

Hepatitis C: An Overview

EIP Meeting
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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.

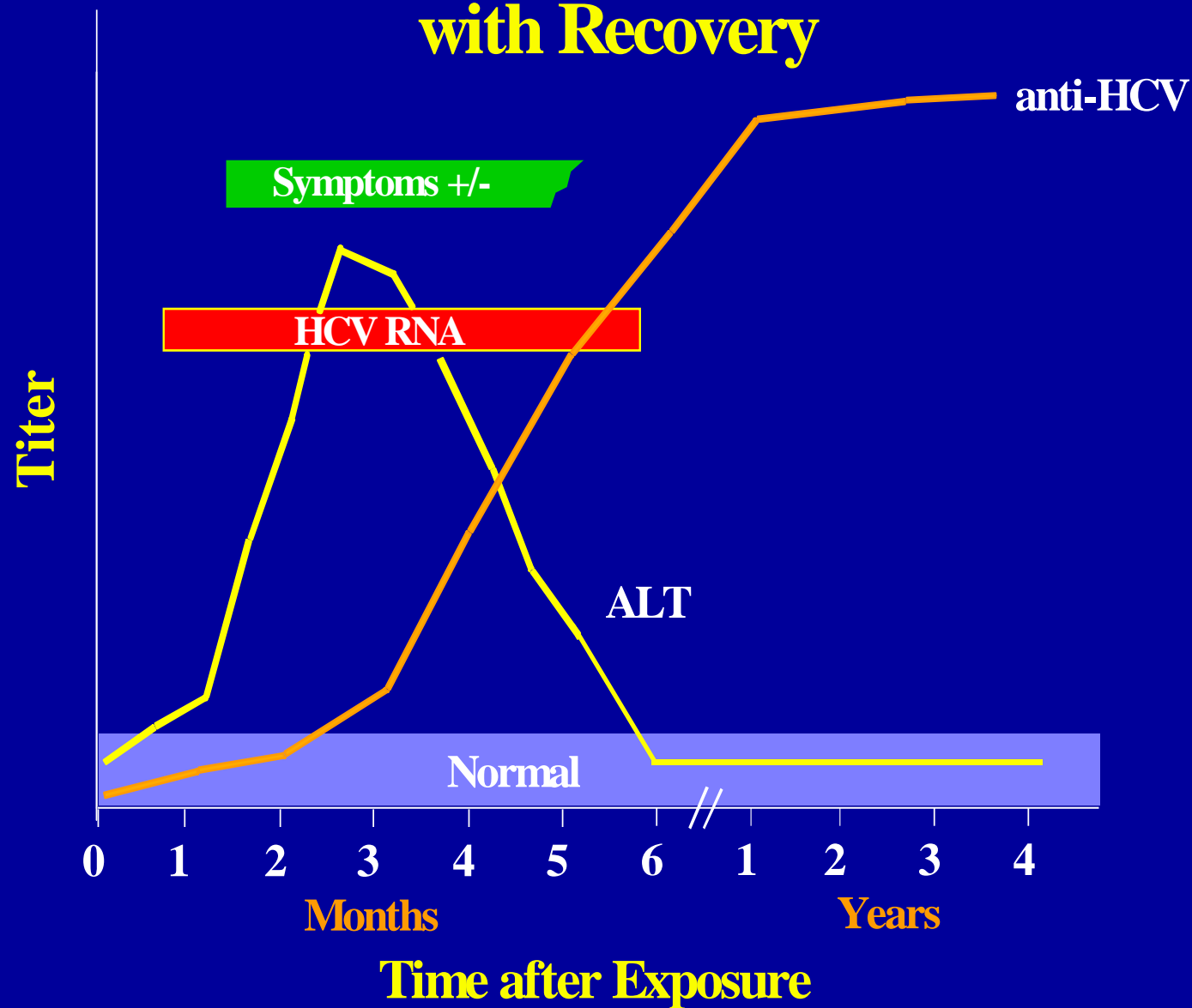
Natural History

**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



Natural History

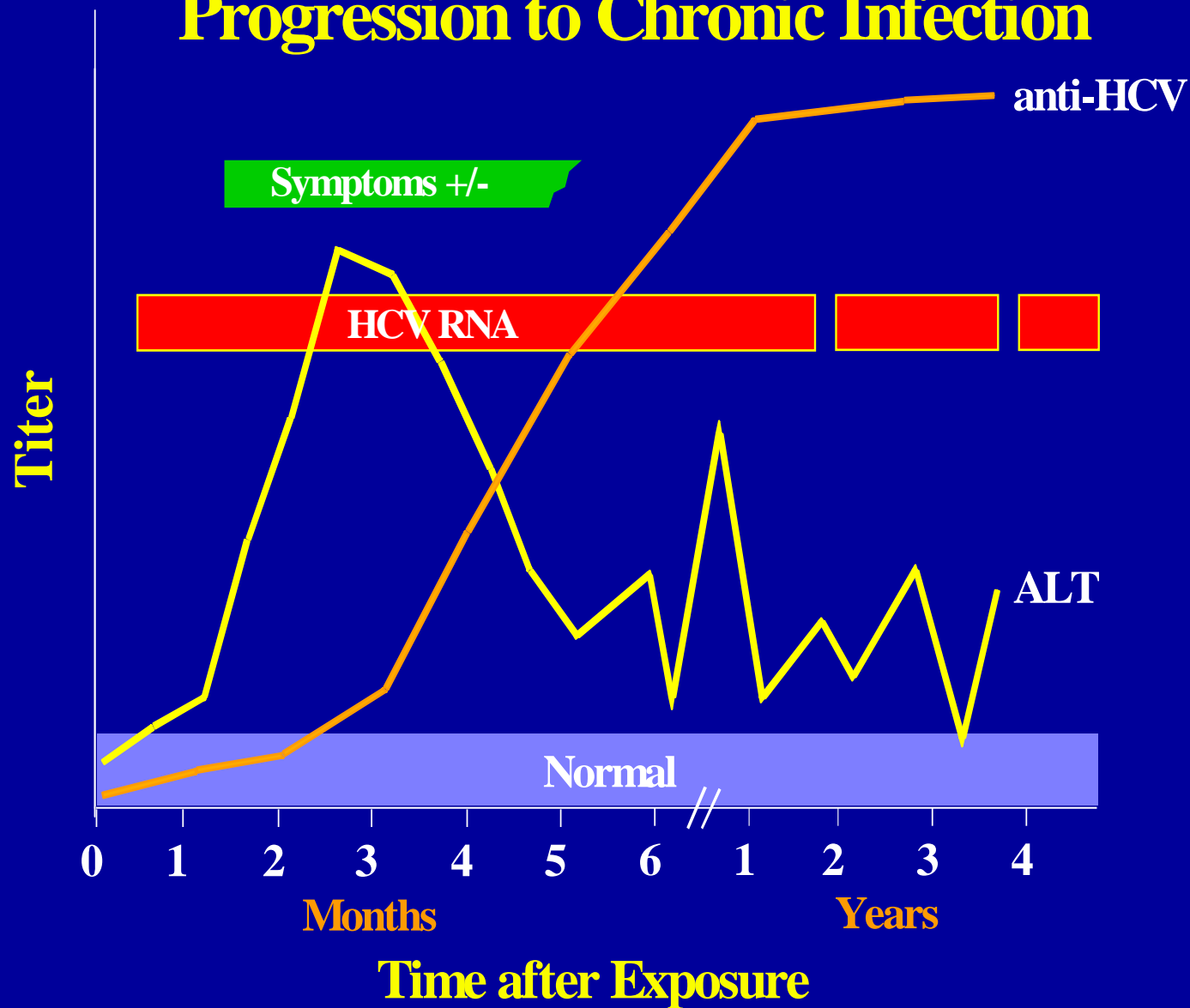
- Chronic Infection
 - 75 to 85 percent of infected people develop chronic infection.
 - Diagnosed by the detection of HCV RNA in the blood for at least six months.
 - 60 to 70 percent of people will have persistent or fluctuating ALT elevations.
 - Chronic liver disease usually progresses at a slow 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



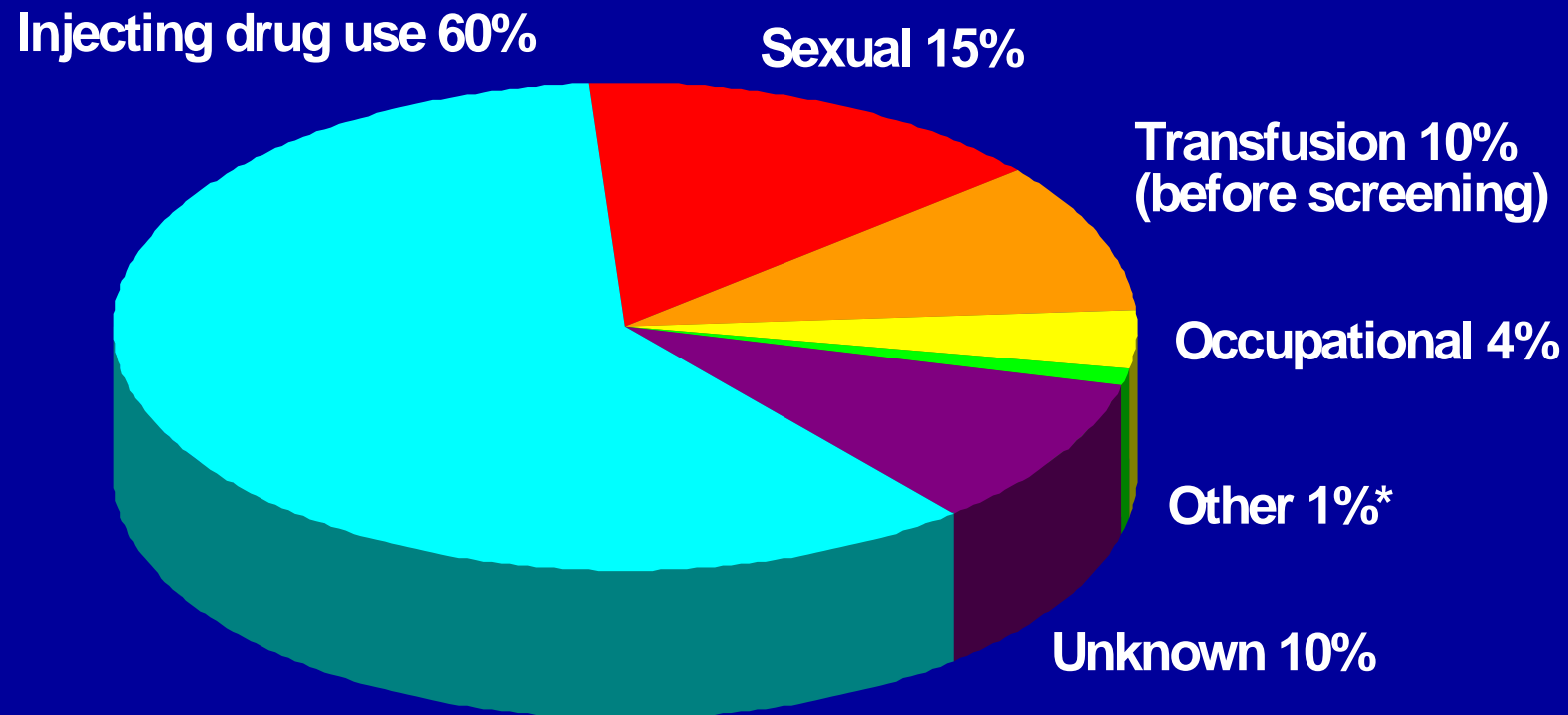
Natural History

- 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%

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

- **Injecting Drug Users:**

- Stop using and injecting drugs.
- Enter and complete substance abuse treatment.
- If continuing to inject drugs:
 - ⑩ Never reuse or "share" syringes, needles, water, or drug preparation equipment.
 - ⑩ If injection equipment has been used by other persons, first clean the equipment with bleach and water.
 - ⑩ Use only syringes obtained from a reliable source (e.g., pharmacies).

Prevention

⑩ Injection Drug Use

- ⑩ 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).
- ⑩ Use a new or disinfected container ("cooker") and a new filter ("cotton") to prepare drugs.
- ⑩ Clean the injection site prior to injection with a new alcohol swab.
- ⑩ Safely dispose of syringes after one use.
- ⑩ 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 immunosuppressed 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.

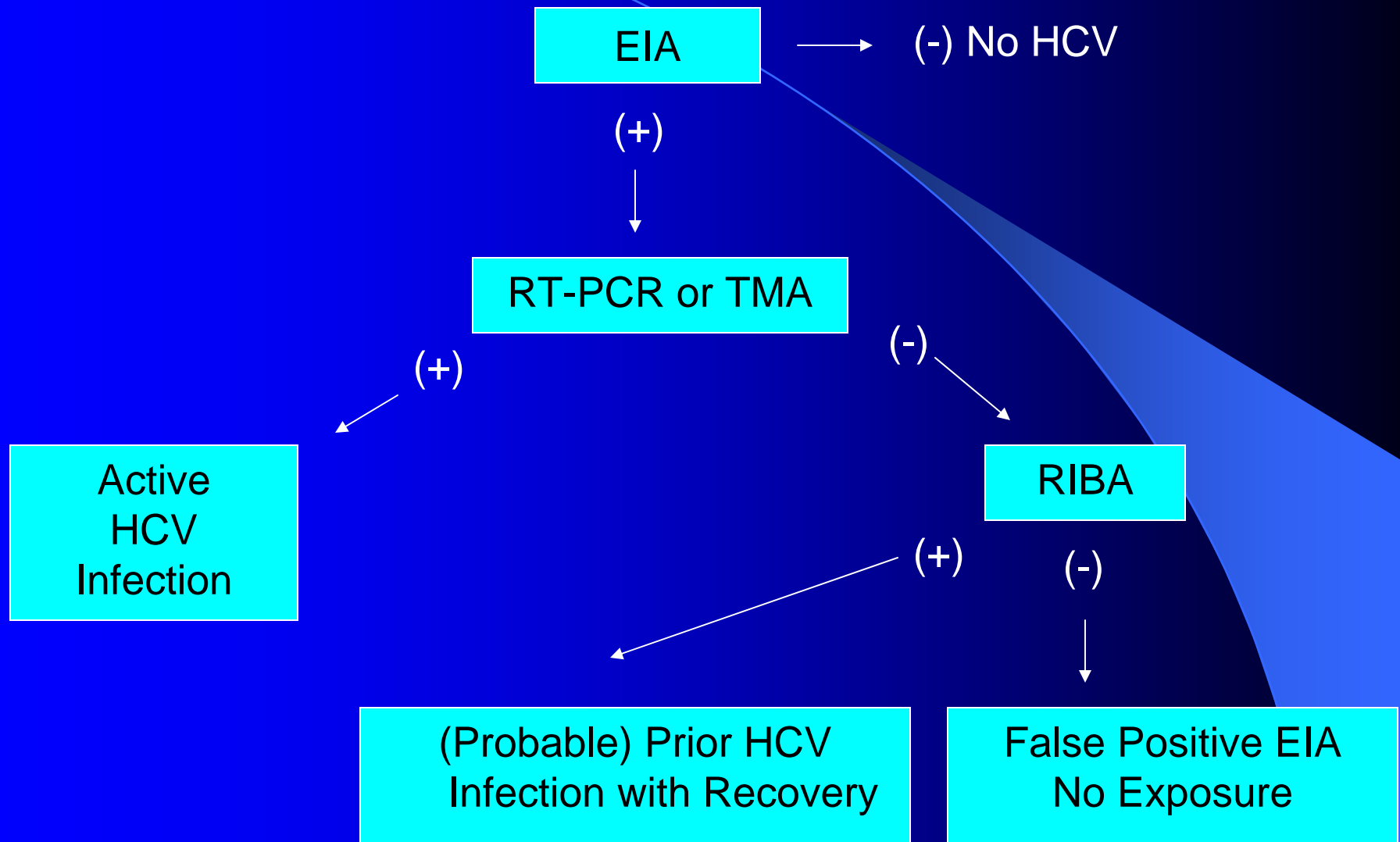
HCV Testing

- 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



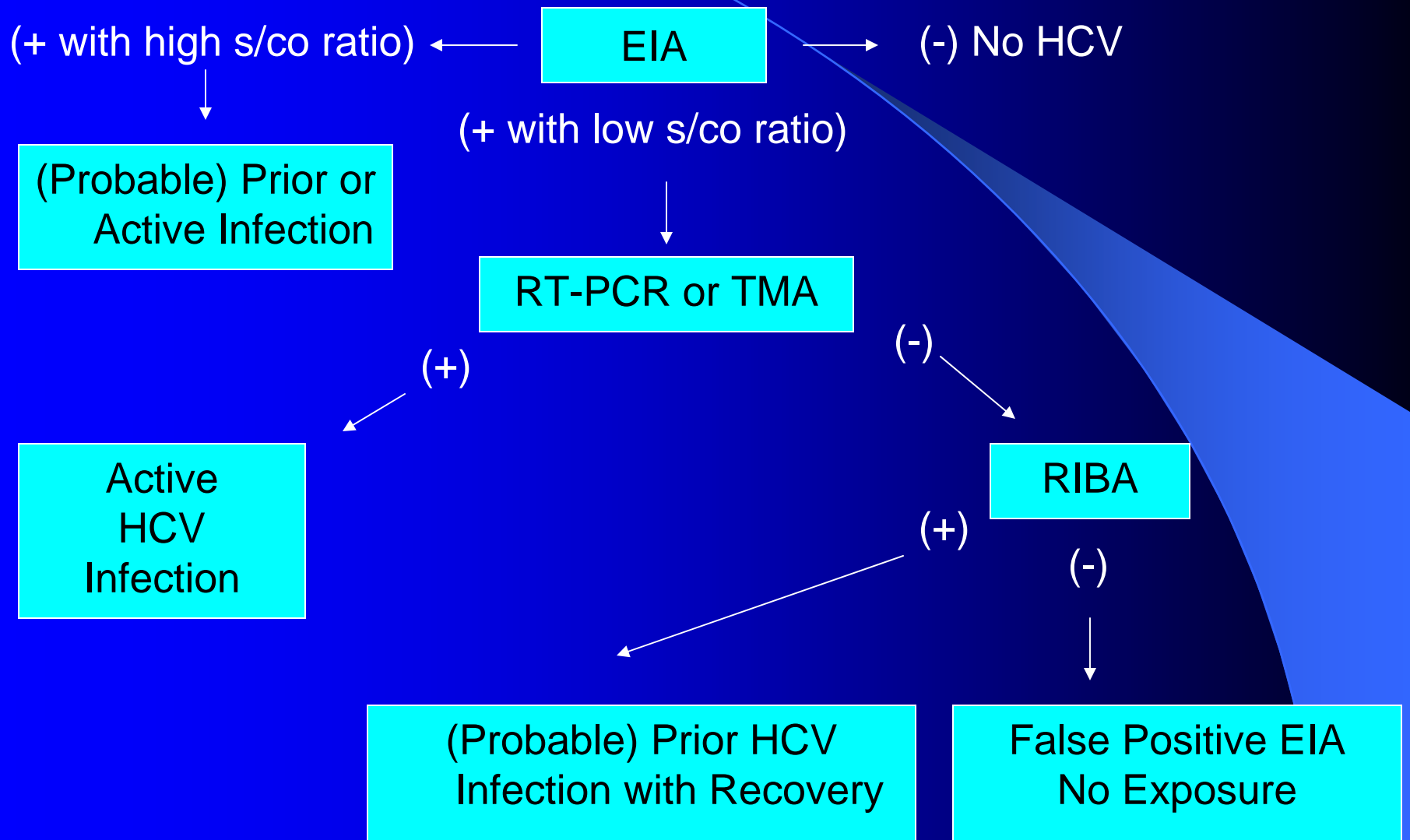
AMA Update on the Screening and Management of Hepatitis C. Adapted From CDC Guidelines for Laboratory Testing and Result Reporting of Hepatitis C. (MMWR. 2003; 52:1-13)

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 indicated 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 SVR 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

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.