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.
**Table I: Virological and clinical characteristics of hepatotropic viral infections**

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

* 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.

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 angiomata 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.

**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 pleomorphism 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, nonspecific, 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 amino- transaminase 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 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

**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 measures 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 transcriptase 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 Figure 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

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**Figure 1: Algorithm outlining therapeutic approach to chronic hepatitis B**

- Persistence of HBsAg beyond 6 months or anti-HBc IgM -ve
  - Test HBeAg, ALT, HBVDNA by quantitative PCR
    - Normal ALT HBeAg -ve HBVDNA <10⁵ copies/ml
    - Raised ALT HBeAg +ve HBVDNA >10⁵/ml
  - Asymptomatic carrier... No treatment necessary
    - INF alfa 2a or 2b for 16 to 24 weeks of pegylated IFN
    - Sustained response Normal ALT HBeAg -ve HBVDNA -ve
  - Liver biopsy
    - INF failed or contraindicated
    - IFN failed or contraindicated
    - Sustained response HBeAg -ve HBVDNA -ve
  - Laminudine x 1 year
    - No treatment but monitor
    - Partial response or relapse
    - Chronic lamivudine therapy or adefovir in lamivudine-resistant HBV
  - Normal ALT HBeAg +ve HBVDNA >10⁵/ml
  - Raised ALT HBeAg +ve HBVDNA >10⁵/ml

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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.

**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 bloodborne. 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.

**Further reading**

- Conjeevaram HS, Lok ASF. Management of chronic hepatitis B. J Hepatol 2003; 38(suppl.):S90-S103.