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# Hepatitis A to E: what's new?

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## Abstract

Viral hepatitis contributes to significant morbidity and mortality worldwide. While acute infection may be self-limiting, unrecognised chronic infection and under-utilisation of guideline-based approaches to therapy contribute to increasing rates of cirrhosis, hepatocellular carcinoma and death. Our aim was to review the current evidence for screening, diagnosis and treatment in hepatitis A to E. Evidence for this review was sourced from international and Australian guidelines and high-quality clinical trials. MEDLINE was searched using structured key word strategy and retrieved articles were reviewed methodically to inform a brief and up-to-date synopsis of hepatitis A to E. We share some of the recent developments in viral hepatitis, specifically the new therapies for hepatitis C. Direct-acting antiviral therapies are safe, well-tolerated and effective. Subsidies allow access for all Australians with most strains of hepatitis C. We outline evidence underpinning efficacy and safety of treatment for hepatitis B, while clarifying some of the nuances in the setting of pregnancy and immunosuppression. We provide a simplified concept to facilitate understanding of the five phases of hepatitis B; practical for real-world setting. Hepatitis A to E is a broad topic, not all aspects of these viruses can be covered in this short review. We provided suggestions for evidence based guidelines, which are a suitable supplement to this article.

## Introduction

Viral hepatitis causes significant morbidity and mortality worldwide. While often self-limiting, it can lead to chronic infection, cirrhosis, hepatocellular carcinoma (HCC) and death. The aim of this is review, is to provide a simple and up-to-date synopsis of hepatitis A to E. Understanding of pathogenesis, impact and therapeutics has all changed appreciably in the past few years. Changes have occurred specifically with (i) direct-acting antiviral (DAA) therapy for the treatment and cure of hepatitis C, (ii) evaluation and diagnoses of cirrhosis, and (iii) evaluation and treatment of hepatitis B in special settings, like pregnancy and immunosuppression. It is time for a refresher. This review focuses on the key features for each virus that a general physician should be familiar with.

## Hepatitis A

Hepatovirus A is a non-enveloped picornavirus, containing a single-stranded RNA packaged in a protein shell. There is only one serotype of the virus, but multiple genotypes exist. Infection with hepatitis A virus (HAV) causes acute viral hepatitis, although rarely leads to chronic hepatitis.[1] The prevalence of HAV varies greatly throughout the world with high prevalence in developing countries and low in developed countries. Hepatitis A infection usually results from exposure to contaminated food or water. Infection may be transmitted horizontally, from person to person, although occasionally community outbreaks are reported. A recent hepatitis A outbreak in Australia was reported in 18 patients due to exposure to contaminated frozen berries. These products were successfully recalled and no deaths were reported.[2] Due to improvements in both hygiene and sanitation over the last decade, most countries are moving towards a lower prevalence of hepatitis A. In Australia, there are approximately 300–500 cases of hepatitis A reported every year. These cases occur mostly in returned travellers, who have not been vaccinated.[3]

Vaccination or previous exposure to hepatitis A gives long-term immunity. Post-exposure prophylaxis with immunoglobulin may be indicated when exposure was less than 14 days prior. Vaccine may also be effective. The time from exposure to clinical manifestations is approximately 30 days (range 15–50). Symptoms may be non-specific and include jaundice, anorexia, nausea,

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vomiting, abdominal pain and mild fever. Diagnosis is confirmed by identifying anti-HAV immunoglobulin class M (IgM) antibody, detectable 2 weeks after exposure and persisting for up to 14 weeks. The presence of IgG antibodies confirms lifelong immunity from the virus. Jaundice recovers after an average of 6 weeks (range 1–10 weeks).[4,5]

Rarely, acute liver failure (characterised by jaundice, hepatic encephalopathy and coagulopathy) can result from acute hepatitis A infection. Patients with unrelated liver disease are at increased risk of developing acute liver failure from HAV and as such vaccination should be considered in these patients.[4] A relapsing form of acute hepatitis with subsequent peaks of aminotransferase elevation is described in about 10% of patients with hepatitis A.[5] A cholestatic form of hepatitis A with prolonged pruritus is also described.

## Hepatitis B

Hepatitis B virus (HBV) infection is highly prevalent and responsible for significant rates of morbidity and mortality from liver cancer and liver cirrhosis, in untreated chronically infected individuals. There are estimated 240 million people infected worldwide. The prevalence of chronic hepatitis B (CHB) in Australia is estimated to have increased by more than 50 000 people in the past decade, affecting approximately 1% of the population. This is largely the result of infection in those migrating from high-prevalence countries. Most chronic infection is attributable to mother to child transmission in the absence of accessible infant vaccination programmes.

### Screening strategies

Studies in Australia and the United States demonstrate between 30 and 65% of chronically infected adults are unaware they are infected until they were screened. Thus, it is paramount that healthcare providers routinely screen for infection in at risk groups. Screening should include those from hepatitis B endemic countries, renal dialysis patients, patients in correctional facilities, patients who have had household contact or sexual contact and those with other blood-borne viruses. Screening in pregnancy is mandatory to allow appropriate immune prophylaxis and consideration of anti-partum antiviral therapy for the mother, to interrupt the high risk of mother to child transmission (see Pregnancy section below for further information). Patients undergoing chemotherapy or other immunosuppressive treatment are at significant risk of reactivation with serious consequences. These patients should be screened.[6–8] Screening is by testing for hepatitis B surface antigen (HBsAg). Further serological testing will distinguish newly acquired or chronic infection (see Table 1). Virology (HBV DNA) and general laboratory (liver function tests (LFT), full blood count (FBC), coagulation) testing allows further characterisation of the phase and consequences of chronic infection.

**Table 1** Interpreting hepatitis B serology

| | HBsAg | Anti-HBc | Anti-HBs |
|---|---|---|---|
| Acute hepatitis B | Positive | IgM positive | Negative |
| Chronic hepatitis B (≥6 months) | Positive | IgG positive | Negative |
| Resolved hepatitis B† | Negative | IgG positive | Positive |
| Vaccinated | Negative | Negative | Positive |
| Susceptible | Negative | Negative | Negative |

†May be at risk of reactivation after intense immunosuppression.

### Phase of infection: immune–virus interactions

The HBV itself is not directly hepatotoxic, despite high viral levels in liver and blood. The clinical outcome is determined by the immunological response. The immune response is minimal in exposed infants after birth with correspondingly few symptoms and minimal biochemical hepatitis. Clearance of infection is rare and chronic hepatitis develops in greater than 90% of those infected at this time. In contrast, exposure to infection, later in life results in symptoms and biochemical hepatitis due to an effective immune response. Clearance usually occurs and chronic infection develops in less than 5% of cases.[5,9]

### Chronic hepatitis B

CHB (HBsAg > 6 months) is a lifelong infection. At any time point, the phase of infection should be characterised, as well as the degree of accumulated liver injury. The five phases of HBV infection are defined according to (although somewhat controversial) pathogenic mechanisms. Patients and clinicians find this terminology hard to understand and remember. In our large volume clinic, we have developed simpler, patient friendly terminology (Table 2).

### Treatment

There are currently two classes of drugs approved for the treatment of HBV infection: (i) direct antiviral agents, nucleos(t)ide analogues (NA), entecavir and tenofovir disoproxil fumarate (TDF); and (ii) pegylated interferon (PEG-IFN). PEG-IFN acts as an immunomodulator, with some weak direct antiviral activity. PEG-IFN has significant side effects, including flu-like symptoms, headache,

**Table 2** Simple information for patients about the phases of hepatitis B

| Phase: (traditional name) | 1: Silent (immune tolerant) | 2: Damage (immune clearance) | 3: Control (immune control) | 4: Escape (immune escape) | 5: Clear (resolved) |
|---|---|---|---|---|---|
| What happens in this phase? | Your liver is not being damaged | The body is trying to clear the infection<br>The liver is being damaged in the fight | Liver damage stops but there may be damage from previous phases | Liver damage is occurring | Infection is gone, liver damage does not occur<br>There may be damage from previous phases |
| What should you do? | Your family doctor should monitor liver tests every 6 months<br>No treatment required | Review by a specialist may be required<br>You may require treatment | Monitor liver tests every 6–12 months<br>Review to identify liver damage from previous phases<br>Regular ultrasounds monitoring for liver cancer might be required | Is there any other reason your liver tests are abnormal?<br>You need review by a specialist to plan best action<br>You might need some treatment | The infection is gone and should not return<br>Regular ultrasound to screen for liver cancer, especially if there is liver damage from previous phases |
| What do your blood tests show? | Liver function tests (ALT) are normal<br>Levels of virus are high (HBV DNA >20 000 IU/mL)<br>Hepatitis B sAg and eAg is positive | Liver function tests (ALT) become abnormal<br>Levels of virus are high (HBV DNA >20 000 IU/mL)<br>Hepatitis B sAg and eAg is positive | Liver function tests return to normal (ALT)<br>Levels of virus come under control (HBV DNA < 2000 IU/mL)<br>Hepatitis B eAg is negative/eAb positive | Liver function tests (ALT) become abnormal<br>Levels of virus rise again (HBV DNA > 2000 IU/mL)<br>Hepatitis B eAg is negative/eAb positive | Liver function tests are normal<br>Virus is undetectable<br>Hepatitis B eAg is negative/eAb positive<br>Hepatitis B sAg is negative/sAb positive |

ALT, alanine aminotransferase.

fatigue, poor appetite, exacerbation of depression and other psychiatric disorders. Furthermore, it does not have a clear therapeutic advantage, so it remains a less popular alternative.[10] Some evidence suggests that HBsAg seroconversion is more likely with PEG-IFN therapy, when compared with NA although a paucity of controlled trials, using matched populations convincingly demonstrate this.[11–13] Combination PEG-IFN and NA therapy has recently been shown in a controlled trial to increase the chance of HBsAg clearance from 2.8 to 9%, although these data are encouraging, it is a small difference, not reproduced in other similar studies, and has yet to influence clinical practice greatly.[14]

The safety and durable potency of long-term NA therapy is well described, without appreciable emergence of viral resistance. Monitoring for toxicity is required, as nephrotoxicity and osteoporosis, although uncommon, may occur. A recent, real-world study using 53 500 subjects showed that NA do not increase the risk of renal and bone events, if appropriate toxicity monitoring and dose adjustments are made.[15] A new prodrug formulation tenofovir alafenamide has been shown to have improved renal and bone safety parameters, resulting from targeted hepatocyte exposure with lower systemic drug levels. The long-term clinical relevance and cost effectiveness of this improved safety profile has yet to be proven.[16]

While NA effectively suppress hepatitis B replication and reduce the risk of disease progression, they cannot clear the replication template of covalently closed circular DNA. HBsAg seroconversion rarely occurs. As a result, most patients require indefinite treatment.[17] The reservoir of DNA template that remains in the liver cell nucleus including covalently closed circular DNA and integrated DNA is not impacted by current therapies . There are several potential therapies for hepatitis B, based on the greater understanding of the hepatitis B life cycle. These therapies aim to achieve a more durable off therapy control or even cure. A target of the sodium/taurocholate co-transporting polypeptide receptor, which inhibits viral entry, Myrcludex B, is an example of such research entering clinical trial phase with some promising very early results.[18,19]

Decisions to commence therapy are based on the phase of infection, estimated accumulated liver injury and the risk of liver cancer. The primary goal of treatment is to improve patient survival by preventing or delaying the development of cirrhosis and HCC. Secondary goals include (i) HBV DNA suppression, (ii) biochemical and histological improvement and (iii) immunological control of the virus, particularly HbsAg loss and HBsAb development, although rarely achieved.[6,8] Thus, guidelines recommend that treatment should not be terminated until there is durable HBeAg seroconversion with minimum of

**Table 3** End point of hepatitis B therapy with nucleos(t)ide analogues

| Chronic hepatitis B treatment guidelines | *European Association of the Study of the Liver* EASL (2012)[9] | *American Association of the Study of Liver Diseases* AASLD (2016)[6] | *Asian Pacific Association of the Study of the Liver* APASL (Feb)[10] |
|---|---|---|---|
| HBeAg positive | Until HBeAg seroconversion followed by 12 months of consolidation | Until HBeAg seroconversion followed by 12 months of consolidation and undetectable DNA | Until HBeAg seroconversion followed by 12 months of consolidation + undetectable DNA |
| HBeAg negative | HBsAg clearance | HBsAg clearance† | Treatment for at least 2 years + DNA undetectable three times 6 months apart |

†Insufficient evidence to support stopping HBV therapy in this group of patients. Persons who stop antiviral therapy should be monitored every 3 months for at least 1 year for recurrent viraemia, ALT flares and clinical decompensation.

6 months consolidation or in patients who are HBeAG negative, HBsAg clearance[8–10] (Table 3).

Initiation of therapy in the damage (immune clearance) and escape (immune escape) phase to prevent injury or in patients with established liver cirrhosis to reverse injury is recommended. Treatment is not usually indicated in young patients during the silent (immune tolerant) phase, although viral levels are high, liver injury is not occurring. In addition to clinical parameters, patient's wishes, anticipated compliance and consideration of any contraindications to treatment are considered prior to commencing treatment.

## Special groups

### Hepatitis B infection and immunosuppressive therapy

As the immune system response to hepatitis B is critical for its control, it is not surprising that immunosuppressive therapy such as chemotherapy, biologic therapy or corticosteroids (high dose or greater than 4 weeks duration) result in increased viral replication. Subsequent immune reconstitution, occurring usually after the completion of chemotherapy may precipitate a powerful response to virus and severe liver injury. The risk of reactivation in HBsAg-positive patients undergoing chemotherapy is between 33 and 60%.[20] Reactivation can lead to liver failure, death or interrupt cancer treatment, increasing morbidity and mortality. Mortality (primarily related to liver failure) is between 5 and 50%. High baseline serum HBV DNA or high alanine aminotransferase (ALT) prior to commencing immunosuppressive therapy increases risk.[6,21] Universal HBsAg screening is critical prior to initiation of immunosuppressive therapy. Multiple studies have shown that pre-emptive antiviral therapy with NA will prevent complications and is proven superior to a response at the time reactivation occurs.[22] Antiviral therapy should be continued for between 6 and 12 months after completion of immunosuppressive therapy. Stopping antiviral therapy may not always be appropriate, such as when there is significant liver injury at baseline, a viral load > 2000 IU/mL or if repeated courses of immunosuppressive therapy are required.[5,8,10]

Intense immunosuppression, such as with haemopotetic stem cell transplantation, or B-cell ablation with agents such as rituximab, can result in reactivation of resolved HBV infection (anti-HBcAb positive). While less likely, overall this large at risk population will get into trouble if ignored, as fulminant hepatitis and hepatitis-related mortality can occur. For example, HBV reactivation occurred in 17 out of 150 lymphoma patients with resolved HBV infection treated with R-CHOP (rituximab, cyclophosphamide, doxirubicin, vincristine and prednisone).[20] Despite this evidence, universal HBV screening and initiation of treatment prior to immunosuppressive therapy is not routinely practised by all oncologists. A survey in 2011 showed that only 19% of oncologists practised universal screening.[23] Guidelines recently reported by American Gastroenterological Association for most settings of immunosuppression report risk of reactivation with each HBV and immunosuppressive scenario. Where the risk is low (1%), such as in those with resolved HBV infection and treatment with biologic antibiologic modifier therapies, the choice between monitoring and pre-emptive therapy is based on cost and patient preference.[24]

### Pregnancy

Mother to child (perinatal) transmission through exposure to blood or blood contaminated fluids at or around, the time of birth[25] is the most common mechanism for transmission of HBV worldwide. In Australia perinatal transmission despite immune-prophylaxis occurs in HBeAg-positive mothers (7%) and from mothers with high viral loads (HBV DNA ≥7 $\log_{10}$ IU/mL) approaching 10%.[26] The mode of delivery or breastfeeding is not relevant. Antepartum antiviral therapy when HBV DNA ≥6.5–7 $\log_{10}$ IU/mL (to allow room for minor laboratory

variation) commencing at 32 weeks of gestation reduces the risk of perinatal transmission effectively.[27] Tenofovir is safe and well tolerated, by mother and baby, with no increase in detectable congenital malformations or negative obstetric outcomes reported.[22,28] The threshold at which to introduce TDF has been a topic of some controversy in the literature, and some guidelines suggesting a lower threshold, such as 5 $\log_{10}$ IU/mL while acknowledging the data to support this is limited.[6,29] Risks and benefits of antiviral therapy should be discussed with mothers with a high viral load, prior to the third trimester.

The optimum management post-partum is uncertain. High rates of post-partum flares are reported.[30] Extended therapy post-partum beyond the indication of preventing mother to child transmission is not of proven benefit. At the present time, continuation to between 4 and 12 weeks post-partum is reasonable, unless another indication such as significant liver disease is present. The majority of post partum flares settle spontaneously within 6 months and extended therapy is not usually required in a large reported Australian cohort.[28]

## Hepatitis C

Chronic hepatitis C virus (HCV) infection affects approximately 230 000 Australians, who are at risk of progressive liver fibrosis leading to cirrhosis, liver failure and HCC. HCV infection is now curable, and viral eradication is associated with multiple clinical benefits, including improvement in quality of life, loss of infectivity, regression of cirrhosis, reduction of mortality, lower risk of liver failure and HCC. Until recently, the treatment of HCV involved interferon therapy, which had limited efficacy and was poorly tolerated. Since March 2016, DAA therapies have become available for any Australian with HCV. DAAs are highly effective and well tolerated.[31,32]

### Screening and diagnosis

Infection with hepatitis C is usually associated with identifiable risk factors, particularly history of intravenous drug use, non-sterile tattooing, blood transfusion before 1987 and immigrants from developing countries who may have been exposed to HCV during non-sterile procedures. In addition to screening at risk populations, the Centre for Disease Control and Prevention recommends universal screening in those born between 1945 and 1965.[33] This acknowledges that risk factors may not always be evident. HCV antibody is recommended for HCV screening, indicating current or past exposure. Current HCV infection is confirmed by a polymerase chain reaction assay for HCV RNA. A minority (25%) of acute HCV infections will clear spontaneously within 6 months. There are seven different HCV genotypes (genotypes 1–7). The common genotypes in Australia are genotypes 1 and 3. HCV genotyping is necessary prior to treatment initiation as approved regimens are genotype-specific.[32]

### Evaluating for the presence of cirrhosis

Identification of cirrhosis is important prior to treatment for two reasons: (i) treatment duration for some genotypes need be longer to achieve cure and (ii) those with cirrhosis continue to have a risk of hepatocellular cancer following successful eradication of the HCV, thus surveillance with regular ultrasounds is required.[34]

Liver biopsy was once the gold standard for the diagnoses of cirrhosis now rarely performed due to pain, risk of serious adverse consequences and non-invasive alternatives.[35] Transient elastography, or Fibroscan is a well-validated non-invasive tool to measure liver stiffness. Fibroscan is available in most metropolitan centres. A liver stiffness above 12.5 Kpa is a reliable threshold for identifying cirrhosis. The Fibroscan result, coupled with clinical examination, biochemical and radiological information are used synergistically to identify those with advanced fibrosis and cirrhosis. A reliable reading may be unachievable in 10% of patients, particularly those who are obese or with ascites.[36] Reasonably accurate identification of cirrhosis is also possible with formulas incorporating serum biomarkers, such as the validated APRI score (aspartate aminotransferase (AST) to platelet ratio index). A systematic review including 172 studies conducted in patients with hepatitis C reported a median Area under Receiver Operator Characteristic (AUROC) of 0.77 and 0.84 for the APRI score, when used to identify patients with cirrhosis.[37]

### Treatment

All patents with HCV (genotypes 1–4) should be considered for short-term (8–24 weeks) Pharmaceutical Benefits Scheme (PBS)-funded interferon-free DAA therapy. DAA agents target multiple steps in the HCV replication life cycle (Table 4). DAAs are highly effective and safe; they are used in combination to avoid resistance. The goal is cure proven by undetectable plasma HCV RNA at least 12 weeks after treatment is completed (sustained virological response). Previous treatment experience, presence of cirrhosis, genotype and renal failure (EGFR <30) all influence the choice and duration of treatment (Table 5). Zepatier (elbasvir/grazoprevir) is the most recently approved interferon-free regimen, also effective for genotype 1 but extending opportunity for those with genotype 4, and those with EGFR <30. PBS supported

treatment for the uncommon genotypes[5,6] continues to support PEG-IFN-alpha and ribavirin, although alternative pan-genomic DAA combination therapies are likely to be funded in the next few years. Gastroenterology Society of Australia Guidelines for the assessment and treatment of hepatitis C in the era of DAA therapy include recommended regimens and guide for assessment and monitoring (Table 5).

When prescribing hepatitis C therapy, potential drug interactions should be determined as some may cause adverse reactions, or altered efficacy of the medication or the DAA therapy. Internet-based resources such as University of Liverpool HEP drug interactions (http://www.hep-druginteractions.org) are useful.[38] Assessing and managing anything that may affect adherence is also critical (see Table 6: Checklist prior to commencing DAA therapy for hepatitis C). Primary care doctors may prescribe DAA therapy, after consulting a gastroenterologist or infectious diseases physician or if they have sufficient experience in hepatitis C treatment (PBS requirement). Monitoring after initiation of therapy with a DAA in a non-cirrhotic generally involves a blood test at week 4 of most DAA therapy (EUC, LFT and FBC) or week 8 if the patient is taking Zapatier (elbasvir/grazoprevir). Testing (HCV RNA, EUC, LFT, INR and FBC) 12 weeks after completing treatment to confirm complete eradication of the virus or sustained viral response is also important as some, although only a few, will fail and need a second-line therapy.

Hepatologists and infectious diseases specialists will not have capacity to eradicate hepatitis C without help from community general practitioners, drug health and sexual health doctors. Novel telementoring programmes, such as Project ECHO (Extension for Community Healthcare Outcomes) has been demonstrated to expand expertise and are being tested in pilot form in South West Sydney Local Health District. Project ECHO uses video conference supported group-based learning to share knowledge between specialists and community doctors. It was developed in New Mexico and since its inception, has been validated and replicated in many countries including Ireland, Uruguay and India.[39,40] Access to specialty knowledge for community doctors in rural or underserved areas may increase capacity by permitting patients with drug dependency and those from culturally or linguistically diverse communities to take up treatment with their local community or a drug health specialist. Building expertise will increase treatment numbers with the aim of eradication of HCV in Australia.

**Table 4** Direct-acting hepatitis C therapies according to sites of action

| Mechanism of action | Direct-acting anti-viral |
|---|---|
| NS3 protease inhibitor | Paritaprevir Grazoprevir |
| NS5B nucleotide inhibitor | Sofosbuvir |
| NS5B non-nucleotide inhibitor | Dasabuvir |
| NS5A inhibitor | Ledipasvir Ombitasvir Daclastavir Elbasvir |

## Hepatocellular carcinoma and chronic viral hepatitis

HCC is one of the leading causes of cancer deaths worldwide, with nearly 700 000 deaths attributed to HCC each year. Liver cancer is the fifth most common cancer in men and the eighth in women.[41,42] While the burden of HCC is highest in Asia and Africa, its incidence is rising in the developed world, in countries such as the United Kingdom, France, the United States and Australia.[42] The majority of HCC in both developed and developing countries is attributable to CHB and hepatitis C, although non-alcoholic steatohepatitis is an emerging significant aetiological factor and co-factor. Cirrhosis is present in 80–90% of patients with HCC, in the remainder hepatitis B is regarded as a direct carcinogen.[43] The 5-year cumulative risk for the development of HCC in patients with cirrhosis ranges between 5 and 30%, depending on the underlying aetiology (more common in HCV), region or ethnic group (more common in people from Asia) and stage of cirrhosis (highest risk in patients with decompensated disease).[43]

The risk of HCC in CHB infection is increased in patients who are male, elderly, have long duration of infection and have a family history of HCC.[44] National hepatitis B vaccination programmes have dramatically reduced the prevalence of hepatitis B infection, and the incidence of HCC. Since the inception of a universal vaccination programme in Taiwan, the incidence of HCC in children between 6 and 14 years of age has fallen by 65–75%.[45]

Screening utilising 6 monthly imaging by ultrasound has been recommended by the American Association of the Study of Liver Diseases (AASLD) (Table 7).[46] Testing for alpha-fetoprotein (AFP) tumour marker at the same time is not recommended because of issues with false-positive results in the setting of liver inflammation. In practice, AFP in conjunction with a liver ultrasound is still used in many hepatology practices. Surveillance for HCC is often underutilised in patients with cirrhosis. In a study of 1873 patients diagnosed with HCC above the age of 65, in whom cirrhosis was recorded for 3 or more years, only 29% had received routine surveillance and a further 33% received inconsistent surveillance.[47] Despite limited data from randomised clinical trials, early detection offers the best chance for curative treatment for patients with HCC, increasing the possibility for early curative treatment.[48–50]

**Table 5** Pharmaceutical Benefits Scheme-funded hepatitis C therapies in Australia

| Genotype/ subtype | Treatment naive | | Treatment experienced | |
|---|---|---|---|---|
| | No cirrhosis | With cirrhosis | No cirrhosis | With cirrhosis |
| 1a/b | Ledispasvir/sofosbuvir (12 weeks)† | Ledispasvir/sofosbuvir (12 weeks) | Ledispasvir/sofosbuvir (12 weeks) | Ledispasvir/sofosbuvir (24 weeks) |
| 1a/b | Daclastavir and sofosbuvir (12 weeks) | Daclastavir and Sofosbuvir (24 weeks) Or 12 weeks with ribavirin‡ | Daclastavir and sofosbuvir (12 or 24 weeks)§ | Daclastavir and Sofosbuvir (24 weeks) Or 12 weeks with ribavirin‡ |
| 1a¶ | Elbasvir/grazoprevir (12 weeks) | Elbasvir/grazoprevir (12 weeks) | Elbasvir/grazoprevir and ribavirin (16 weeks) | Elbasvir/grazoprevir and ribavirin (16 weeks) |
| 1b¶ | Elbasvir/grazoprevir (12 weeks) | Elbasvir/grazoprevir (12 weeks) | Elbasvir/grazoprevir (12 weeks) | Elbasvir/grazoprevir (12 weeks) |
| 1a | Paritaprevir-ritonavir, ombitasvir, dasabuvir and ribavirin (12 weeks) | Paritaprevir-ritonavir, ombitasvir, dasabuvir and ribavirin (12 weeks) | Paritaprevir-ritonavir, ombitasvir, dasabuvir and ribavirin (12 weeks) | Paritaprevir-ritonavir, ombitasvir, dasabuvir and ribavirin (12 or 24 weeks) |
| 1b | Paritaprevir-ritonavir, ombitasvir, dasabuvir (12 weeks) | Paritaprevir-ritonavir, ombitasvir, dasabuvir (12 weeks) | Paritaprevir-ritonavir, ombitasvir, dasabuvir (12 weeks) | Paritaprevir-ritonavir, ombitasvir, dasabuvir (12 weeks) |
| 2 | Sofosbuvir and ribavirin (12 weeks) | Sofosbuvir and ribavirin (12 weeks) | Sofosbuvir and ribavirin (12 weeks) | Sofosbuvir and ribavirin (12 weeks) |
| 3 | Daclastavir and sofosbuvir (12 weeks) | Daclastavir and sofosbuvir (24 weeks) | Daclastavir and sofosbuvir (12 weeks) | Daclastavir and sofosbuvir (24 weeks) |
| 4¶ | Elbasvir/grazoprevir (12 weeks) | Elbasvir/grazoprevir (12 weeks) | Elbasvir/grazoprevir and ribavirin (16 weeks) | Elbasvir/grazoprevir and ribavirin (16 weeks) |
| 4 | Sofosbuvir and peg-interferon alfa-2a/ribavirin (12 weeks) | Sofosbuvir and peg-interferon alfa-2a/ribavirin (12 weeks) | Sofosbuvir and peg-interferon alfa-2a/ribavirin (12 weeks) | Sofosbuvir and peg-interferon alfa-2a/ribavirin (12 weeks) |
| 5 and 6 | Sofosbuvir and peg-interferon alfa-2a/ribavirin (12 weeks) | Sofosbuvir and peg-interferon alfa-2a/ribavirin (12 weeks) | Sofosbuvir and peg-interferon alfa-2a/ribavirin (12 weeks) | Sofosbuvir and peg-interferon alfa-2a/ribavirin (12 weeks) |

†Consider 8 weeks of therapy in treatment naive genotype, non-cirrhotic genotype 1a/b if viral load is less than 6 000 000 IU/mL. ‡Ribavirin PO may be added to genotype 1a/b patients with cirrhosis (both treatment naive and experienced). §Recommended treatment duration for sofosbuvir plus daclatasvir (no ribavirin) for people who have failed treatment with a protease inhibitor + peginterferon-alfa + ribavirin is 24 weeks, including people with cirrhosis and people with no cirrhosis; recommended treatment duration for people with no cirrhosis who have previously failed peginterferon-alfa + ribavirin is 12 weeks. ¶Elbasvir/grazoprevir is not approved for patients with Childs Pugh B and Childs Pugh C liver cirrhosis.

**Table 6** Checklist prior to commencing direct-acting anti-viral therapies for hepatitis C

**1** Genotype
**2** Treatment naive or experienced
**3** Cirrhotic (Kpa ≥ 12.5)
**4** Complications of cirrhosis?
**5** Renal dysfunction?
**6** Concomitant medications/drug interactions
**7** Compliance considered
**8** Conflicting priorities addressed
**9** Contraception/pregnancy

## Hepatitis delta

Hepatitis D (delta) virus (HDV) is a small, defective RNA virus that requires HBsAg for transmission and packaging. HDV is considered to be a sub-viral satellite because it can propagate only in the presence of the HBV. The HDV genome consists of a single-stranded RNA, which is folded as a rod-like structure through internal base-pairing.[51] Transmission of HDV can occur either via simultaneous infection with HBV (co-infection) or superimposed on CHB or hepatitis B carrier state (super-infection).[51]

Of the 350 million individuals with chronic HBV infection, approximately 15 million have also been exposed to HDV. While HDV is relatively common in the Mediterranean basin, HDV is not common in Australia.[52] There are approximately 30 cases reported per year. Acquiring HBV and HDV during the same exposure (co-infection) is associated with more severe acute hepatitis and higher mortality, when compared with acute HBV mono-infection. HDV super-infection in an HBV carrier can manifest as an acute hepatitis although usually results in chronic HDV infection. The progression to cirrhosis is faster in patients with chronic HDV, when compared with HBV mono-infection: 80% of patients with chronic HDV will progress to cirrhosis in 5–10 years.[53]

The fate of HDV is determined by the host response to HBV, and HDV is cleared if HBV is cleared. HBV DNA is

**Table 7** American Association of the Study of Liver Diseases hepatocellular carcinoma screening guidelines

| Target population for liver ultrasound every 6 months |
|---|
| Cirrhotic patients |
| Non-cirrhotic hepatitis B carriers with a family history of hepatocellular carcinoma |
| Non-cirrhotic Africans and African Americans with hepatitis B |
| Non-cirrhotic Asian male hepatitis B carriers past the age of 40 years |
| Non-cirrhotic Asian female hepatitis B carriers past the age of 50 years |

usually low or negative in chronic HDV infection, because HDV suppresses HBV replication. HDV IgM is positive in acute infection and can persist in chronic infection; if it does persist, it can be used as a surrogate marker for HDV replication. Qualitative HDV RNA is a marker of viral replication that is positive in chronic infection. HDV RNA is useful to monitor treatment response, but is not readily available. Furthermore, HBsAg is useful to monitor treatment response if quantitative HDV RNA is not available.[54]

The mainstay of treatment for HDV infection is PEG-IFN-alpha for at least 48 weeks. Efficacy is disappointing, with control of infection estimated in only 20–25% of the patients, worse in those with cirrhosis.[55,56] The oral nucleos(t)ides appear to have limited activity against HDV, because the virus uses host enzymes for replication and thus lacks enzyme targets.[56] Nevertheless, control of HBV is always indicated and after long-term therapy, delta viral levels can decline. New targets, such as with Myrcludex B a first in class entry inhibitor inactivating the HBV and HDV receptor are promising but results are preliminary.[57] Patients with HDV should be managed in a specialist centre.

## Hepatitis E

Hepatitis E is one of the most frequent causes of acute hepatitis worldwide. An estimated 70 000 deaths are attributed hepatitis E virus (HEV) genotypes 1 and 2 every year. The majority of infections are thought to remain asymptomatic.[58] HEV is a small, non-enveloped virus with a single-stranded RNA genome. The virus has four genotypes. Genotypes 1 and 2 exclusively infect humans, whereas genotypes 3 and 4 infect humans, pigs and several other mammalian species. HEV is endemic in many countries of Asia, Africa, Middle East and Central America. The transmission of HEV is faecal-oral, usually through contaminated drinking water.[59]

HEV is not a common cause of liver disease in Australia. The first case of HEV was reported in 1993.[2] Over the last 6 years, there have been approximately 30–40 cases of hepatitis E diagnosed every year, predominantly in returned travellers. However, a recent cluster of HEV infection linked to a single restaurant in Sydney in May 2014 was the first reported Australian outbreak of locally acquired HEV infection, and one of the largest linked with a restaurant reported anywhere. A total of seventeen cases were linked to consuming pork liver pâté at this restaurant during a 9-month period.[60]

Clinically, acute HEV infection is similar to hepatitis A; however, a longer incubation period, a longer clinical course, a higher fatality among pregnant women, patients with pre-existing liver disease and patients with HIV and dialysis patients is also described . The clinical course of acute HEV infection is characterised by a 3–8-week incubation period, during which HEV RNA can be detected in the stool or serum. After 8 weeks, symptoms develop in some patients and are usually accompanied by a rise in ALT and the appearance of anti-HEV IgM. IgM persists for months and declines with the resolution of infection.[56] Suspected HEV infection in immunocompromised patients should also be confirmed by HEV RNA testing. Chronic hepatitis does not usually develop after acute HEV infection, except in the transplant setting and possibly in other settings of immunosuppression. Patients with chronic hepatitis E infection may develop liver cirrhosis.[61] Ribavirin has become the drug of choice for chronic HEV and its efficacy has been proven in larger studies.[62] As hepatitis E is normally self-limiting, most patients do not require specific treatment, other than supportive care.

Two candidate vaccines against hepatitis E have undergone successful clinical testing. The first (56-kDa truncated ORF2 protein of HEV) achieved 100% seroconversion and protective efficacy of up to 95.5% during a 2-year follow up of 2000 patients.[63] The second vaccine (ORF2 protein) showed a protective efficacy of 100% during a 13-month follow up. The use of this vaccine was approved in China in 2012.[64] Unfortunately, this vaccine has not been licenced for marketing in other countries, due to lack of profitability. Currently, the best way to prevent hepatitis E is by the provision of safe drinking water, proper disposal of human faeces and education about personal hygiene.

## Conclusion

The aim of this is review was to provide a clear and up-to-date synopsis of hepatitis A to E. Understanding pathogenesis, assessment of their impact and therapeutics is crucial. This field has evolved considerably in the last few years and will continue to do so. There are multiple resources including the Gastroenterological Society of Australia[65] and the American Gastroenterological Association,[66] which can assist physicians with more detailed information, when assessing and treating patients with viral hepatitis.

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