

Hepatitis C

1. DISEASE REPORTING

A. Purposes of Reporting and Surveillance

1. To identify common-source outbreaks, e.g., from contaminated immunoglobulin products
2. To provide counseling as necessary to cases and household contacts of cases.
3. To identify sources of infection.

B. Laboratory and Physician Reporting Requirements

1. Acute Cases

All diagnoses of *acute* hepatitis C are reportable by physicians to the LHD within one working day of diagnosis.

2. Chronic cases

All positive laboratory tests for HCV (including enzyme immunoassay [EIA], recombinant immunoblot assay [RIBA], and polymerase chain reaction [PCR]) must be reported by licensed laboratories to the LHD within one working day.

C. Local Health Department Reporting and Follow-Up Responsibilities

1. Acute cases

Report all acute confirmed and presumptive (see definitions below) cases to OPHD by the end of the calendar week of initial report. Begin follow-up investigation within one week. Use the hepatitis C case investigation form. Send a copy of the completed form to OPHD within seven days of initial report.

2. Chronic cases

Report all chronic cases to OPHD within 7 days of initial report. Because there is currently no test (like an IgM) that is specific for recent infection, it is impossible to distinguish between recently and distantly acquired infections based on laboratory results, and our case definition for acute infections relies on clinical criteria. Since physicians are required to report acute cases of HCV to the LHD, LHDs should investigate all reports from clinicians to ascertain whether the patient meets the case definition for acute illness.

If the LHD receives a positive report for HCV from a laboratory only, the LHD is not required to conduct any further investigation but should simply transmit all of the patient information on the laboratory report (typically name, address, telephone number, age, sex, location of test, ordering physician) to OPHD.

2. THE DISEASE AND ITS EPIDEMIOLOGY

A. Etiologic Agent

The etiologic agent of hepatitis C is a flavivirus (same family as the yellow fever virus) — unrelated to the viruses that cause hepatitis A or B. Specific tests for HCV first became available in 1990, although the existence of the virus was inferred for many years. The overall prevalence of antibody to HCV in the U.S. population is estimated to be 1.6%, corresponding to an estimated 4.1 million Americans. Of these, 80% (estimated 3.2 million Americans) are chronic carriers. Peak prevalence (4.3%) is observed among individuals aged 40–49 years. There are 6 HCV genotypes; genotype 1 accounts for 70% to 75% of all HCV infections in the United States and is associated with a lower rate of response to treatment. As much as 20–40% of acute viral hepatitis in the U.S. may be due to hepatitis C (although it is a much smaller proportion of reported cases).

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B. Description of Illness

Hepatitis C cannot be clinically distinguished from other viral hepatitises with any reliability. Onset of symptoms is usually insidious, with fever, malaise, anorexia, nausea, and abdominal discomfort, followed by jaundice (for most patients). Urine may become unusually dark, and stools quite pale. Infections vary from completely asymptomatic (~80% of infections) to a disabling illness lasting several months. Fulminant hepatitis is rare, but can be fatal. Liver enzyme levels are elevated (between 5 and 20x upper limit of normal in a large number of cases; usually >7x the upper limit of normal).

Between 75% and 85% of infected individuals develop chronic infection, and 50%–60% of these develop chronic liver disease, as evidenced by persistently elevated liver enzyme levels, regardless of whether they became ill at the time of infection.

Long-term carriage is associated with the same long-term sequelae linked to hepatitis B carriage — chronic active hepatitis, cirrhosis, and hepatocellular carcinoma, and the risk of these sequelae increases for patients chronically infected with both HBV and HCV. Patients with signs of chronic liver disease due to HCV are also at an increased risk of fulminant hepatic failure should they acquire Hepatitis A.

Antibodies develop after infection, but are not protective.

C. Reservoir

Human beings.

D. Modes of Transmission

HCV is transmitted through contact with contaminated blood such as via needle sharing, drug paraphernalia sharing, and blood transfusion. Although HCV is transmitted by needle-stick injury, the prevalence of HCV antibodies among health care workers is only 1.4%, lower than the overall prevalence in the U.S. population. Household contact with infected blood (e.g. via toothbrush and razor sharing) can result in infection, but the efficiency of transmission by such sources is unclear. Sexual transmission can occur, but the efficiency of transmission is much lower than with most sexually-transmitted diseases (STDs). For a person with chronic HCV infection, the estimated risk of sexual transmission to an uninfected partner is 0% to 0.6% per year for those in monogamous relationships, and 0.4% to 1.8% per year for persons with multiple sexual partners or those at risk for sexually transmitted diseases. The presence of other STDs or sexual practices that traumatize the mucosa (i.e., receptive anal sex) increase risk.

Mother-to-infant transmission at birth occurs in <5% of births, unless the mother is simultaneously HIV-infected, in which case the probability of vertical transmission increases 4–5 fold.

E. Period of Communicability

The period of communicability following initial infection has not been determined, but is likely lifelong. It is not clear if communicability waxes and wanes, and if so, under what circumstances. HCV viremia is probably low relative to hepatitis B and high relative to HIV.

F. Incubation Period

HCV RNA appears in the blood within 1-2 weeks of infection in a majority of patients. For the ~30% of patients who develop symptoms of acute HCV infection, the onset is 3-12 weeks after infection, with an average of 7 weeks. HCV antibodies generally develop during the same time period, typically 7-8 weeks after infection. Antibody development may be delayed in immunosuppressed patients — up to 24 weeks (or not at all, making PCR the only way to diagnose some of these patients).

G. Treatment

Combination therapy with pegylated interferon (compared to regular interferon, “pegylated” interferon has a longer half-life, so the patient has therapeutic levels in the bloodstream for a longer time after a dose) and ribavirin results in a sustained viral response (absence of HCV RNA 6 months or more after treatment) in approximately 50% of patients. This varies by genotype, with lower response rates (40–45%) in genotype 1, and higher response rates (80%) in genotypes 2 and 3 (most

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infections in the U.S. are genotype 1, unfortunately). Studies of interferon alone in patients with acute infection have shown a sustained viral response in 30–40%, but the number of patients treated with this regimen is small, and treatment for acute illness is still controversial.

Only acute cases of hepatitis C require a full investigation and completion of the hepatitis C case report form. There is no test to determine acute infection. However, a positive HCV test result in a person ≤ 30 years of age may be more likely to represent an acute infection. In this case, OPHD recommends further follow-up. OPHD will request liver function tests (LFTs) on any anti-HCV positive individual ≤ 30 years of age from the reporting laboratory. If the ALT levels are >400 IU/L, OPHD will request the LHD to contact the provider and determine the reason for testing in order to rule out acute infection. If the client experienced any signs and symptoms of acute viral hepatitis, the LHD should conduct the usual investigation for an acute case of HCV.

Although not required, further investigation of cases for whom a positive laboratory report has been received is encouraged if time and resources permit. When possible, such cases should be contacted and referred for confirmatory testing by their primary care physician and counselled about modes of transmission, means of reducing spread to others, alcohol cessation, and the need for hepatitis A and B vaccination. Additional educational information is available at our web site:

<http://oregon.gov/DHS/ph/acd/diseases/hepc/hepc.shtml> or the CDC web site:
<http://www.cdc.gov/ncidod/diseases/hepatitis/index.htm>.

3. CASE DEFINITIONS, DIAGNOSIS, AND LABORATORY SERVICES

A. Confirmed Acute Case Definition

An individual with:

- 1) discrete onset of symptoms (i.e., nausea, vomiting, right upper quadrant pain, pale stools, dark urine); *and*
- 2) jaundice or ALT levels >400 IU/L; *and*
- 3) IgM antibody to hepatitis A virus (IgM anti-HAV) negative and IgM antibody to hepatitis B core antigen (IgM anti-HBc) negative; *and*
- 4) One of the following lab criteria:
 - a. Anti-HCV positive by EIA with a signal to cut-off ratio predictive of a true positive as determined for the particular assay as defined by CDC. (See Table); *or*
 - b. RIBA positive; *or*
 - c. PCR (qualitative or quantitative) positive.

B. Presumptive Acute Case Definition

An individual with:

- 1) discrete onset of symptoms; *and*
- 2) jaundice or ALT levels >400 IU/L; *and*
- 3) IgM antibody to hepatitis A virus (IgM anti-HAV) negative and IgM antibody to hepatitis B core antigen (IgM anti-HBc) negative; *and*
- 4) the only laboratory test performed is an EIA and the signal to cut-off ratio is unknown.

C. Confirmed Chronic Case Definition

An individual with one of the following:

- 1) Anti-HCV positive by EIA with a signal to cut-off ratio predictive of a true positive as determined for the particular assay as defined by CDC. (See Table); *or*
- 2) RIBA positive; *or*
- 3) PCR (qualitative or quantitative) positive; *or*
- 4) genotype result.

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Lastly, if someone is reported as an acute HCV case and subsequently has a positive PCR or genotype result >6 months later, they should be reported again as a confirmed chronic hepatitis C case.

D. Presumptive Chronic Case Definition

An individual who is anti-HCV positive (repeat reactive) by EIA but the EIA has not been verified by a more specific assay and the signal to cut-off ratio is unknown. If the signal to cut-off ratio is low (and no other testing has been done) the individual is not considered to have HCV.

Table 1. Signal-cutoff ratios of HCV screening test kits used by Oregon laboratories, 2008.

EIA/CIA test kit name	Signal-to-cut-of ratio predictive of a true positive $\geq 95\%$ of the time	Labs performing anti-HCV EIA tests
Ortho HCV Version 3.0 ELISA Test System	3.8	<ul style="list-style-type: none"> ● Legacy Laboratory Services ● Interpath Laboratory, Inc ● Kaiser Regional Laboratory ● American Red Cross National Testing Lab ● Oregon State Public Health Laboratory ● Salem Hospital
Ortho Vitros Anti-HCV Assay	8.0	<ul style="list-style-type: none"> ● Quest Diagnostics ● St. Charles Medical Center
Abbott Axsym Antibody to HCV	10.0	<ul style="list-style-type: none"> ● Samaritan Lebanon Community Hospital ● Dynacare
Bayer Advia Centaur HCV Assay	>11	<ul style="list-style-type: none"> ● Providence Laboratory Services ● Providence Medford Medical Center ● McKenzie-Willamette Medical Center ● Oregon Medical Laboratory ● LabCorp ● Rogue Valley Medical Center

E. Confirm that the Case Requires Investigation

Positive reports received from laboratories only do not require further investigation, although the patient information on the laboratory slip should be transmitted to OPHD. Reports from clinicians' offices or emergency departments do require some follow-up to determine if the case is acute or chronic. Only unambiguously *new* HCV infections reported by a clinician or emergency department require a full investigation in Oregon. Typically, contacting the clinician or reviewing the emergency department note will allow you to answer the following questions. If the answer to all of the following three questions is yes, you need to interview the patient and complete a case investigation form.

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1. Does the patient have acute hepatitis?

If so, they should have an actual or approximate onset date for symptoms of hepatitis (e.g., jaundice, nausea, vomiting, right upper quadrant pain or diarrhea). ALT levels should be over 400 IU/L. If liver enzymes were not checked or not found to be high, refer case for confirmatory testing with their primary care provider if possible.

2. Can other causes of acute hepatitis be ruled out?

Because of overlapping symptom manifestation for hepatitis A, B, and C (and alcohol-related hepatitis), it is important to rule out hepatitis A and hepatitis B.

3. Is it reasonable to conclude that HCV is the cause of the acute hepatitis?

This means evidence of HCV infection, either through an elevated signal-cutoff ratio on the EIA, a positive RIBA, or the presence of viral RNA. Note that false-positive EIA tests are common (up to 50% in low-risk populations). Antibody-negative patients can be retested in 6-9 months if there is concern about delayed seroconversion.

F. Services Available at the Oregon State Public Health Laboratory (OSPHL)

OSPHL uses a screening EIA test to assay sera for HCV antibodies (and can report the signal:cutoff ratio). Sera are screened on request or when possibly infected samples test negative for HAV and HBV markers. For the EIA, an elevated signal:cutoff ratio of 3.8 or higher has a positive predictive value of 95%, making a past or present infection with HCV highly likely. Asymptomatic patients with absolutely no risk factors may require further confirmatory testing (such as RIBA or PCR).

4. ROUTINE CASE INVESTIGATION

A. Identify the Source of Infection

For cases with recent infection (the only ones you should report to OPHD), ask about the 3 months prior to onset (although rarely, the incubation may be shorter or longer). Risk factors include:

- Parenteral drug use;
- Occupational or other needlestick injuries;
- Blood transfusion or receipt of immunoglobulins or other blood products;
- Other parenteral exposures within the 3 months prior to onset of current illness, including tattooing, ear piercing, acupuncture, organ or tissue transplant, dialysis, dental or surgical care; **or**
- High-risk sexual contact (multiple partners, history of other STDs, anal sex, etc.).

B. Identify Potentially Exposed Persons

1. Determine if case has donated blood or plasma in the 3 months prior to onset or any time thereafter. If so, notify the relevant blood bank or plasma center with particulars (date, etc.).
2. Identify persons who shared needles with the case or might have otherwise had contact with blood. Inform these contacts about the signs and symptoms of hepatitis C and the need for testing regardless of symptoms (since the majority of those acutely infected are asymptomatic).
3. Sexual and household contacts should be queried about recent signs and symptoms of hepatitis; those with such a history should be referred for medical follow-up. Since the risk of transmission in these settings is low, testing is not automatically performed.

C. Environmental Evaluation

None.

5. CONTROLLING FURTHER SPREAD

A. Education

Cases should be counseled about the natural history of disease, modes of transmission and means of preventing further spread (e.g., if still injecting, they should not share needles or works; keep wounds and skin lesions covered; do not share razors or toothbrushes with anyone). HCV-positive persons with one long-term steady sex partner do not need to change their sexual practices, although they

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should discuss the risk of transmission with their partner. HCV-positive persons engaged in high-risk sexual activities should be counseled to use latex condoms correctly every time they have sex. Active injection drug users should be encouraged to stop injecting and referred to methadone maintenance programs or other drug rehabilitation services. Since the risk of progression to cirrhosis is increased among heavy drinkers, cases should be advised to abstain from alcohol (or at least significantly reduce their intake). They should also be cautioned to ask their provider about use of over-the-counter drugs (e.g., acetaminophen) that could be hepatotoxic and advised of the need for hepatitis A and B vaccine (if negative for hepatitis A and B). If possible, they should be referred to a primary care provider for further follow-up.

B. Isolation and Work or Day Care Restrictions

Blood should be assumed to be infectious; standard precautions suffice for hospitalized patients. No occupational, school, or day-care restrictions are necessary for HCV-infected individuals.

C. Follow up of Cases

None required. The majority (75%–85%) of HCV-infected individuals become chronic carriers, and they should understand their elevated risk of long-term sequelae (chronic or recurrent hepatitis, cirrhosis, hepatocellular carcinoma).

D. Protection of Contacts

1. Active Immunization

None.

2. Passive Immunization

None. Immune globulin (IG, HBIG, etc.) is *not* effective against HCV.

E. Environmental Measures

Ensure that surfaces and objects contaminated with blood are properly disinfected using gloves and appropriate disinfectant solutions.

6. MANAGING SPECIAL SITUATIONS

A. Needlesticks and Similar Exposures

The risk of HCV transmission to a health care worker or similar stick-ee is real (approximately 2%), and unfortunately there isn't much you can do about it after the fact. Current CDC guidelines recommend an HCV antibody test and ALT level at baseline and at 6 months to fully capture the full seroconversion time-window. Infection can be usually be detected within 2 weeks by PCR. Risk for HIV and hepatitis B virus should also be assessed using current CDC guidelines.

B. Other Situations

On-the-job, scene of an accident, or in-home blood-to-blood transfers place persons at risk. In the case of any other unusual possible infection occurrences, consult with ACDP epidemiologists. ■

7. GLOSSARY OF TERMS

ALT/AST: these are both liver enzymes classified as serum aminotransferases or transaminases and are useful indicators of liver damage. Alanine aminotransferase is usually abbreviated as ALT (or SGOT) and is particularly sensitive for assessing liver damage secondary to HCV. Aspartate aminotransferase is referred to as AST (or SGPT). In acute hepatitis A or B, an elevation in either one is required to meet the case definition, while the hepatitis C case definition requires an elevation in the ALT to over 400 IU/L.

Anti-HCV EIA: enzyme immunoassay to measure HCV antibody. Indicates presence of antibody only and cannot be used to distinguish between recent and past infection. Additional testing is required to determine if the individual is chronically infected.

HBsAg: hepatitis B surface antigen, a marker of replicating virus. It occurs as part of acute infection and persists in chronic infection. Its presence indicates that the patient is considered to be infectious.

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HBeAg: hepatitis B e antigen, a core protein exported from infected liver cells and a marker of high levels of infectivity. Similar to HBsAg, it occurs (albeit transiently) as part of acute infection and may persist in the chronic carrier state.

HBe Ab: hepatitis B e antibody is produced by the immune system temporarily during acute HBV infection and may persist in chronic infections. Spontaneous conversion from e antigen to e antibody (a change known as seroconversion) is a predictor of long-term clearance of HBV in patients undergoing antiviral therapy and indicates lower levels of HBV. Chronic hepatitis B surface antigen carriers can be positive for either HBeAg or anti-HBe, but are less infectious when anti-HBe is present.

HBV DNA: signifies active replication of the virus and indicates that the patient is infectious. It is usually measured to test for chronic infection, and the viral load may be used to decide whether treatment is warranted.

HCV genotype: HCV can be divided into at least 6 different genotypes. Genotype 1 is the most common in the US, accounting for 70%-75% of infections.

IgM anti-HAV: IgM antibody to HAV. Indicates acute infection with HAV.

IgM Anti-HBc: IgM antibody to hepatitis B core antigen, indicative of recent infection with HBV. Antibody to core antigen only occurs following infection, not immunization.

RIBA: recombinant immunoblot assay, a more *specific* test for anti-HCV antibody (in other words, it's good for ruling out false positives). It is not as *sensitive* as the anti-HCV EIA and should not be used as an initial screening test, but it is useful for ruling out false-positive EIA tests.

PCR: polymerase chain reaction, used to measure HCV RNA and indicates active replication of the virus (e.g., the chronic carrier state). The qualitative PCR is more sensitive than the quantitative assay and is preferred for the initial test. The quantitative PCR is often used to guide initial treatment decisions and to follow the progress of individuals undergoing treatment.

Signal-cutoff ratio: can be used to help determine the likelihood that a positive anti-HCV EIA represents a true positive. Each assay has a cut-off value that is considered a "positive" result; the signal-cutoff ratio can be calculated by dividing the optical density (OD) value of the sample being tested (e.g., the client's test result) by that particular assay's cut-off value. As seen in the Table, each test kit or assay has a signal-cutoff ratio above which the client has a 95% probability of being HCV-positive. If a client's signal-cutoff ratio is equal or above the ratios listed in the Table, they can be counseled that they have antibodies to HCV. However, they would still need a PCR test to determine if they are chronically infected. For surveillance purposes, a patient reported with low signal-cutoff ratio (i.e., their Abbott HCV EIA 2.0 test result is above the threshold for a positive test, but the signal-cutoff ratio is below 3.8) would not be considered a case (and thus does not have to be reported).

1. Centers for Disease Control and Prevention. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. MMWR 2001;50(RR-11):15-32. Available on the web at <http://www.cdc.gov/mmwr/PDF/RR/RR5011.pdf>.

UPDATE LOG

May 2007: Updated case definition to reflect CSTE changes. Added Glossary of Terms for hepatitis seretologies.

October 2008: Updated Table 1 "Signal cut off ratio of HCV screen test kits used by Oregon laboratories."

November 2008: Added details on OPHD requesting LFTs for anti-HCV+ people <30. Updated case definition: acute cases with positive PCR/genotype results >6 months later should be reported as a chronic.