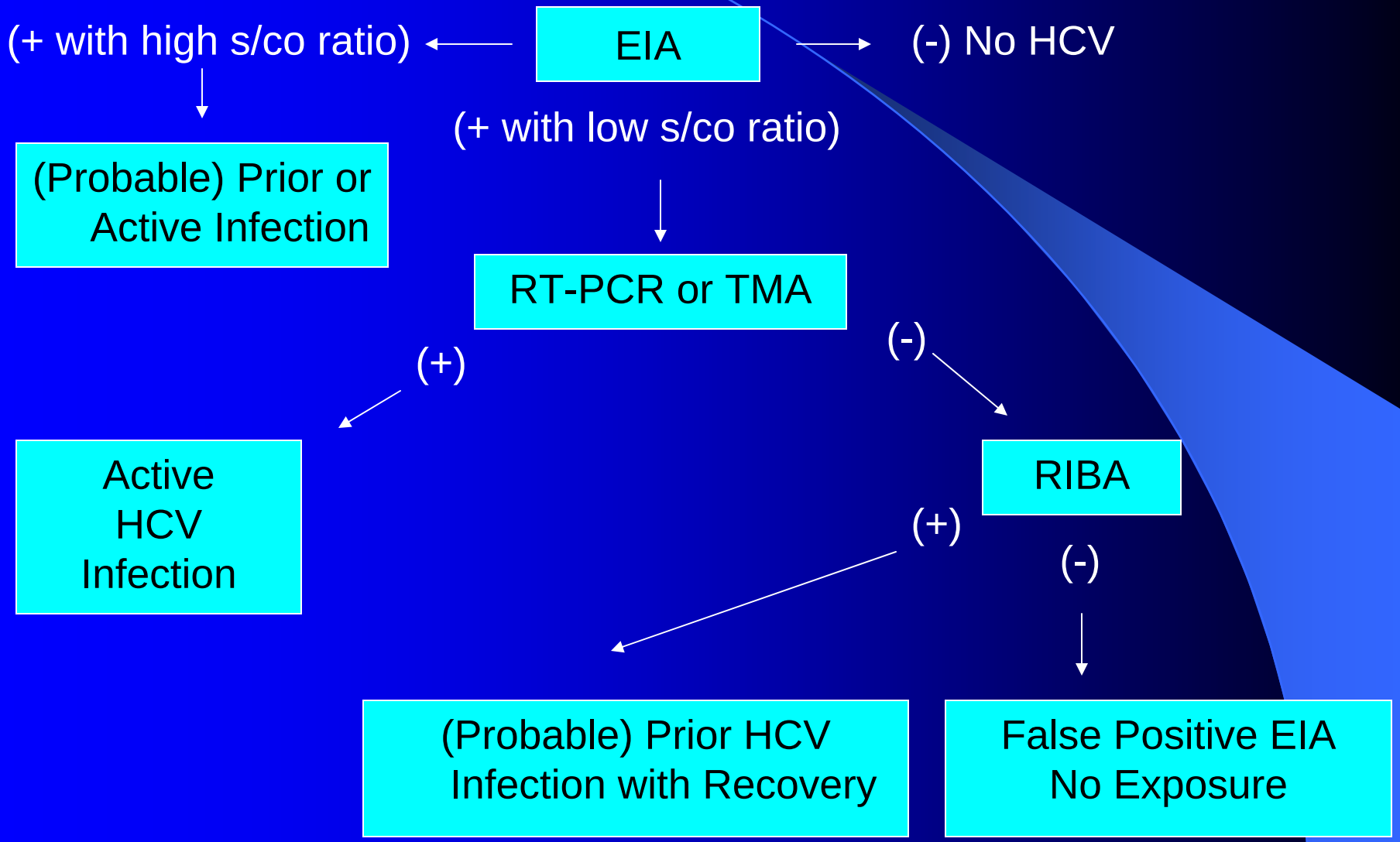


AMA Update on the Screening and Management of Hepatitis C. Adapted From CDC Guidelines for Laboratory Testing and Result Reporting of Hepatitis C. (MMWR. 2003; 52:1-13)

S/Co Ratios

- 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



Testing

If a person is chronically infected

what other tests

will they do?

Genotyping

- 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

Treatment

Who should be treated?

Treatment

- 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.

Treatment

- 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 pegintron 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

Treatment

- 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

Treatment Side Effects

- Common Side Effects of Ribavirin
  - Occurring in more than 20 percent of patients
    - Anemia
    - Fatigue and irritability
    - Itching
    - Rash
    - Nasal stuffiness, sinusitis, and cough
    - Ribiviran 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

- 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.