

# Viral hepatitis (Particularly D and E)

## Important information

This disease is notifiable in the UK – see [NOIDs](#) article for details.

## What is viral hepatitis?<sup>[1]</sup>

Hepatitis is a general term that refers to inflammation of the liver. This condition may result from various infectious (viral, bacterial, fungal, and parasitic organisms) and non-infectious (medications, toxins, and autoimmune disorders) causes; however, this article considers hepatitis caused by viral infection. In the UK and the USA, viral hepatitis is most commonly caused by hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV). HAV, HBV and HCV are covered in separate articles detailed below under their individual headings.

HAV, HBV and HCV can all result in acute illness with symptoms of nausea, abdominal pain, fatigue, malaise, and jaundice. HBV and HCV can also lead to chronic infection. Patients who are chronically infected may go on to develop cirrhosis and hepatocellular carcinoma. Chronic hepatitis carriers remain infectious and may transmit the disease for many years.

## Causes

The term viral hepatitis is generally used to refer to liver inflammation caused by the hepatotropic viruses including: HAV, HBV, HCV, hepatitis D (HDV) and hepatitis E (HEV). Other viruses, which may cause hepatitis but which do not primarily infect the liver, include:

- [Cytomegalovirus \(CMV\)](#).
- [Epstein-Barr virus](#).
- Adenovirus.

- [Herpes simplex virus](#) (rarely).

Despite their name, the hepatropic viruses (particularly B and C) can cause extrahepatic disease. Viral agents can cause acute, chronic and subclinical liver disease.

## How common is viral hepatitis? (Epidemiology)

The epidemiology of viral hepatitis has changed. Since the introduction of safe and effective vaccines for HAV and HBV in the 1980s, the incidence of acute infections caused by these viruses has been declining in the UK. At the same time, HEV has been recognised as an increasingly important cause of acute hepatitis <sup>[2]</sup> .

## Viral hepatitis symptoms (presentation) <sup>[1]</sup>

### Acute infection

- Nausea and vomiting
- Myalgia
- Fatigue/malaise
- Right upper quadrant pain
- Change in sense of smell or taste
- Coryza
- Photophobia
- Headache

Diarrhoea (with pale stools and dark urine) may also be present. However, often no signs are seen unless jaundice develops. Hepatomegaly, splenomegaly and lymphadenopathy may then be present. May present with [liver failure](#).

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### Chronic infection

This is most commonly a consequence of infection with HBV, HCV or HDV. Presentation is very varied and may be asymptomatic. Subclinical infection causes only vague symptoms like fatigue and dyspepsia. Chronic infection may lead to [chronic hepatitis](#), [cirrhosis](#) and [hepatocellular carcinoma](#). Chronic hepatitis and cirrhosis can take months to decades to develop. Signs of chronic liver disease may be apparent.

## Investigations

- FBC.
- U&Es.
- LFTs (see also the separate article [Abnormal Liver Function Tests](#)).
- Clotting studies, including INR.
- Hepatitis serology.
- Imaging with ultrasound/CT/MRI scanning to assess for presence of cirrhosis or other causes of symptoms.

## Differential diagnosis of 'any' hepatitis

### Acute

- Drugs, toxins, alcohol.
- [Infectious mononucleosis](#), [CMV](#), [Q fever](#), [leptospirosis](#), [syphilis](#), [malaria](#), [yellow fever](#).
- Any other cause of [jaundice](#).

### Chronic

- Alcohol, drugs.
- [Autoimmune hepatitis](#).
- [Haemochromatosis](#).
- [Wilson's disease](#).

# Hepatitis A

HAV may occur in outbreaks in institutions. It is common in travellers. Most infections pass unnoticed in childhood. It is a small, unenveloped, symmetrical RNA virus (picornavirus). See the separate article [Hepatitis A](#).

# Hepatitis B

- HBV is a double-stranded DNA virus which replicates by reverse transcription (*Hepadnaviridae* family).
- It is endemic with more than 350 million people infected worldwide. [3] See the separate article [Hepatitis B](#).

# Hepatitis C

HCV is an enveloped RNA virus in the *Flaviviridae* family with a narrow host range (humans and chimpanzees). See the separate article [Hepatitis C](#).

# Hepatitis D<sup>[1]</sup> <sup>[4]</sup> <sup>[5]</sup>

HDV is an unusual, defective, single-stranded RNA virus. It requires the presence of HBV to replicate. HDV infection develops only in patients who are positive for the hepatitis B surface antigen (HBsAg). Infection may be acquired along with HBV (co-infection) or after HBV infection (superinfection).

## Epidemiology

- An estimated 15–20 million people infected with HBV worldwide are also infected with HDV.
- It is an important cause of acute and severe chronic liver damage in some parts of the world (Mediterranean, parts of Eastern Europe, Middle East, Africa, and South America).

## Route of transmission

It needs hepadnavirus to function and for its propagation in hepatocytes, and is therefore acquired as a co-infection with HBV, or as a superinfection in those with existing chronic HBV infection. Therefore transmission is, like HBV, by exposure to infected blood and blood products. It can be transmitted percutaneously and sexually. Perinatal transmission is rare.

## Clinical features

HDV replicates only in liver cells and so the cellular damage associated with HDV infection involves mainly the liver. Immune-mediated liver damage is thought to be implicated in HDV infection. HDV co-infection with HBV may be associated with increased risk of severe clinical hepatitis, fulminant hepatic failure, chronic liver disease, cirrhosis and hepatocellular carcinoma.<sup>[6]</sup>

## Investigations

Anti-HDV antibody. Other investigations as indicated for hepatitis, liver failure, cirrhosis and hepatocellular carcinoma.

## Management

Current treatments include pegylated interferon alfa and liver transplantation, which can be curative.<sup>[6]</sup> Management is otherwise supportive.

### Editor's note

[Dr Krishna Vakharia](#) 27th June 2023

#### **Bulevirtide for treating chronic hepatitis D**<sup>[7]</sup>

NICE recommend bulevirtide as an option for treating chronic hepatitis D in adults with compensated liver disease if there is evidence of significant fibrosis (METAVIR stage F2 or above or Ishak stage 3 or above) and their hepatitis has not responded to peginterferon alfa-2a (PEG-IFN) or they cannot have interferon-based therapy.

Evidence shows that bulevirtide is effective compared with standard care but there are some uncertainties on how long it works for.

## Prevention

As for HBV.

## Hepatitis E<sup>[1] [5] [8]</sup>

HEV genotype 3 and 4 can cause liver disease in humans. The main reservoir is pigs. In humans, the infection may vary in severity from inapparent to fulminant. The mortality is between 1% and 4%, and can reach 25% in pregnant women.

In resource-limited countries, HEV infection is endemic and spreads mainly through contamination of water supplies.

Transmission of virus from domestic pigs to humans is common and higher rates of HEV seroprevalence are detected in slaughterhouse workers and vets. It is evaluated that one third of the worldwide population has been in contact with the virus.

## **Epidemiology**

- In some areas it is the most common viral cause of hepatitis in adults and older children, causing major epidemics in the Indian subcontinent, Central and Southeast Asia, the Middle East, and parts of Africa.
- Mortality is high in pregnancy. Intrauterine infection ( $\pm$  stillbirth) is common.

## **Route of transmission**

- This is by the faecal-oral route and similar to HAV.
- Contaminated drinking water is the most common source of infection.
- Person-to-person transmission is rare but maternal-neonatal transmission does occur.
- Zoonotic spread may occur, as other animals (primates, cows, pigs, sheep, goats, and rodents) are susceptible to infection.

## **Clinical features**

- These are also similar to HAV with no apparent risk of chronic liver disease.
- Incubation is 2-9 weeks.
- It is usually a self-limiting illness.
- There are no reports of chronic infection with HEV.
- HEV usually causes an acute self-limiting illness like HAV. Fulminant disease occurs in about 10% of cases.

- In pregnancy, the mortality rate may be as high as 15–20%.

## Investigations

Hepatitis serology.

## Management

This is mainly supportive, as HAV.

## Prevention

- Good hygiene and sanitation.
- Avoidance of tap water in high-risk areas (most outbreaks are associated with contaminated drinking water).
- Gammaglobulin is ineffective.
- No vaccine is currently available.

## Hepatitis G viruses<sup>[9] [10]</sup>

GB virus C (GBV-C), formerly known as hepatitis G virus (HGV), is a lymphotropic human virus that is related to HCV. To date, GBV-C has not been convincingly associated with any disease. However, it appears to be protective against HIV infection.

- Two distinct viruses were identified initially when tamarind monkeys were inoculated with the serum of this patient (GBV-A and GBV-B).
- The third virus, GBV-C, was later isolated from a human specimen (this was the new 'hepatitis G' virus separately identified in 1996).
- All three are members of the *Flaviviridae* family of viruses and share significant homology with HCV.

## Epidemiology

GBV-C infection is common and is distributed worldwide. It may establish persistent infection without clinical symptoms or disease in either immunocompromised or healthy individuals. In developed countries, 1–5% of healthy blood donors are viraemic at the time of blood donation. The prevalence is higher in developing countries, with up to 20% of blood donors being viraemic in some studies.

## Prognosis

Although GBV-C infection is common and may persist for decades, most healthy individuals clear viraemia within two years of infection.

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## Further reading

- [Hepatitis E](#); British Liver Trust
- [Hepatitis E: symptoms, transmission, treatment and prevention](#); Public Health England, 2020
- [Pisano MB, Giadans CG, Flichman DM, et al](#); Viral hepatitis update: Progress and perspectives. *World J Gastroenterol.* 2021 Jul 14;27(26):4018–4044. doi: 10.3748/wjg.v27.i26.4018.
- [Chilaka VN, Konje JC](#); Viral Hepatitis in pregnancy. *Eur J Obstet Gynecol Reprod Biol.* 2021 Jan;256:287–296. doi: 10.1016/j.ejogrb.2020.11.052. Epub 2020 Nov 19.
- [Leoni S, Casabianca A, Biagioni B, et al](#); Viral hepatitis: Innovations and expectations. *World J Gastroenterol.* 2022 Feb 7;28(5):517–531. doi: 10.3748/wjg.v28.i5.517.
- [Easterbrook PJ, Roberts T, Sands A, et al](#); Diagnosis of viral hepatitis. *Curr Opin HIV AIDS.* 2017 May;12(3):302–314. doi: 10.1097/COH.0000000000000370.

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<b>Last updated by:</b> Dr Colin Tidy, MRCP 10/05/2023	
<b>Peer reviewed by:</b> Dr Hayley Willacy, FRCGP 10/05/2023	<b>Next review date:</b> 08/05/2028

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