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Viral hepatitis an A, B, C guide

Viral hepatitis is a common cause of liver disease in Australia with a spectrum of clinical manifestations. Although an acute illness with jaundice may mark infection, often viral hepatitis remains silent until the complications of cirrhosis or liver cancer arise.

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Viral hepatitis is a major cause of both acute and chronic liver disease in Australia. Acute viral hepatitis can be caused by infection with hepatitis A virus (HAV), B virus (HBV; Figure 1), C virus (HCV), D virus (HDV; in association with HBV) or, occasionally, E virus (HEV) in returned travellers. Chronic infection with HBV or HCV can result in substantial morbidity and mortality. In 2005, hepatitis B and C were the underlying causes of liver disease in 10% and in 37%, respectively, of patients undergoing liver transplantation in Australia.[1]

Chronic hepatitis B and C remain very prevalent in Australia. Currently, an estimated 197,000 people have chronic hepatitis C and between 90,000 and 160,000 have chronic hepatitis B.[1,2]

Patients may present to GPs at any stage of infection – for example, they may present with an acute, self-limiting, icteric infection; they may be asymptomatic and diagnosed incidentally; or they may present with end stage liver disease. Accurate diagnosis and appropriate management of patients in the primary care setting are vital steps in dealing with the large disease burden of viral hepatitis.

The following two cases of hepatitis, an acute and a chronic presentation, illustrate some of the diagnostic and management issues that are relevant for GPs.

Acute hepatitis

Case 1. Acute hepatitis in a young man

Ben, a 22-year-old man who had returned from Cambodia one week previously, presented with a few days of lethargy, malaise and jaundice. During his six-month holiday backpacking in South East Asia, he had drunk only bottled water but eaten mainly from street stalls. He had also engaged in unprotected sex on one occasion as well as intravenous drug use and binge drinking on numerous occasions. He had overlooked vaccinations for viral hepatitis before his departure.

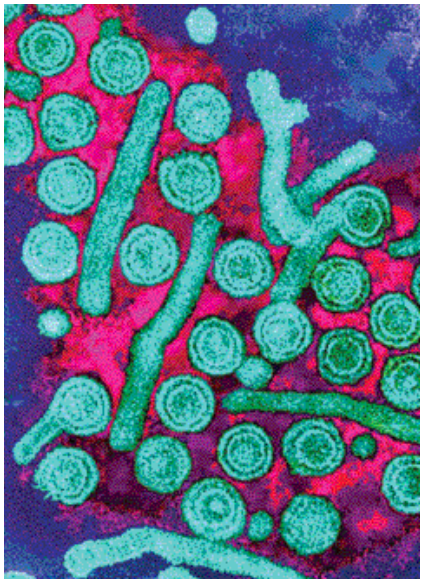
On examination, he was jaundiced and mildly unwell. He had mild tender hepatomegaly but no stigmata of chronic liver disease, splenomegaly, ascites or oedema.

Differential diagnosis

Ben is likely to have acute hepatitis. He has risk factors for both the enterally transmitted HAV and HEV, as well as for HBV and HCV, which are parenterally transmitted through sexual contact

IN SUMMARY

- **Acute hepatitis is usually self-limiting in patients with hepatitis A and in adults with hepatitis B but progresses to chronic infection in those with hepatitis C and children with hepatitis B.**
- **Screening of patients in risk groups or those with abnormal liver function tests will help diagnose chronic cases of viral hepatitis.**
- **Provision of simple patient advice on prevention of transmission of the hepatitis viruses and implementation of vaccinations required are key roles of the GP.**
- **Treatment efficacies have improved and treatment indications widened, thus ensuring more patients have access to therapy is a priority.**



PHOTOLIBRARY

Figure 1. Coloured transmission electron micrograph of hepatitis B viruses.

(HBV) or intravenous drug use (HBV and HCV).

Other possible diagnoses include drug-induced hepatitis, thus medications taken, including alternative medicines and paracetamol in overdosage, should be noted. Infections with other viruses, such as Epstein Barr virus, cytomegalovirus, adenovirus and parvovirus, may also cause hepatitis, and serology can help identify these viral infections.

Clinical features

Clinical features of acute viral hepatitis may include a prodrome of lethargy, anorexia, and nausea. During icteric periods, the liver is often enlarged and tender. Jaundice is seen in about 50% of cases of acute hepatitis B but is less common in hepatitis A. Acute hepatitis C is often subclinical.

Fulminant hepatitis (massive hepatic necrosis) is a rare complication of acute viral hepatitis and has a high mortality. Early referral of patients with fulminant hepatitis is essential. Ominous signs are listed in Table 1. Clinicians should not be reassured by a falling alanine aminotransferase (ALT) level in the presence of any of the listed features. Particular risk factors for developing fulminant hepatitis include:

- hepatitis A in patients with chronic liver disease or in older adults
- hepatitis E in pregnant women
- cases in which HDV coinfects acutely with HBV or superinfects a chronic HBV carrier.

Table 1. Signs of fulminant hepatitis

Clinical signs
Encephalopathy (confusion, disorientation, somnolence)
Ascites, oedema
Worsening jaundice
Laboratory investigations
Rapidly rising bilirubin
Markedly prolonged prothrombin time
Rapidly shrinking liver size
Hypoglycaemia
Low serum albumin

Investigations

Laboratory investigations are the key to diagnosis in the patient with acute viral hepatitis. Investigations should include liver function tests (LFTs), which will show a predominant elevation of ALT and aspartate aminotransferase (AST). Peak ALTs in patients with acute hepatitis may range from 400 to 4000 U/L (normal range <34 U/L), or more. The degree of the rise does not necessarily reflect the degree of liver damage. Bilirubin is also usually elevated in acute viral hepatitis, although clinical jaundice may not be seen. INR will be raised in patients with severe attacks.

Acute viral hepatitis can be diagnosed by serology. The tests that should be requested are IgM antibody to HAV (HAV IgM), hepatitis B surface antigen (HBsAg), and HCV antibody (HCV Ab).

Case continued

Blood tests were requested for Ben, including LFTs. His ALT was 1400 U/L, bilirubin 162 μmol/L (<20 μmol/L) and INR 1.6 (0.8 to 1.2). Serology was negative for HAV IgM and HCV Ab but positive for HBsAg.

Diagnosis

Hepatitis B

Ben's diagnosis is acute HBV infection, with the likely route of transmission being sexual or through intravenous drug use. HBsAg is the first virological marker detectable in the serum following infection with HBV (see Table 2). Typically in adults this antigen is lost one to two months after the onset of jaundice and is replaced several weeks later by hepatitis B surface antibody (HBsAb), which signifies immunity.

If a patient presents in the period between HBsAg and HBsAb positivity, the presence of hepatitis B core antibody IgM (HBc IgM) will enable a diagnosis of hepatitis B to be made. HBc IgM is not, however, specific for acute infection with HBV as it is raised in 10 to 20% of cases of flares of chronic hepatitis.

If the patient in the above scenario had been of South East Asian, African or Mediterranean background, he may have had hepatitis B since childhood, with the current episode representing an exacerbation rather than a new infection. To ensure there is no doubt about the question of chronicity, in such cases it is important to document the disappearance of HBsAg after recovery from the episode of hepatitis.

Hepatitis A

Hepatitis A outbreaks in Australia have been linked most often to the consumption of uncooked shellfish, especially oysters. HAV IgM becomes detectable during acute illness and persists for several months before falling. During this time, HAV IgG rises, conferring immunity.

Table 2. Features of the different types of viral hepatitis

Virus	Incubation period (mean)	Transmission	Serology in acute infection	Progression to chronicity
Hepatitis A virus	4 weeks	Faecal–oral	HAV IgM	None
Hepatitis B virus	4–12 weeks	Percutaneous, sexual or perinatal	HBsAg, HBc IgM	Adults <5% Infants 90%
Hepatitis C virus	7 weeks	Percutaneous	HCV Ab plus HCV RNA	70%
Hepatitis D virus	4–12 weeks	Percutaneous, sexual	HDV IgM	Common; as for HBV
Hepatitis E virus	5–6 weeks	Faecal–oral	HEV IgM	None

Hepatitis C

Antibodies to HCV are usually detectable during acute hepatitis C infection (within seven to eight weeks of exposure). HCV RNA is present in the serum within one to two weeks of infection (Table 2).

Hepatitis D

HDV is a defective RNA virus that replicates only in the presence of HBV. Antibody to HDV is used to diagnose hepatitis D and is of the IgM class in acute infection and both IgM and IgG class in chronic infection.

Hepatitis E

HEV is an enterically transmitted virus that occurs mainly in India, Asia, Africa and Central America and causes an acute hepatitis, especially in young adults. IgM to HEV is the marker of acute hepatitis E and, although serological testing for HEV is not routinely available, it can be performed at special reference laboratories if patients have a relevant travel history.

Clinical course and management

Hepatitis B

In the immunocompetent adult, acute hepatitis B is a self-limiting illness. Resolution of the infection with subsequent immunity to hepatitis B is the norm. This contrasts with infection in infancy or childhood, where chronicity results in most cases. For adults with acute hepatitis B, no specific therapy is required but patients must be counselled to prevent HBV transmission (see the box on this page).

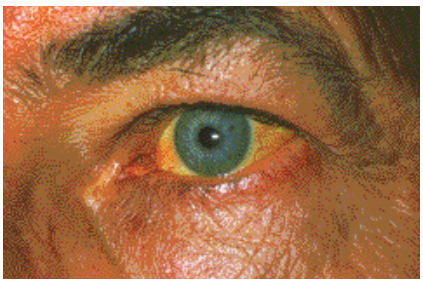
Hepatitis A

Patients with hepatitis A can usually be managed as outpatients with supportive treatment. Patient education on hygienic precautions, especially hand washing, is vital to prevent spread. Infectivity reduces soon after jaundice appears (Figure 2). The risk of transmission to contacts can be reduced by immunoglobulin given intramuscularly within two weeks of exposure.[3] Immunoglobulin is recommended for:

- household and sexual contacts of patients with hepatitis A
- staff and children at a childcare centre or preschool when there are two or more cases occurring in different households associated with that centre
- food handlers in same establishment if the affected patient is a food handler.

Preventing HBV and HCV transmission: advice for patients

- Do not donate blood, organs or any body tissue.
- Do not share items of personal hygiene such as razors and toothbrushes.
- Wipe up blood spills with concentrated household bleach.
- Cover all cuts and wounds with adequate dressings.
- Do not share needles or any other injecting drug equipment.
- For casual sexual contacts, practise safe sex. This means using condoms for all intercourse and avoiding trauma or blood contact.
- Consider informing health care providers of your condition when undergoing any medical or dental procedure, although there is no legal obligation to do so.
- If you have hepatitis B, advise your regular sexual partners and household contacts, including children, to have hepatitis B vaccination.



PHOTOLIBRARY

Figure 2. Jaundiced eye of a 61-year-old man with hepatitis A. Jaundice is less common in patients with acute hepatitis A than in those with acute hepatitis B. In patients with hepatitis A, infectivity reduces soon after jaundice appears.

continued

Hepatitis C

Hepatitis C, if detected acutely, may be treated with interferon and ribavirin; treatment has a high chance of preventing chronicity (up to 98%). Thus, when acute hepatitis C is recognised, referral of treatment candidates is advisable.

Patients with any type of acute viral hepatitis should be followed regularly until LFTs normalise or they should be referred if the infection does not resolve or any worrying signs, particularly a rise in INR, develop. The flowchart on this page summarises the management of patients with acute hepatitis.

Vaccination

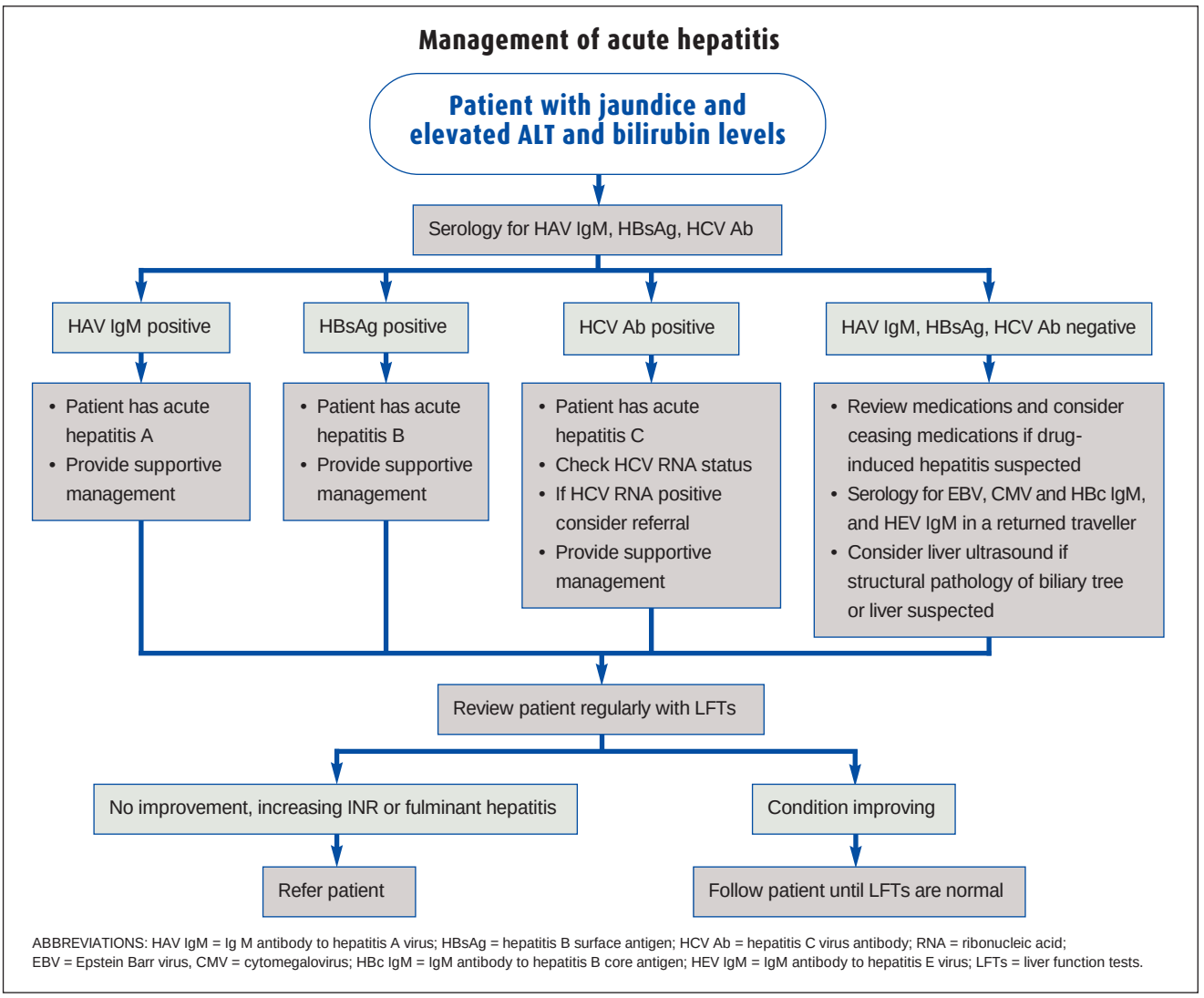
Hepatitis B

Hepatitis B vaccination was introduced to the Australian Childhood Immunisation Schedule in 2000, and adults in certain risk groups should also receive the vaccine (Engerix-B, H-B-Vax II). These groups include injecting drug users, people with many sexual partners, men who have sex with men and people with chronic liver disease and hepatitis C.

The duration of protection afforded by hepatitis B vaccination is unknown, but booster doses are not routinely recommended (except in certain situations – e.g. immunocompromised individuals with HIV or renal failure) even when HBsAb becomes undetectable, since memory in immunity is thought to protect against clinical hepatitis B.

Hepatitis A

For travellers to areas where hepatitis A is endemic, a regimen of two doses of hepatitis A vaccine (Avaxim, Havrix, VAQTA Hepatitis A Vaccine) given six to 12 months apart confers immunity for up to 10 to 20 years, whereas one dose provides cover for 12 months and is effective within two weeks. Vaccination is



ABBREVIATIONS: HAV IgM = Ig M antibody to hepatitis A virus; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; RNA = ribonucleic acid; EBV = Epstein Barr virus, CMV = cytomegalovirus; HBc IgM = IgM antibody to hepatitis B core antigen; HEV IgM = IgM antibody to hepatitis E virus; LFTs = liver function tests.

strongly preferred to immunoglobulin for hepatitis A prophylaxis in travellers.

Free hepatitis A vaccination was introduced in November 2005 for indigenous children aged under 5 years living in Queensland, the Northern Territory, South Australia and Western Australia. This followed the deaths of six indigenous children due to hepatitis A in the 1990s. Hepatitis A is endemic in many remote parts of Australia.

Hepatitis E and C

A new hepatitis E vaccine has been shown to be effective in a recent trial. Although prospects for a hepatitis C vaccine are brighter now than a decade ago, an effective vaccine remains some years away.

Chronic hepatitis

Case 2. Chronic hepatitis in a man of Mediterranean background

Luigi, a 56-year-old man of Italian origin, presented for a general check up. His past history included mild hypertension, for which he has been taking an ACE inhibitor. He is a nonsmoker and drinks two to three glasses of red wine a day.

On examination he had three small spider naevi and palmar erythema but no hepatosplenomegaly. His weight was 79 kg and his BMI 30 kg/m^2 (obese).

His blood tests showed a haemoglobin of 145 g/L and white cell count of 7.2 x 10^9/L but mildly reduced platelets (135 x 10^9/L). His LFTs showed an ALT of 60 U/L (normal range <34 U/L), but otherwise they were normal. Iron studies showed his serum iron to be 4 µmol/L (9 to 30 µmol/L), ferritin 680 µg/L (15 to 200 µg/L) and transferrin saturation 60% (20 to 50%). His fasting blood glucose was 5.2 mmol/L and total cholesterol 6.2 mmol/L.

Differential diagnosis

Luigi's elevated ALT is indicative of hepatic inflammation. This may be due to chronic viral hepatitis B or C. HBsAg and HCV Ab testing are indicated after appropriate counselling. Nonalcoholic steatohepatitis (NASH) may also be a possibility given Luigi's risk factors for metabolic syndrome (obesity, hypertension and hyperlipidaemia). His level of alcohol intake may be potentiating the liver injury due to chronic viral hepatitis. A moderately elevated ferritin and transferrin saturation can occur with any form of chronic hepatitis; however, haemochromatosis can be further evaluated with genetic testing. Autoimmune hepatitis (uncommon in men) and other more rare causes of liver disease, such as Wilson's disease and alpha-1 antitrypsin deficiency, can also be excluded with simple blood tests.

Luigi's peripheral stigmata of liver disease suggest chronic hepatitis (which is defined as inflammation persisting for more than six months) and advanced fibrotic liver disease. His mild thrombocytopenia is a worrying feature that may be an indicator of cirrhosis and portal hypertension.

Case continued

Further testing revealed that Luigi was HCV Ab positive but HBsAg negative. The rest of the liver screen was negative.

Investigations for hepatitis C

A hepatitis C RNA test (by polymerase chain reaction) is the next test that needs to be performed and will most likely be positive confirming ongoing infection. A negative RNA test means that there is no current infection and the HCV Ab is indicative of previous exposure to the virus. Importantly, a positive antibody test does not signify immunity to hepatitis C.

In Luigi's case, an ultrasound may also be useful to look for evidence of cirrhosis (for example, a coarse and nodular liver) and portal hypertension (splenomegaly, reversal of flow in the portal vein and recanalisation of the umbilical vein).

Epidemiology of hepatitis C

In Australia, almost 90% of newly acquired cases of hepatitis C are attributable to the sharing of contaminated equipment in the setting of intravenous drug use. Blood transfusion before 1990, body piercing, tattooing and incarceration are also risk factors for hepatitis C. In people of ethnic backgrounds (especially Asian and Mediterranean), injection therapies, vaccination programs and traditional medicine practices using inadequately sterilised equipment are often responsible for the transmission (as in the case of Luigi).

The risk of sexual transmission is thought to be low, and for people in stable monogamous relationships, barrier contraceptive methods are not considered necessary. Mother to baby transmission is also low, in the order of 4% (unless the mother is coinfected with HIV), and hepatitis C positivity does not preclude breastfeeding.

Clinical features and natural history of hepatitis C

Clinically, hepatitis C is usually asymptomatic; however, some patients may report tiredness, vague right upper quadrant pain and poor concentration. About 70% of patients who are exposed to HCV will become chronically infected; however, of these, only 5 to 20% will develop cirrhosis over a 20-year period. The likelihood of cirrhosis increases with the duration of infection.

Other liver toxins (especially alcohol), NASH, hepatitis B and iron overload may all accelerate disease progression. Hepatocellular carcinoma (HCC) in patients with hepatitis C develops only in the setting of advanced fibrosis or cirrhosis, at a rate of 1 to 4% per year.

Treatment of chronic hepatitis C

The combination of peginterferon plus ribavirin (Pegasys RBV Combination Therapy, Pegatron Combination Therapy) is now the standard treatment for hepatitis C. Peginterferon has immunomodulatory and antiviral effects that mimic the actions of the body's naturally occurring interferons. A polyethylene glycol chain (PEG)

Hepatitis C and B: suggestions for rural GPs

- Hepatitis C occurs often in young injecting drug user groups in rural Australia.
- Referral of patients with hepatitis C or B for an assessment to a liver clinic may be advisable because ensuring confidentiality and time for counselling are often difficult in busy practices in small country towns. Subsequently, shared care may be possible.
- In the obstetric care of HBV-positive mothers, immediate vaccination and administration of hepatitis B immunoglobulin to the infant are critical.
- In the obstetric care of HCV-positive mothers, routine caesarean section does not need to be performed, and the infection does not preclude breastfeeding.

prolongs the drug's half-life, allowing once weekly dosing and less fluctuation in serum levels. Ribavirin is a synthetic nucleoside analogue.

The chances of a sustained virological response (SVR), which is defined as a negative HCV RNA six months after cessation of therapy, are dependant mostly on the HCV genotype. Viral load and the degree of fibrosis are also factors. Patients infected with HCV genotype 1 require 48 weeks of treatment and have SVR rates of about 40 to 50%. Those infected with HCV genotypes 2 and 3 respond much better, with SVR rates of about 70 to 80% after only 24 weeks of treatment. Patients with cirrhosis are less likely to respond to treatment.

Treatment is an intensive undertaking. Potential side effects of interferon include low blood counts, tiredness and emotional lability (and less often depression). Hair loss, rashes, weight loss and autoimmune thyroid disease may also occur. Ribavirin has teratogenic potential, thus avoidance of pregnancy in both female patients and female partners of men taking ribavirin is critical during treatment and for six months afterwards.

Due to the rigours of treatment and the need for nurse educators and other support services (for example, psychiatric services), patients with hepatitis C are most often treated at hospital liver clinics. Currently, only a small proportion of patients with hepatitis C access treatment (roughly 2000 patients per year). This is despite the recent widening of eligibility criteria for peginterferon plus ribavirin treatment to include patients with normal LFTs and the removal of liver biopsy as a prerequisite in April 2006. Liver biopsy may still be performed, however, as the decision to start treatment depends on several factors, including histology.

Good links between GPs and liver clinics and referral of all patients diagnosed with hepatitis C for at least an assessment will probably remain key factors in trying to increase the numbers of patients treated. Adherence to treatment enhances the chance of a SVR. GPs can play an important part in supporting patients taking treatment and optimising their adherence. Shared care with interested GPs is likely to become increasingly important, especially for rural patients (see the box above).

Treatment of chronic hepatitis B

Treatment options for patients with chronic hepatitis B have expanded recently, with new drugs (including lamivudine [Zeffix], adefovir [Hepsera], peginterferon [Pegasys] and entecavir [Baraclude]) being licensed in Australia. It is appropriate to refer any patient who is HBsAg positive with an abnormal ALT and/or signs of chronic liver disease to a specialist as the evaluation of chronic hepatitis B can be complex. Chronic hepatitis B will be the subject of a forthcoming article in *Medicine Today*.

The flowchart on page 56 summarises the management of patients with chronic hepatitis.

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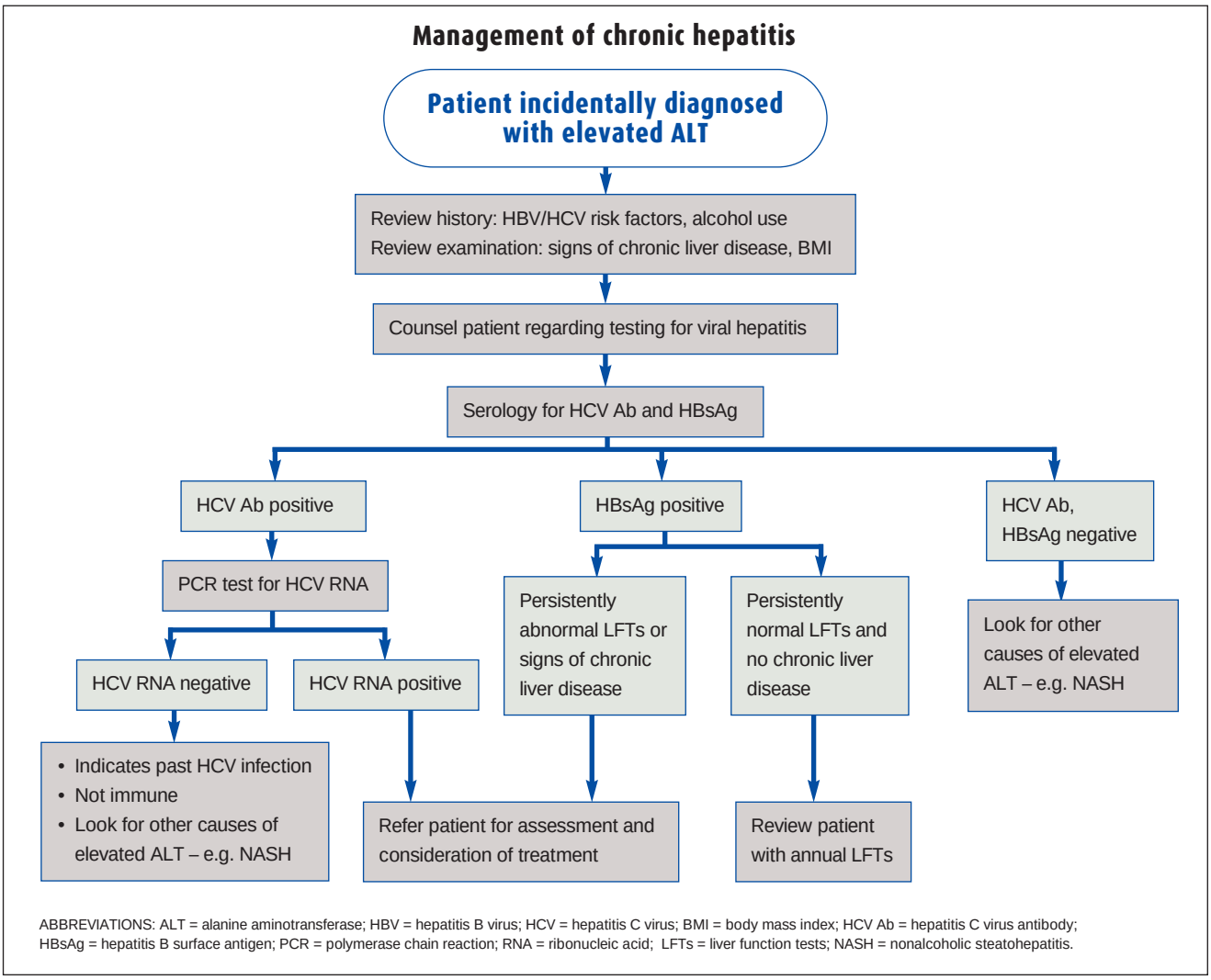

ABBREVIATIONS: ALT = alanine aminotransferase; HBV = hepatitis B virus; HCV = hepatitis C virus; BMI = body mass index; HCV Ab = hepatitis C virus antibody; HBsAg = hepatitis B surface antigen; PCR = polymerase chain reaction; RNA = ribonucleic acid; LFTs = liver function tests; NASH = nonalcoholic steatohepatitis.

Conclusion

Viral hepatitis is common in our community. In general practice, it may be seen in symptomatic, jaundiced patients, but more often it may be diagnosed only by screening patients with abnormal LFTs or who have risk factors for the disease.

GPs have a key role in preventing transmission of viral hepatitis through patient education and vaccination programs. Efficacy of therapies has improved, and referral of patients to enable access to these treatments is vital. MT

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DECLARATION OF INTEREST. Associate Professor Desmond has served on advisory boards for Roche, Gilead, Schering-Plough and Bristol-Myers Squibb. Dr Croagh has no potential conflict of interest.