

Hepatitis C

1. DISEASE REPORTING

1.1 Purpose of Reporting and Surveillance

1. To identify common-source outbreaks, e.g., from contaminated reuse of multi-dose vials in the healthcare setting.
2. To provide counseling as necessary to cases and household contacts of cases.
3. To identify sources of infection.

1.2 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], and polymerase chain reaction [PCR]) must be reported by licensed laboratories to the LHD within one working day.

1.3 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

2.1 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 is observed among individuals born between 1945 and 1965. In 2012 CDC recommended that all Americans born in this period be tested once for HCV infection. CDC estimates that this age group comprises 75% of hepatitis C cases in the United States; among Oregon cases 67% belong to this age group. There are 6 HCV genotypes; geno-

Hepatitis C

type 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).

2.2 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.

2.3 Reservoir

Human beings.

2.4 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.

2.5 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.

2.6 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).

2.7 Treatment

Combination therapy with pegylated interferon and ribavirin has been the mainstay of therapy for hepatitis C. However, while 80% of persons with genotypes 2 or 3 achieve sustained viral response (SVR) following 24 weeks of therapy, only 40–45% of persons with genotype 1 achieve SVR following 48 weeks of treatment. Two new drugs, telaprevir and boceprevir, which are NS3 protease inhibitors, received FDA approval in 2011. When used in combination with standard-dose peginterferon alfa plus ribavirin therapy, either telaprevir or boceprevir may boost SVR rates in patients with HCV genotype 1 to as high as 75%.

Hepatitis C

However, resistance to both telaprevir and boceprevir develops in vivo within days, so that combination therapy with ribavirin and pegylated interferons are still necessary.

3. CASE DEFINITIONS, DIAGNOSIS, AND LABORATORY SERVICES

3.1 Confirmed Acute Case Definition

An individual with:

1. discrete onset of symptoms* (e.g., 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 (if done) and IgM antibody to hepatitis B core antigen (IgM anti-HBc) negative (if done); *and*
4. one of the following lab criteria
 - 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 p. 6); *or*
 - PCR (qualitative, quantitative, or genotype) positive for HCV RNA.

*A documented negative HCV antibody test result within 6 months prior to a positive test (either anti-HCV with s/co ratio, or HCV RNA PCR) result does not require an acute clinical presentation to meet the case definition.

3.2 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 (if done) and IgM antibody to hepatitis B core antigen (IgM anti-HBc) negative (if done); *and*
4. the only laboratory test performed is an EIA and the signal to cut-off ratio is unknown.

3.3 Confirmed Chronic Case Definition

An individual with:

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 p.6); *or*
2. PCR (qualitative, quantitative, or genotype) positive for HCV RNA.
Please note: a child <18 months of age should be called a confirmed case ONLY if PCR positive for HCV RNA.

3.4 Presumptive Chronic Case Definition

An individual who is anti-HCV positive (repeat reactive) by EIA, and has ALT or SGPT values above the upper limit of normal, 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 on next page).

3.5 Suspect Chronic Case Definition

An individual whose only positive test result is a single anti-HCV antibody and the signal to cut-off ratio is unknown or has a positive test result from a rapid screening test (e.g., Oraquick). Lastly, a child <18 months of age born to an anti-HCV positive mother should not be considered a confirmed chronic hepatitis C case based on a positive EIA result for anti-HCV, regardless of the signal-to-cutoff ratio, because this result may indicate the presence of maternal antibodies. A child <18 months of age is considered a confirmed chronic case only with a positive PCR result for HCV RNA. If anti-HCV is the only positive serology available, the child should be called a suspect case until further testing can be done.

3.7 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 un-

Hepatitis C

Table 1. Signal-cutoff ratios of HCV screening test kits used by Oregon laboratories, 2013

EIA/CIA test kit name	Signal to cutoff ratio predictive of a true positive $\geq 95\%$ of the time	Laboratories performing anti-HCV EIA tests
Ortho HCV Version 3.0 ELISA Test System	3.8	<ul style="list-style-type: none"> • American Red Cross National Testing Lab • Kaiser Regional Laboratory/OHSU • Oregon State Public Health Laboratory
Abbott Architect anti-HCV assay	5.0	<ul style="list-style-type: none"> • Salem Hospital • Samaritan Lebanon Community Hospital
Ortho Vitros anti-HCV assay	8.0	<ul style="list-style-type: none"> • Interpath Laboratory, Inc. • Mayo* • Quest Diagnostics • St. Charles Medical Center* • Schryver Medical Lab
Abbott Assym antibody to HCV	10.0	<ul style="list-style-type: none"> • Dynacare • Tillamook County General Hospital
Bayer Advia Centaur HCV assay	>11	<ul style="list-style-type: none"> • Adventist • ARUP • Clinical Reference Labs, Lenexa, Kansas • Labcorp • Legacy Laboratory Services • McKenzie-Willamette Medical Center • Mercy Medical Center • PAML • PeaceHealth (formerly OML; sometimes called Central Laboratory or Specialty Lab)* • Providence Laboratory Services* • Providence Medford Medical Center* • Rogue Valley Medical Center

* These labs may not report the s/co ratio. However, all positive reports have s/co ratios above the cut-off predictive of a true positive. Persons with positive results from these labs are considered confirmed cases.

ambiguously 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.

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.

Hepatitis C

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. LHD should 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, LHD should 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 counseled about modes of transmission, means of reducing spread to others, alcohol cessation, and the need for hepatitis A and B vaccination.

3.8 Services Available at the Public Health Lab

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 (see table 1 for values for different commercial assays) 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 PCR).

4. ROUTINE CASE INVESTIGATION

4.1. Identify the Source of the Infection

For cases with recent infection, ask about the 6 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 (notify ACDP's on-call epi if you suspect the inspection may be healthcare associated); or
- High-risk sexual contact (multiple partners, history of other STDs, anal sex, etc.).

4.2. Identify Potentially Exposed Persons

- 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.).
- 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).
- 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.

4.3. Environmental Evaluation

None.

5. CONTROLLING FURTHER SPREAD

5.1. 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 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 rehabilita-

Hepatitis C

tion 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.

5.2. Isolation and Work or School/Day Care Restrictions

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

5.3. Follow-Up

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).

5.4. Protection of Contacts

1. Active immunization

None.

2. Passive Immunization

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

5.5 Environmental Measures

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

6. MANAGING SPECIAL SITUATIONS

6.1. 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 after the fact. Current CDC guidelines recommend an HCV antibody test and ALT level at baseline and at 6 months to capture the full seroconversion time-window. Infection can be usually detected within 2 weeks by PCR. Risk for HIV and hepatitis B virus should also be assessed using current CDC guidelines.

6.2 Possible Healthcare-Associated Infections

Particularly in patients >50 years of age without the usual behavioral risk factors associated with the acquisition of HCV, further questioning into possible healthcare exposures should be pursued. ACDP has a handy questionnaire specifically for this purpose that can be obtained by calling the ACDP on-call epi at 971-673-1111; you can either do the extended questionnaire or turn it over to our hepatitis epidemiologist(s) in ACDP.

6.3 Other Situations

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

In addition, according to current CDC guidelines, children born to HCV-positive women should be tested for HCV infection. Testing of infants for anti-HCV should be performed no sooner than age 18 months, when passively transferred maternal anti-HCV declines below detectable levels. If testing is performed, only a positive PCR would indicate current infection. Presence of viral RNA can be intermittent, so false negatives can occur.

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.

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.

HBeAb: 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. **This test is no longer available.**

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).

UPDATE LOG

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

October 2008. Updated Table 1 "Signal cut off ration of HCV screen tests used by Oregon laboratories.

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

Hepatitis C

April 2010: Added guidelines for anti-HCV testing for infants born to HCV-positive women, per CDC guidelines.

November 2010: Updated age guidelines for anti-HCV testing for infants born to HCV-positive women per CDC, the American Association for the Study of Liver Disease and the American Academy of Pediatrics. (Van Ness)

September 2011. Updated anti-HCV assay and s/co ratio for Salem Hospital laboratory. Updated new treatment therapies. Updated acute case classification for clarity. (Poissant)

January 2012. Updated case classifications per CDC/CSTE guidelines. Asymptomatic seroconverters may now be classified as confirmed acute cases. Presumptive chronic cases must have elevated ALTs to meet the case definition. Added suspect case definition. Updated assay and s/co ratio for Interpath Laboratory and Legacy. Updated labs that may not report the s/co ratio. (Poissant)

March 2012. Removed “3.3 4. previously reported as acute HCV (or presumptive chronic HCV) with a subsequent positive RIBA, PCR or genotype result >6 months later.” from confirmed chronic case definition in order to follow CDC/CSTE guidelines. (Poissant)

October 2012. Inserted reference to CDC screening guidelines for 1945-1965 birth cohort and updated Table 1 (s/co ratio). (Cunningham)

January 2013. Updated Table 1, s/co ratio. Moved Samaritan Lebanon Community Hospital from the “Abbott Assym” to Abbot Architect. (Cunningham)

December 2013. Removed RIBA confirmatory test from guidelines as it is no longer available. Removed statement that OHA will request LFTs on positive persons <30 years of age. Recommended that LHDs perform this follow-up. (Poissant)