

ACUTE AND CHRONIC VIRAL HEPATITIS

Acute and chronic hepatitis are common worldwide.



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Many viruses can infect the liver, but are usually not able to enter hepatocytes due to certain barriers such as the activity of Kupffer cells. Viruses such as Epstein-Barr virus and cytomegalovirus frequently cause hepatitis as part of a systemic illness, but this is seldom the main symptom. The typical hepatitis virus is able to enter and replicate in the hepatocyte and causes hepatitis as the primary disease. Only these hepatotropic viruses, hepatitis A, B, C, and E, will be discussed here. These viruses are collectively responsible for most acute and chronic hepatitis worldwide. For example, chronic hepatitis B and C currently affect approximately 600 million people, and hepatitis A and E have been responsible for large point-source outbreaks affecting hundreds of thousands of people. Because hepatitis D and E are not thought to be endemic in South Africa, they will not be discussed in this article in any detail. The virological, epidemiological and clinical characteristics of these viruses are contrasted in Table I.

ACUTE VIRAL HEPATITIS

General symptomatology

The early prodromal phase

The illness may be heralded by a serum sickness-like syndrome, probably resulting from circulating immune complexes, particularly in those incubating hepatitis B. The syndrome consists of fever, urticaria, arthralgia and arthritis. These manifestations, when they do occur, precede jaundice by 14 - 21 days and disappear with the onset of icterus.

The pre-icteric phase

There may be an abrupt or insidious onset of nonspecific constitutional symptoms. These include malaise, fatigue, anorexia, myalgia, nausea and vomiting. There may be changes in taste and smell with aversion to food and cigarettes. An influenza-like illness may also be seen, especially with hepatitis A. Mild to moderate epigastric or right upper quadrant pain is a common concomitant symptom.

Physical examination may be unremarkable or may reveal hepatomegaly, splenomegaly and posterior cervical lymphadenopathy. Hepatomegaly is usually slight, with mild tenderness to palpation or percussion. Spider angiomas are rarely found.

Icteric phase

With the onset of jaundice approximately a week after the pre-icteric phase, fever and constitutional symptoms subside. Occasionally, anorexia, nausea and vomiting may be transiently worsened. The patient may notice dark urine and pale stools. Additional physical findings include yellowing of the sclera and skin. Scratch marks of the skin suggest itch.

Table I. Virological and clinical characteristics of hepatotropic viral infections

Characteristic	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D*	Hepatitis E
Epidemiological features					
Transmission					
Faecal-oral	Yes	Not usually	No	No	Yes
Parenteral	Rare	Yes	Yes	Yes	No
Maternal-infant	No	Yes	Low risk	No	No
Sexual	Yes	Yes	Low risk	Yes	No
Incubation period					
Range (days)	15 - 50	28 - 160	14 - 160	Varies	15 - 45
Mean (days)	±30	±80	±50	Varies	±40
Age predilection	Mainly young	All ages	All ages	All ages	Mainly adults
Clinical features					
Onset	Abrupt	Insidious	Insidious	Abrupt/insidious	Abrupt
Arthritis, rash	Infrequent	Frequent	Infrequent	Infrequent	Frequent
Pyrexia	Frequent	Infrequent	Infrequent	Frequent	Frequent
Anorexia, nausea and vomiting	Frequent	Frequent	Frequent	Frequent	Frequent
Jaundice	Infrequent in children	Less common than hep. A	Infrequent	Frequent	Frequent
Laboratory features					
Duration of transaminitis	Short	Prolonged	Prolonged	Variable	Short
Virus location					
Faeces	Yes	No	No	No	Yes
Blood	Transient	Prolonged	Prolonged	Prolonged	Transient
Natural history					
Acute illness	Mild	Moderate	Mild	Can be severe	Severe in pregnancy
Chronic hepatitis	No	Yes	Yes	Yes	No
Frequency after exposure		5% in adults, 90% in neonates	85%	5% - 10% of HBsAg +ves	
Hepatocellular carcinoma	No	Yes	Yes	?No	No
Mortality	Low	Low	Low	High	High in pregnancy
Immunoprophylaxis					
Passive (immune globulin)	Yes (ISG)	Yes (HBIG)	No	No	No
Active (vaccine)	Yes	Yes	No	No	No

* Hepatitis D (or delta virus) is a defective virus which only causes co- or superinfection in the presence of the helper virus, hepatitis B. ISG = immune serum globulin; HBIG = hepatitis B immune globulin.

Convalescent phase

Jaundice wanes rapidly in children over days, but tends to persist longer in adults (6 weeks or more). The symptoms encountered in the pre-icteric phase disappear and the liver and spleen begin to shrink. Itching abates and a sense of well-being returns. Weight loss is common.

Diagnostically relevant laboratory tests

Rises in serum alanine aminotransaminase (ALT) and aspartate aminotransaminase (AST) indicate hepatocellular necrosis. These 2 enzymes are the most sensitive for establishing the diagnosis of acute viral hepatitis. They

may reach levels in excess of 100 times the upper limit of normal and always precede jaundice. The levels of ALT are generally higher than the levels of AST. Abnormal values are usually greater in those who develop jaundice, but cannot be used prognostically. Recovery is associated with a decline of the transaminase levels

which may take 6 months. Falling levels are also seen in patients whose clinical condition is worsening, as in fulminant hepatitis. Total serum bilirubin levels may vary considerably. Deep jaundice usually implies a protracted clinical course. Serum gamma glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) levels are only modestly raised, usually less than 3 times the upper limit of normal. Aetiological diagnosis depends on specific serologic and other specialised testing (Table II).

Liver histopathology

The classic lesion of acute viral hepatitis is acute hepatitis with 'spotty necrosis', which is characterised by panlobular disarray, increased cellularity and pleiomorphism of liver cells. A combination of changes gives rise to this appearance and consists of hepatocellular degeneration and necrosis, regeneration of hepatocytes, activation of sinusoidal cells and inflammation. However, mainly because of its lack of specificity, liver biopsy is not usually required for the diagnosis of acute viral hepatitis.

CHRONIC VIRAL HEPATITIS

General symptomatology

Chronic viral hepatitis is a syndrome characterised by persistent liver disease with the histological features of inflammation and hepatocellular necrosis. It is defined as chronic if disease lasts for 6 months or more and is due primarily to hepatitis B, C and D. Symptoms are generally vague, non-specific, mild or intermittent and even absent. Thus, many cases are identified incidentally, for example, during a routine check up. In others, symptoms do not develop until cirrhosis supervenes. Fatigue is the most common symptom and is often mistakenly ascribed to other causes such as stress or ageing. Other less common symptoms include mild right upper quadrant discomfort, loss of appetite, myalgia, nausea and arthralgia. Symptoms do not correlate with the height of aminotransaminase levels or with histological changes, but are probably related to the production of inflammatory cytokines. Symptoms may become more marked with the development of cirrhosis and/or hepatocellular carcinoma, and additional symptoms become evident, such as jaundice, anorexia, weight loss, abdominal pain, weakness, pruritus, easy bruising, abdominal swelling, pedal oedema, gastrointestinal bleeding and hepatic encephalopathy. In a small percentage of patients, extrahepatic manifestations may be the presenting features of chronic viral hepatitis. For example, necrotising vasculitides (in hepatitis B and C), palpable purpurae of mixed essential cryoglobulinaemia (in hepatitis C), membranoproliferative or membranous glomerulonephritis (in hepatitis B and C), porphyria cutanea tarda (in hepatitis C), lichen planus (in hepatitis C), lymphoma (in hepatitis C), Sjögren's syndrome (in hepatitis C), thyroid disease (in hepatitis C) and insulin resistance with type 2 diabetes mellitus (in hepatitis C).

Physical examination may reveal no or few signs. Some have mild hepatomegaly or an expanded left lobe and liver tenderness. Spider

Table II. **Diagnostic laboratory tests for acute and chronic viral hepatitis**

Disease	Test*	Result
Acute hepatitis A	Hepatitis A antibody IgM	Positive
Acute hepatitis B	Hepatitis B surface antigen	Positive
	Hepatitis B surface antibody	Negative/positive
	Hepatitis B core antibody IgG	Positive
	Hepatitis B core antibody IgM	Positive
	Hepatitis B e antigen	Positive/negative
	Hepatitis B e antibody	Negative/positive
	Hepatitis B DNA by PCR	Positive
Acute hepatitis C	Hepatitis C antibody	Positive
	Hepatitis C RT PCR	Positive
Acute hepatitis D	Hepatitis D antibody rising titres	Positive
	Hepatitis D antigen	Positive
	Hepatitis D RT PCR	Positive
Acute hepatitis E*	Fluorescent antibody blocking assay	Positive
	Western blot for anti-HEV	Positive
Chronic hepatitis B	Hepatitis B surface antigen	Positive
	Hepatitis B surface antibody	Negative
	Hepatitis B core antibody IgG	Positive
	Hepatitis B core antibody IgM	Negative/low positive
	Hepatitis B e antigen	Positive/negative
	Hepatitis B e antibody	Negative/positive
	Hepatitis B DNA by PCR	Positive/undetectable
Chronic hepatitis C	Hepatitis C antibody	Positive
	Hepatitis C RT PCR	Positive
	Genotyping by PCR	Genotypes 1 - 6
Chronic hepatitis D	Hepatitis D antibody	Positive (high titre)
	Hepatitis D RT PCR	Positive

* Testing performed by enzyme immunoassay (EIA) unless otherwise stated.

† These tests are specific, but of low sensitivity.

angiomata and palmar erythema may be found in those with active disease. Jaundice usually signifies advanced disease such as cirrhosis, as does splenomegaly, muscle wasting, ecchymoses, ascites, peripheral oedema, excoriations, hepatic encephalopathy and gynaecomastia.

Biochemical tests and aetiological diagnosis

Chronic elevations of ALT and AST are the hallmark of chronic viral hepatitis and levels range from minimally elevated to 20 times the upper limit of normal. The ALT is generally higher than the AST in ratios that range between 1:1 and 2:1. In patients who have cirrhosis, this pattern may be reversed. Serum GGT and ALP may be normal or modestly raised to levels that do not usually exceed 2 times the upper limit of normal. Jaundice is rare except with hepatic failure or severe exacerbations. Likewise, the INR and

serum albumin are normal in the absence of decompensated cirrhosis. Relatively modest hyperglobulinaemia is another feature of chronic viral hepatitis, ranging in levels between 20 and 30 g/l. Low titre autoantibodies such as antinuclear antibodies and antismooth muscle antibodies are not uncommonly seen. However, liver function tests may be persistently normal (as defined by normal tests performed serially at regular intervals over a 6-month period) in about 20 - 25% of patients with chronic hepatitis C, and in patients with chronic hepatitis B who are immunotolerant to the virus, particularly those who have been infected in the perinatal period. Aetiological diagnosis again depends on specific serological and other specialised testing (Table II).

Liver histopathology

Chronic hepatitis is typified by infiltration of the portal tracts by chronic

inflammatory cells with piecemeal necrosis, also termed interface hepatitis (injury or death of hepatocytes in the limiting plate at the interface between the portal tract and liver lobule). The presence of fibrosis in portal areas may link each other ('portal-to-portal bridging') or with central venules ('portal-to-central bridging'). The latter is the most important lesion that heralds the development of cirrhosis. Several histological scoring systems assess the severity of chronic hepatitis. The Metavir Score, which evaluates the extent of chronic inflammatory activity (A) and fibrosis (F), is currently in common use. Liver biopsy plays a vital role in the assessment and management of chronic viral hepatitis. It is useful in:

- confirming the diagnosis
- determining the severity of liver disease, particularly in aiding treatment decision-making
- excluding other forms of chronic

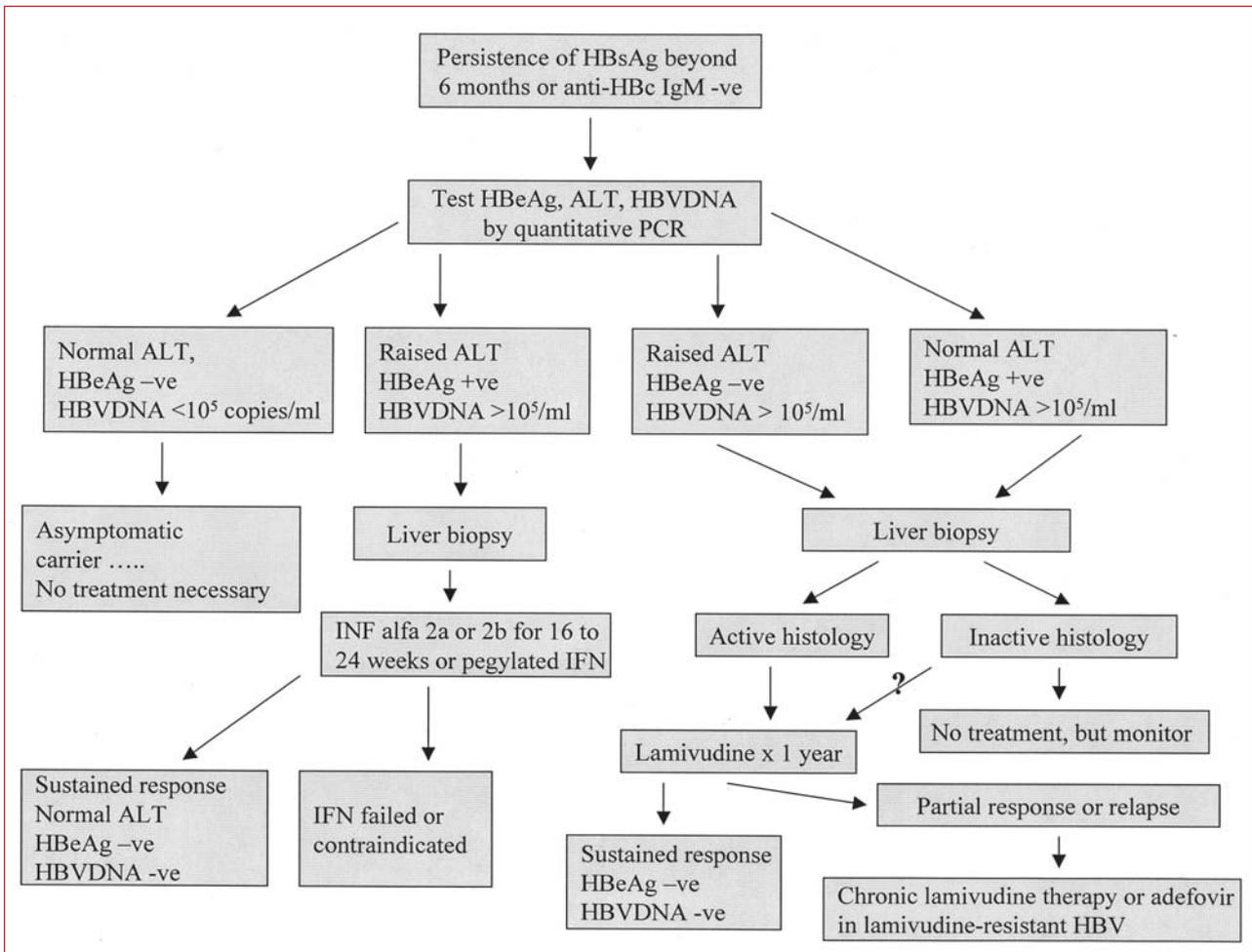


Fig. 1. Algorithm outlining therapeutic approach to chronic hepatitis B.

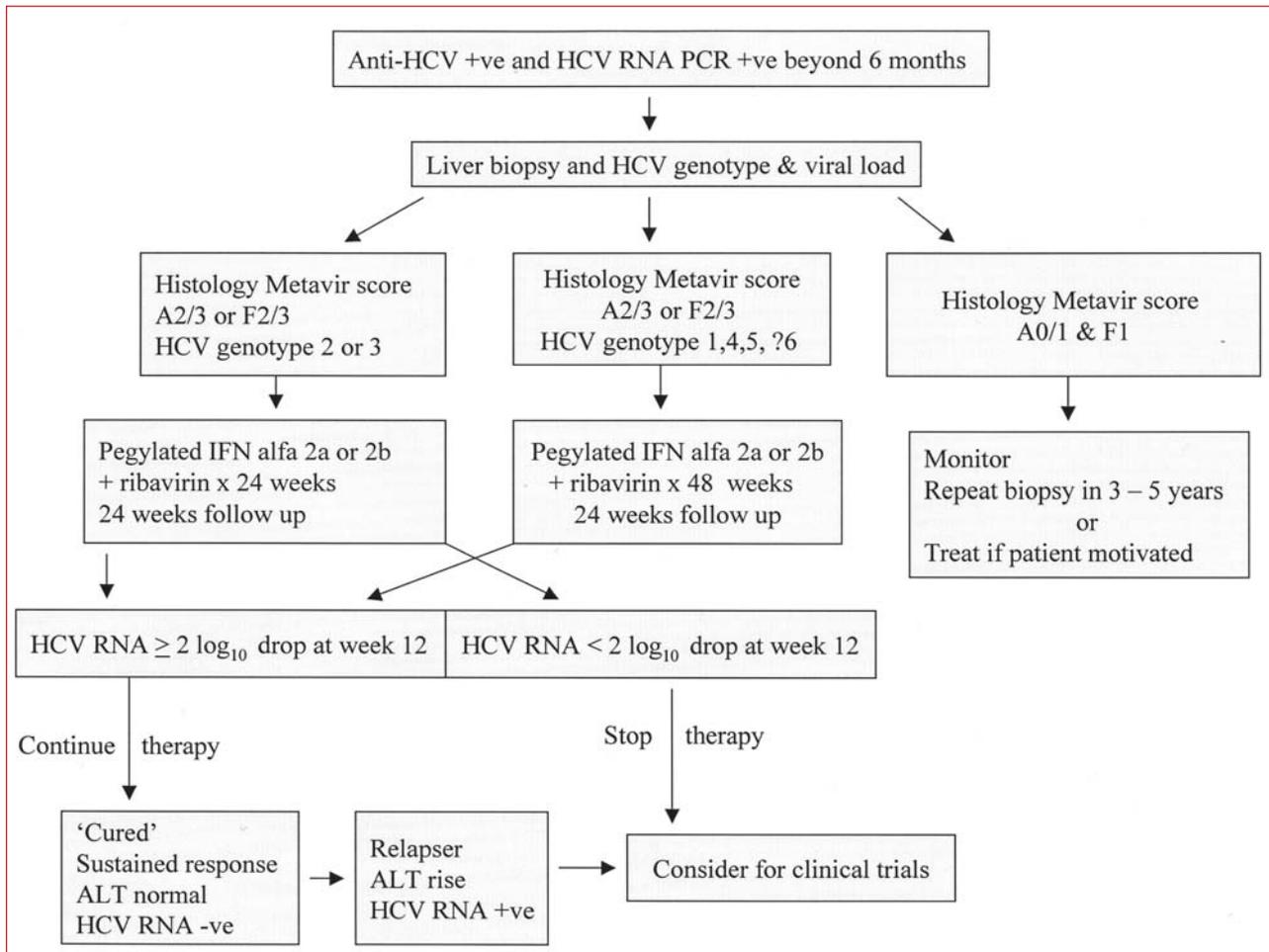


Fig. 2. Algorithm outlining therapeutic approach to chronic hepatitis C.

liver disease such as hepatic steatosis and alcoholic liver disease.

Treatment

Acute viral hepatitis

No proven specific therapy is available for acute viral hepatitis. Management consists of rest and regarding all attacks as potentially serious since the course of the disease may be unpredictable at the outset. Rest is advised until jaundice subsides, but young and previously healthy patients may be allowed moderate activity when they feel well, regardless of jaundice, provided transaminases have normalised. The clinical diagnosis is usually made well after the late incubation and prodromal phases of hepatitis A virus (HAV) infection when faecal viral shedding has ceased. Therefore, strict isolation control meas-

ures are not necessary. The spread of the disease is limited by simple hygiene and sanitary disposal of excreta. Because of the extremely high risk of chronic infection in hepatitis C, attempts have been made to institute antiviral treatment in the acute phase in the hope of reducing progression to chronicity. Several small uncontrolled trials have used differing regimens of interferon monotherapy with promising results. Sustained virological response rates of greater than 90% have been reported. Larger randomised control trials are needed to confirm these preliminary results. In acute hepatitis B, there is no convincing evidence that antiviral therapy curtails the illness.

Chronic viral hepatitis

Recombinant alfa interferon and the nucleoside analog reverse transcrip-

tase inhibitor, lamivudine, are registered in South Africa for the treatment of chronic hepatitis B. The approach to the management of chronic hepatitis B is outlined in Fig. 1. Improved efficacy over standard interferons has recently been demonstrated for pegylated interferon in chronic hepatitis B, but this agent is currently not registered in South Africa for this indication. The overall efficacy of standard interferon therapy using seroconversion of hepatitis B e antigen as the end-point in hepatitis B e antigen-positive patients is 30 - 40% with doses of 5 million units daily or 10 million units thrice weekly for 16 - 24 weeks. The efficacy of lamivudine at doses of 100 mg daily over 52 weeks is approximately 20%. It is a potent inhibitor of viral replication with few side-effects, but suffers

from the disadvantage of frequent emergence of viral drug resistance.

Pegylated interferon alfa and ribavirin are registered for the treatment of chronic hepatitis C infection and the therapeutic approaches are shown in Fig. 2. The overall efficacy using loss of detectable viraemia by the PCR 24 weeks after the end of treatment is 50 - 60%. The dose of pegylated interferon alfa-2a is 180 µg weekly and 1.5 µg/kg weekly for pegylated interferon alfa-2b together with daily doses of ribavirin ranging from 800 mg to 1 200 mg daily depending on body weight and viral genotype. There are 6 known genotypes of hepatitis C and dosage and duration of treatment depends on the genotype. The duration of treatment is 48 weeks except for patients with genotype 2 or 3 where 24 weeks of treatment usually suffice and efficacy rates of 70 - 80 % can be expected.

Because of the high side-effect and toxicity profiles of interferon and ribavirin therapy, most patients with chronic viral hepatitis are best referred to specialised centres for management.

PREVENTION

Personal hygiene, the safe disposal of excreta and the provision of clean water sources are among the primary measures for preventing the spread of hepatitis A and E. Immune serum globulin (ISG) together with a highly immunogenic and safe inactivated hepatitis A vaccine are available for pre- and postexposure immunoprophylaxis. Persons with chronic viral hepatitis who are not immune to other hepatotropic viruses are strongly advised to receive the available appropriate vaccinations at the earliest opportunity. The implementation of universal vaccination against hepatitis B during infancy in many developing countries has dramatically reduced the chronic carrier rates and brought about a decline in the incidence of hepatocellular carcinoma among children, making this the first human cancer to be prevented by vaccination. Because of the high mutation rate of hepatitis C, an effective vaccine does not currently exist for this disease.

Further reading

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IN A NUTSHELL

There are five clinically important hepatotropic viruses, hepatitis A - E.

Hepatitis A and E are spread by the faecal-oral route.

Hepatitis B, C and D are blood-borne.

Their clinical manifestations are protean.

Fatigue is a common symptom of chronic viral hepatitis.

Specific diagnosis depends on serological and molecular testing.

Chronic viral hepatitis is a serious illness which can lead to cirrhosis and liver cancer.

Effective antiviral therapy exists for chronic hepatitis B and C.

Effective vaccines are available for hepatitis A and B.

SINGLE SUTURE TURBOCHARGED HEART

A New Zealand man is the first patient to be fitted with a device designed to 'turbocharge' a failing heart without massively increasing the risk of blood clots and other major complications associated with current artificial heart pumps. The device, called a C-Pulse, comprises an inflatable polyurethane balloon pressed against the aorta, kept in place by a polyester wrap that is stitched around the vessel. These together form a cuff that follows the contours of the aorta. The balloon reinforces the pumping action of a weakened heart. Surgically implanted leads on the surface of the heart monitor its activity and transmit data back to a processor carried by the patient in a pack. The device is powered by a battery and can also be plugged into the mains when the patient is not moving about. The device is not yet proven, but the surgical team in Auckland have approval to operate on 5 more patients with moderate heart failure as part of a pilot study.

Reported in *New Scientist*, 21 May 2005: 27.