Hepatitis E
Investigative Guidelines
September 2017

1. DISEASE REPORTING

1.1 Purpose of Reporting and Surveillance

1. To better characterize the epidemiology of infectious hepatitis due to hepatitis E virus (HEV).
2. To recommend appropriate preventive measures.

1.2 Laboratory and Physician Reporting Requirements

Laboratories, physicians and others providing health care must report confirmed or suspected cases to the Local Health Department (LHD) within one working day of identification or diagnosis.

1.3 Local Health Department Reporting and Follow-Up Responsibilities

1. Report all confirmed and presumptive (but not suspect) cases (see definitions below) to the Oregon Public Health Division (OPHD) within one working day.
2. Begin follow-up investigation within one working day. Submit all case data electronically.

2. THE DISEASE AND ITS EPIDEMIOLOGY

2.1 Overview

Hepatitis E is a leading cause of enterically transmitted viral hepatitis worldwide, particularly in Asia and Africa. Burden of disease is greatest in parts of the world where clean drinking water is scarce. Accumulating data indicates the epidemiology is more complex than previously assumed. Currently, two major epidemiologic profiles associated with four genotypes are recognized with distinct differences in geographic distribution, affected population groups, routes of transmission, and disease characteristics.

- In developing countries, HEV is the most common cause of acute viral hepatitis; genotypes 1 and 2 are endemic and are associated with large outbreaks from fecally-contaminated water. Frequent sporadic cases are also common. Genotypes 1 and 2 manifest most commonly in young, otherwise healthy people as acute, self-limiting hepatitis associated with endemic disease with disproportionately high morbidity and mortality in pregnant women and children.

- In developed countries including the U.S., genotypes 3 and 4 produce sporadic, locally acquired hepatitis primarily affecting the elderly and those with comorbid conditions. Large outbreaks have not been reported. Infection due to genotype 3 and 4 is typically associated with foodborne transmission, linked to the consumption of raw or undercooked infected meat from wild (deer and boar) and domestic (pig and probably rabbit) animals. Zoonotic transmission through direct contacts with infected animals has also been reported. Emerging evidence points to particular risk of chronic infection to immunocompromised and transplant patients.

2.2 Etiologic Agent

The hepatitis E virus (HEV) is the only member of the genus Hepevirus in the family Hepeviridae. It is a spherical, nonenveloped, single-stranded RNA virus. HEV has one serotype; four genotypes (1-4) have been identified.

2.3 Description of Illness

Persons infected with HEV exhibit a wide clinical spectrum, ranging in severity from asymptomatic infection to fulminant hepatitis. Two clearly distinct disease profiles have been recognized.

1. **In endemic areas,** most infection is due to genotypes 1 and 2 and symptoms manifest most often in youth and adults 14-40 years old. Illness begins with a short prodromal period followed within a few days by symptoms similar to those of acute viral hepatitis A, including fever, fatigue, jaundice, loss of appetite, nausea, vomiting, abdominal pain, dark urine, joint pain, and clay colored stools. Clinical symptoms are usually concurrent with increases in liver enzyme levels: bilirubin, aspartate aminotransferase and alanine aminotransferase. Symptoms are often indistinguishable from those experienced during other liver illnesses and typically last between 1–6 weeks. With rare exceptions, acute HEV infection is self-limiting and generally does not result in chronic disease. Case fatality rates are reported between 0.5% and 4.0%[1].

   Rarely, severe cases of fulminant hepatitis E put patients, particularly pregnant women, at risk of death. Disproportionately high rates of fulminant hepatitis occur among pregnant women, resulting in high rates of mortality (up to 25% in the third trimester of pregnancy) following fulminant hepatic failure. HEV infection during pregnancy is also associated with miscarriage, prematurity, low birth weight, and increased risk of perinatal mortality. High rates of mortality among children under the age of 2 have also been observed.

   Cases due to genotypes 1 and 2 are sometimes seen in non-endemic areas in travelers returning from developing countries. These cases follow the course described above.

2. **In non-endemic areas and developed countries,** most reported cases of locally acquired disease are sporadic and due to genotypes 3 and 4, and

symptoms tend to be mild. In these areas, affected persons tend to be elderly adults, often with coexisting conditions like diabetes, cardiovascular disease, and prior liver disease[2]. Particularly in older men, disease may be accompanied by serious complications including “acute-on-chronic” liver failure, neurologic disorders, and chronic hepatitis[3]. Cases of chronic hepatitis E infection have also been reported in immunosuppressed patients, especially organ transplant patients on immunosuppressive therapy.[4] In the United States, locally acquired hepatitis E is rarely reported, although seroprevalence studies show a high proportion of US residents are seropositive for IgG anti-HEV, indicating that exposure to HEV is common in the US population.[5]

2.4 Reservoir & Modes of Transmission

In developing countries where HEV is endemic (Indian subcontinent, Asia, Middle East, and Africa), HEV genotypes 1 and 2 are common and restricted to humans. In developed countries, these two genotypes were diagnosed only in persons after travel to highly endemic areas.

Transmission of genotypes 1 and 2 is by the fecal-oral route via contaminated water. Most epidemics have been traced to contaminated water supplies. In sporadic cases the route of transmission is less clear although fecal contamination of food or water appears to be responsible for most cases.

HEV genotypes 3 and 4 are autochthonous in several industrialized countries. Occasional foodborne outbreaks have occurred in Europe, North America, Japan, and New Zealand from consuming raw or undercooked meat contaminated with HEV. Genotypes 3 and 4 are found in humans and in other species such as pig, wild boar, and shellfish.

With all genotypes, person-to-person transmission appears infrequent in both epidemic and sporadic settings.

2.5 Incubation Period

The range is 15 to 64 days; the mean incubation period is around 6 weeks but has varied from 26 to 42 days in different epidemics.[6]

2.6 Period of Communicability

Infected persons are thought to shed the virus beginning one week prior to 3-4 weeks after onset of symptoms.[7] Hepatitis E virus was detected in stools 14 days after onset of jaundice and about 4 weeks after consuming contaminated food or water, persisting for about 2 weeks.[7]

2.7 Serologic Markers

After 2 to 8 weeks incubation, viremia increases, followed by IgM and IgG anti-HEV antibodies. HEV is also shed in stool at this time. During recovery, viral load is cleared, IgM decreases, and IgG increases. The duration of viral shedding and presence of antibodies is variable[4].

Serologic markers of HEV infection are identified by antigen and antibody assays and by nucleic acid amplification test for HEV RNA (i.e., RT-PCR). Markers tested for are anti-HEV IgM, IgG, and viral RNA.

Serologic evidence of prior exposure via anti-HEV IgG has been found in most areas worldwide. Seroprevalence estimates for the United States range from <1% to 32%.[6,8]

2.8 Treatment

Treatment, when indicated, is usually supportive. Acute hepatitis E is generally mild and usually resolves on its own without treatment. There is no specific antiviral therapy for acute hepatitis E, although treatment with ribavirin may be indicated for those with poor prognosis or at high risk of fulminant liver failure. Patients are typically advised to rest, get adequate nutrition and fluids, avoid alcohol, and check with their physician before taking any medications that can damage the liver, especially acetaminophen. Hospitalization is sometimes required in severe cases and should be considered for pregnant women.

3. CASE DEFINITIONS, DIAGNOSIS AND LABORATORY SERVICES

3.1 Confirmed Case Definition

An individual with:

1. Discrete onset of symptoms consistent with viral hepatitis (e.g., nausea, vomiting, abdominal discomfort, pale stools, dark urine); and
2. Jaundice or elevated serum ALT levels > 200 IU/L; and
3. IgM anti-HEV positive or positive result for hepatitis E RNA detection by RT-PCR;
4. IgM anti-HAV negative (if done); and
5. IgM anti-HBc negative (if done) or HBsAg negative; and
6. Anti-HCV negative.

3.2 Presumptive Case Definitions

An individual with:

1. Discrete onset of symptoms consistent with viral hepatitis (e.g., nausea, vomiting, abdominal discomfort, pale stools, dark urine) ; and
2. Jaundice or elevated serum ALT levels > 200 IU/L; and
3. An epidemiological link with a person who has confirmed hepatitis E (e.g., household contact, meal sharing, travel partner) during the 2-9 weeks before the onset of symptoms.

3.3 Suspect Case (*not* reportable to Oregon PHD)

Anyone with discrete onset of symptoms or elevated liver enzymes without epi linkage to a confirmed case, and no available laboratory information or lab confirmation. Serologic testing for viral hepatitis A, B, C and E should be encouraged.

3.4 Diagnosis

Diagnosis of hepatitis E depends on clinical and epidemiologic features and exclusion of other etiologies of hepatitis, especially hepatitis A, by serologic means.

Several diagnostic tests are available including enzyme immunoassays and Western blot assays to detect IgM and IgG anti-HEV in serum; polymerase chain reaction tests to detect hepatitis E virus RNA in serum and stool; and immunofluorescent antibody blocking assays to detect antibody to hepatitis E antigen in serum and liver.

3.5 Services Available at the Oregon State Public Health Laboratory

The OSPHL does not test for hepatitis E but testing is available at many commercial laboratories.

3.6 Specimen Collection

All specimens must be properly packaged in double containers with absorbent material around them. Serum and other specimens should be refrigerated and transported cold. Follow specific guidelines provided by the testing facility.

4. ROUTINE CASE INVESTIGATION

4.1 Confirm the Diagnosis

It is important to differentiate hepatitis E disease from the other viral hepatitis infections. Confirm that the case's illness is consistent with acute viral hepatitis. Diagnosis is supported by presence of risk factors such as international travel, and by ruling out other viral sources of hepatitis infection. If patient is pregnant, see §5.

4.2 Identify Potential Sources of Infection

Interview the case or others who may be able to provide pertinent information.

Ask the case about potential exposures 2-8 weeks before onset of illness, including any persons (e.g., household member, persons that shared a meal, others in travel group) who had a compatible illness. Obtain each person's name and contact information. Newly identified suspected cases should be reported and investigated in the same manner as the index case.

4.3 Identify Close Contacts or Others Potentially Exposed to the Patient

1. There is no post-exposure prophylaxis for hepatitis E.
2. Symptomatic close contacts of a confirmed case should be referred to a healthcare provider for evaluation.
3. Secondary cases of hepatitis E infection are rare, but hygiene measures are recommended.

4.4 Environmental Evaluation

None, unless a commercial food service/production facility, child care center, or public water supply appears to be implicated as the source of the infection.

4.5 Infection Control

Patients infected with hepatitis E virus who are still susceptible to hepatitis A or B should be vaccinated against hepatitis A or B.

Hospitalized patients should be cared for using standard precautions. Also use contact precautions for diapered or incontinent individuals while symptomatic.

5. MANAGING SPECIAL SITUATIONS

5.1 Hepatitis E Case is Pregnant

Depending on the causative genotype, hepatitis E virus infection can be severe in pregnancy, causing acute liver failure and premature delivery or stillbirth. Ensure that the patient's prenatal provider is consulted about further management.

5.2 Hepatitis E Case is Immunocompromised or an Organ Transplant Patient

Therapeutic interventions should be considered for immunocompromised patients with HEV infection.[1] A subspecialist knowledgeable about the patient's underlying immunosuppressive condition should be consulted for consideration of antiviral treatment.

5.3 Hepatitis E Case Works or Volunteers in a High Risk Setting

Limited literature and guidelines discuss the transmission of hepatitis E, especially in the setting of sporadic disease. Although person to person transmission of HEV is uncommon, it may occur.[9] Food-borne outbreaks have been documented.[10] Should a food handler be diagnosed with hepatitis E, consult with Acute and Communicable Disease Prevention.

5.4 Outbreak of Hepatitis E

Follow investigative guidelines for foodborne or waterborne outbreaks. For specific measures related to control of water-borne hepatitis E outbreaks, see the following WHO guidance:

http://apps.who.int/iris/bitstream/10665/129448/1/9789241507608_eng.pdf?ua=1&ua=1

5.5 Case is a Recent Blood Donor or Recipient

HEV may be a transfusion-transmitted pathogen of concern.[1] Should a hepatitis E patient be a recent blood donor, consult with Acute and Communicable Disease Prevention.

6. ROUTINE PREVENTION

6.1 Immunization Recommendations

None. No vaccine for hepatitis E is currently available in North America. Multiple viral hepatitis infections can result in liver damage, so universal immunization is recommended to prevent hepatitis A and B.

6.2 Prevention Recommendations

Routine precautions should be taken during travel in risk areas to assure safe food and water, particularly for women who may be pregnant. Hepatitis E is highly endemic is many parts of Asia and Africa, but is also present in the Americas and Europe. For travel information related to hepatitis E see:

http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/hepatitis-e

In low-endemic areas with zoonotic transmission, sanitary handling and proper cooking of pork products and wild game like deer may be important.

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UPDATE LOG

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