Complex situations Co-infection and Immunosuppression

KEY POINTS

- Co-infection with hepatitis B virus (HBV) and human immunodeficiency virus (HIV) and hepatitis C and D viruses (HCV and HDV) results in worse outcomes for patients in terms of all-cause mortality, liver disease and hepatocellular carcinoma (HCC).
- All individuals with chronic hepatitis B (CHB) should be tested for co-infection following appropriate pre-test discussion.
- People with ongoing risk factors for co-infection should be offered repeat testing, particularly in the setting of clinical deterioration.
- People with HCV co-infection should be offered treatment with direct-acting antiviral (DAA) therapy and the need for HBV treatment reassessed before commencing HCV therapy. If not on antiviral therapy for HBV, additional monitoring during DAA therapy may be required.
- The approach to treatment for patients with co-infection is more complex than in the setting of mono-infection, and can be associated with increased risk of adverse outcomes.
- All patients undergoing significant immune suppression should be tested for HBV infection as viral reactivation and associated flares of hepatitis can occur, which can be fatal.

Introduction

There are a number of special situations in which the complexity of managing the care of a patient with hepatitis B virus (HBV) infection is increased. Primary care practitioners are optimally placed to recognise and respond to these situations, and to coordinate management and referral to specialist services to maximise the health and wellbeing of people living with chronic hepatitis B (CHB).

Co-infection

HBV, hepatitis C and D viruses (HCV, HDV) and human immunodeficiency virus (HIV) have shared modes of transmission. The prevalence of co-infections varies widely globally depending of the endemicity of HBV and HDV (See: Prevalence and epidemiology of hepatitis B) and the predominant modes of transmission for HIV and HCV. All patients with CHB should be offered testing for the presence of all these co-infections following appropriate pre-test discussion (1, 2). Each virus alters the natural history of CHB infection and complicates treatment approaches. The management of co-infection is complex and usually requires shared care with a specialist physician.

specialist physician.

HBV/HIV co-infection

Epidemiology

Globally, where CHB prevalence is high (> 8%) or intermediate (2-8%) and most often acquired in early childhood, co-infection in people with HIV infection is common and reflects the background population prevalence. In Australia, a low-prevalence country for both viruses, new HBV infections are most commonly transmitted though parenteral exposure or sexual contact and may be transmitted simultaneously with, before or after exposure to HIV (3). Approximately 5% of Australia's estimated 26,500 people living with HIV are estimated to have HBV/HIV co-infection (4). Incident HBV infections are more common in people with HIV infection and men who have sex with men (a population also at increased risk for HIV infection) with recent Australian studies estimating rates around 10 times that of the general population at approximately 2 per 1000 person years (5). These rates highlight the importance of testing, vaccination and (for people with HIV infection) boosting vaccination when the anti-HBs titre falls below 10 mIU/mL (5-8) (See: Primary prevention of hepatitis B virus infection).

Natural history

Co-infection with HIV has a significant impact on the natural history of CHB. Progression to chronic infection following acute HBV is more common in people with HIV infection compared with immune-competent adults, with the likelihood of failing to clear HBV related to the degree of immunodeficiency (5). High HBV DNA levels and detectable HBeAg are more common in patients with HIV co-infection, and the rate of viral reactivation is also higher, particularly in more immunocompromised patients (9). Occult infection, defined as detectable HBV DNA in the serum in the absence of detectable HBsAg, is more common in patients with HBV/HIV co-infection and so testing should be considered in patients who are isolated anti-HBc positive (note this test is not Medicare rebatable in the absence of HBsAg). Anti-HBs positive patients with a history of resolved HBV infection can undergo reactivation, with reappearance of HBsAg (reverse seroconversion) and HBV DNA. This is a rare event which has been described in the context of advanced immunodeficiency, and is now rarely seen in Australia (10).

Progression to advanced liver disease such as cirrhosis and HCC is more rapid and liver-related mortality is higher in the setting of HBV/HIV co-infection, despite typically lower alanine aminotransferase (ALT) values and reduced inflammatory activity on biopsy (11). This disparity of less necroinflammatory activity, but faster disease progression is incompletely understood. In contrast to the significant impact of co-infection on the natural history of HBV, there is little evidence to suggest that HBV affects progression of HIV infection (11).

With the reduction in acquired immune deficiency syndrome (AIDS)-related mortality and incidence of opportunistic infections since the advent of antiretroviral therapy (ART), the burden of liver-related morbidity and mortality has increased (11). HBV infection contributes to liver-related illness either alone or in combination with other factors. Antiretroviral agents can cause liver toxicity; this toxicity is more pronounced in patients with pre-existing liver disease such as chronic viral hepatitis (3).

Management of HBV/HIV co-infection

In Australia, ART is now recommended for all patients with HIV regardless of CD4 count. People with HBV/HIV co-infection should be treated with an ART regimen containing tenofovir or tenofovir alafenamide (TAF) (3). Monotherapy for HBV with any agent (including tenofovir and entecavir) must be avoided, as this can induce HIV resistance mutations (12). As ALT levels can be low in the presence of significant liver damage, fibrosis assessment with either FibroScan™ or liver biopsy, or both, is recommended to determine the degree of liver fibrosis. Although there is an increased risk of HCC, particularly at lower CD4 counts, routine 6-monthly screening for people with HBV/HIV co-infection is not currently recommended and

routine 6-monthly screening for people with HBV/HIV co-infection is not currently recommended and screening for HCC should occur according to guidelines based on the presence of cirrhosis, family history of HCC, age and region of birth (See: Clinical Assessment of patients with hepatitis B virus infection) (3). Lifestyle advice regarding weight management and alcohol consumption should be given.

HBV flares can occur if ART is withdrawn and people with HBV/HIV co-infection should be warned that flares can occur if they stop treatment. Caution is also required when changing ART regimens in people with co-infection as ceasing HBV-active agents can cause reactivation. The immune reconstitution inflammatory syndrome (IRIS) occurs when there is a resurgent immune response to chronic infections in people living with HIV following commencement of ART. HBV flares in the setting of immune reconstitution are more common in patients with a high baseline HBV viral load (13) and low starting CD4 count (e.g. < 200) and can result in significant liver disease and mortality, particularly in patients with advanced liver disease. However flares can also lead to HBeAg clearance and sustained suppression of viral replication in some patients.

HBV/HCV co-infection

Epidemiology

HBV/HCV is the most common co-infection in people living with CHB in Australia. HCV infection in Australia is most commonly associated with parenteral exposure, and people with HBV/HCV co-infection can either be exposed due to this shared mode of transmission or have an independent risk factor for CHB such as country of birth, Aboriginal and Torres Strait Islander status, or sexual risk (See Prevalence and epidemiology of hepatitis B). Approximately 5% of Australians living with CHB are estimated to have HCV co-infection.

Natural history

In contrast to co-infection with HIV, reduced replication of HBV is common in HCV co-infection, with lower viral loads than in patients with HBV mono-infection, although viral load may fluctuate over time (11). The suppression of HBV is through the direct interference with replication by HCV. As with HIV, occult (HBsAg-negative) CHB is also more common in patients with HCV co-infection and consideration should be given to testing for the presence of HBV DNA in people living with chronic hepatitis C with isolated anti-HBc on serological testing (note this test is not Medicare rebatable in the absence of HBsAg). HBV/HCV co-infection is associated with more severe liver disease, an increased risk of progression to cirrhosis and a higher incidence of HCC (9,14). People with HBV/HCV co-infection experience higher mortality rates (liver related and all cause) than infection with either HBV or HCV alone. Patients with co-infection had mortality rates approximately three times higher than patients with HBV mono-infection (15).

Acute co-infection (usually acquired through injecting drug use) has been associated with an increased incidence of fulminant hepatitis.

Management

The recent advances in HCV cure and the availability in Australia of highly effective direct-acting antiviral (DAA) therapy has changed the treatment choices for people with HBV/HCV co-infection. All need to be assessed fully for both viruses and for evidence of liver fibrosis and offered DAA therapy. The aim of DAA for HCV is cure with sustained viral suppression at week 12 (SVR 12). Response rates are similar in people with HBV/HCV co-infection to people with HCV mono infection. It is recommended that treatment be offered to all people with HCV infection regardless of ongoing exposure risk, including injecting use and should be offered to people with co-infection even if HBV infection predominates. Guidelines on HCV treatment can be found at http://cart.gesa.org.au/membes/files/Resources/Hepatitis%20C/hepatitis_C_virus_infection_consensus_stateme (16). After SVR 12 advice should be given to patients to prevent HCV reinfection and retesting offered yearly (HCV RNA) if the exposure risk is ongoing.

Reactivation of previously suppressed and low-level HBV replication can occur while on DAA therapy and HBV DNA should be monitored at regular intervals during and after therapy is ceased. This is more commonly seen for those in the immune control phase of CHB infection, but reactivation in patients who were HBsAg negative (anti-HBc positive) has also been documented. Addition of presumptive HBV treatment (tenofovir or entecavir) should be considered in all people who have HBV/HCV co-infection especially in those with advanced liver disease (F3-F4) (15). There are no large studies that support the routine addition of an HBV oral antiviral as a standard approach to people with HBV/HCV co-infection who are undergoing treatment where HBV replication is suppressed.

HBV/HDV co-infection

Testing in HBV/HDV co-infection

All patients should be tested for HDV co-infection (see Clinical assessment of patients with hepatitis B virus infection)

A positive HDV antibody test should always be followed with HDV RNA PCR testing

(HDV RNA PCR tests are available at a limited number of laboratories - check for availability and charges)

HBV/HDV co-infection requires specialist management as outcomes are worse than mono-infection and there are special considerations around the treatment approach

Epidemiology

Hepatitis D virus (HDV, sometimes called hepatitis delta) relies on HBV infection to replicate. Worldwide HDV is more common in parts of sub-Saharan Africa, eastern and Mediterranean Europe, the Amazon Basin and parts of Asia, but can vary within countries and regions (17). HDV prevalence varies widely between populations but is estimated to affect around 5% of people with HBV infection in Australia (18). As with other co-infections it can be acquired simultaneously with HBV infection or as a superinfection. In non-endemic countries such as Australia, HBV/HDV infection has been more commonly associated with injecting drug use (IDU) although the epidemiology is changing as migration from higher HDV prevalence areas increases and country of birth becomes an increasingly important determinant (18). HDV/HBV co-infection appears to be rare in Aboriginal and Torres Strait Islander people who do not have other risk factors for infection, based on a recent study from the Northern Territory[i], however, evidence on prevalence among Indigenous people in other areas of Australia is lacking (19).

Natural history

HDV is a satellite virus that requires HBV co-infection to synthesise new virions and therefore cannot infect hepatocytes in the absence of HBV. Similar to the situation of HBV/HCV co-infection, HDV infection usually results in suppression of HBV replication with low or undetectable HBV DNA levels, although this is not uniformly the case (20).

Acute co-infection with HBV/HDV is typically indistinguishable from HBV mono-infection, but has been associated with a higher incidence of fulminant hepatitis. The rate of progression to chronicity is no different from that for HBV infection alone. HDV superinfection in a person with CHB can present as an acute hepatitis flare, and progression to chronic HDV infection is usual. Chronic HBV/HDV co-infection has been associated with more severe liver disease; evidence regarding the influence on HCC incidence is mixed (17).

Management

People with HBV/HDV co-infection need to be assessed as usual (See Clinical assessment of patients with hepatitis B virus infection) and the decision for treatment is made on similar criteria. Initial testing of HDV antibody for all people with CHB should be followed with HDV RNA polymerase chain reaction (PCR) for any patient with a positive result (18); serum HDV RNA results fluctuate, and referral for specialist management is advisable. Antiviral agents for HBV infection are not effective against HDV but may be required for the treatment of HBV infection depending on viral predominance and degree of underlying liver disease (20). The current recommended treatment of HBV/HDV co-infection is with a prolonged 48-week course of pegylated interferon-alfa. Treatment is successful in a minority of patients with relapse following therapy common (20). There are promising trials of new agents currently underway which may alter treatment possibilities (21).

Multiple co-infections

Multiple co-infections with a combination of HBV, HCV, HDV and HIV occur uncommonly and in the Australian context are most likely to be associated with a history of injecting drug use. Consultation with a specialist service about these patients is advised.

Immunosuppression and reactivation

All patients should be offered testing for the presence of resolved or current HBV infection before immunosuppression (1). This is particularly the case when considering that one-third of all people living with CHB in Australia are estimated to remain undiagnosed (22). Universal testing for people undergoing cancer chemotherapy or other significant immunosuppression is recommended in Australia's National HBV Testing Policy (available at: http://testingportal.ashm.org.au/hbv) (23). Increasing use of biologics (drugs that modify the body's immunological responses e.g. rituximab, infliximab and adalimubab) in the setting of cancer therapy, rheumatological, dermatological and other specialist fields, means the primary-care provider needs to be aware of the potential impact of CHB infection in diseases where immunosuppression is a treatment modality. Reactivation of CHB is also observed with other immunosuppressant medications including steroids, methotrexate and in the setting of organ transplantation. The short-term (< 2 weeks) use of low-dose steroids (< 20 mg/day) in people without advanced liver disease is unlikely to result in significant HBV reactivation.

Primary-care providers should be aware of the need for this testing especially for priority population groups (See Chapter 1: Prevalence and epidemiology of hepatitis B) as not all specialist services routinely perform HBV testing for people undergoing immunosuppression (24).

There are two clinical scenarios to consider in the setting of planned immunosuppression once a full panel of HBV testing has been performed (see Chapter 3: Hepatitis B virus diagnosis and interpreting test results):

- An HBsAg-positive individual (chronic HBV infection)
- Individual with resolved infection (anti-HBc positive +/- anti-HBs positive > 10 IU/mL) at risk of seroreversion and reactivation in the setting of profound immunosuppression

The natural history of HBV infection is fundamentally related to the dynamic balance between viral replication and host immune response (Natural history of hepatitis B virus infection). It is therefore not surprising that immunosuppressive therapy (ongoing, or cyclical, as in the case of cancer chemotherapy)

surprising that immunosuppressive therapy (ongoing, or cyclical, as in the case of cancer chemotherapy) can have a marked impact on chronic HBV infection.

Significant immunosuppression is associated with a reactivation in viral replication and rising HBV DNA. Immunosuppression-associated HBV reactivation and flares have been observed in patients undergoing chemotherapy, organ transplantation, treatment for autoimmune diseases and glucocortocoid therapy. Glucocorticoid therapy both suppresses the host immunity and acts directly on the virus to enhance transcription.

Profound immunosuppression can also cause reactivation of HBV infection in patients with serologically resolved infection (called seroreversion: HBsAg negative à positive in an anti-HBc positive patient) as patients with this serological pattern have HBV DNA present in hepatocytes. This has particularly been noted in the setting of the treatment of haematological malignancies, with B-cell depleting agents (e.g. rituximab) and in stem-cell transplants (24).

Reactivation of HBV replication, in either scenario, can be followed by a flare of hepatitis with rising ALT levels. This is particularly noted following the reduction or withdrawal of immunosuppressive treatment, commonly over a period of weeks-months but can occur after a prolonged delay. The mechanism is similar to flares post pregnancy (Managing hepatitis B virus and pregnancy) or in IRIS seen with ART for HIV infection (see above), where the restoration of immune function leads to an increase in the destruction of HBV-infected hepatocytes.

Although many hepatitis flares in the context of immunosuppression are asymptomatic, a full spectrum of presentations is possible, through to fulminant hepatitis, liver failure and death. Risk factors for reactivation (Table 11.1) include the intensity and duration of immunosuppression, the use of glucocorticoids or rituximab, high baseline HBV DNA viral load, HBeAg positivity, young age and male gender (24). The rate of withdrawal of immunosuppression is an important determinant of the severity of flares. The increased incidence of flares observed in the setting of cancer chemotherapy compared with other immunosuppressive regimens may relate to the cyclical nature of such therapy, with repeated episodes of immune suppression and restoration.

Table 11.1 Risk factors for reactivation
Intensity of immunosuppression /chemotherapy regime
Specific agents including glucocorticoids and biologics e.g. rituximab, infliximab and adalimubab
Longer duration chemotherapy
High Baseline HBV DNA
HBe Ag positivity
Young age
Male gender
Cyclical therapy
Absence of anti-HBs in HbsAg negative, anti-HBc positive

Management

Presumptive treatment with antiviral therapy has been shown to substantially reduce the incidence of hepatic flares and associated mortality. This prophylaxis should be given to all HBsAg-positive patients before chemotherapy or other immunosuppressive therapy (25); such pre-emptive treatment has been shown to be superior to starting treatment once reactivation has been detected. Prophylactic antiviral therapy is recommended for people who are HBsAg positive when co administered a dose of prednisolone greater than 20 mg/day and for longer than 2 weeks. It should commence before initiation of therapy and continued 6 months to 1 year after cessation of therapy (26).

While lamivudine has historically been most commonly used in this context, largely due to cost

considerations, with generic versions of entecavir and tenofovir now available many experts advise using these more potent antivirals whenever presumptive antiviral therapy is indicated (Treatment of chronic hepatitis B virus infection). Pegylated interferon is not used in this context.

When B cell depleters (e.g. rituximab) are used, antiviral prophylaxis for HBV is recommended for 24 months after ceasing the immunosuppressive therapy. For other agents, prophylaxis should continue for 12 months post cessation of therapy.

Conclusion

Special situations including co-infection and immunosuppression are potentially associated with worse outcomes and need coordinated primary and specialist care to prevent unnecessary morbidity and mortality. As patients living with CHB age and are treated with immunosuppressive therapy for cancers and other conditions, primary care should be involved in screening and detection of those at risk of reactivation.

References

1. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370-98.
2. Terrault N, Bzowej N, Chang K, Hwang JP, Jonas MM, Murad MH; American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63:261-83.
3. Cowie BC, Dore G, Sasadeusz J, editors. Co-infection: HIV and viral hepatitis - a guide for clinical management. 4th ed. Darlinghurst: Australasian Society for HIV Medicine; 2010.
4. The Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia: Annual Surveillance Report 2017. Sydney: The Kirby Institute, The University of New South Wales; 2017.
5. Body A, Hoy JF, Cheng AC, Giles ML. Incident hepatitis B virus (HBV) infection subsequent to the diagnosis of HIV infection in a Melbourne cohort; missed opportunities for prevention. Sex Health 2014;11:5-10.
6. Gamagedara N, Weerakoon AP, Zou H, Fehler G, Chen MY, Read TR, et al. Cross-sectional study of hepatitis B immunity in MSM between 2002 and 2012. Sex Transm Infect 2014;90:41-5.
7. Allard N, Cowie B. Hepatitis B in men who have sex with men and HIV-infected individuals: missed opportunities and future challenges. Sex Health 2014;11:1-4.
8. Australian Government. Australian Technical Advisory Group on Immunisation (ATAGI). The Australian Immunisation Handbook 10th ed. (2017 update). Canberra: Australian Government Department of Health; 2017.
9. Shukla NB, Poles MA. Hepatitis B virus infection: co-infection with hepatitis C virus, hepatitis D virus, and human immunodeficiency virus. Clin Liver Dis 2004;8:445-60, viii.
10. Thio CL, Locarnini S. Treatment of HIV/HBV coinfection: clinical and virologic issues. AIDS Rev 2007;9:40-53.
11. Thio CL. Hepatitis B and human immunodeficiency virus coinfection. Hepatology 2009;49(5 Suppl):S138-45.
12. Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). Antiretroviral Guidelines. US DHHS Guidelines with Australian commentary [internet]. Available at: http://arv.ashm.org.au (last accessed 2 July 2018).
13. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42:1208-36.
14. Amin J, Dore GJ, O'Connell DL, Bartlett M, Tracey E, Kaldor JM, et al. Cancer incidence in people with hepatitis B or C infection: a large community-based linkage study. J Hepatol 2006;45:197-203.
15. Amin J, Law MG, Bartlett M, Kaldor JM, Dore GJ. Causes of death after diagnosis of hepatitis B or hepatitis C infection: a large community-based linkage study. Lancet 2006;368:938-45.
16. Hepatitis C Virus Infection Consensus Statement Working Group. Australian recommendations for the

management of hepatitis C virus infection: a consensus statement (August 2017). Melbourne: Gastroenterological Society of Australia; 2017. Available at: http://cart.gesa.org.au/membes/files/Resources/Hepatitis%20C/hepatitis_C_virus_infection_consensus_state (last accessed 3 July 2018).
17. Hughes SA, Wedemeyer H, Harrison PM. Hepatitis delta virus. Lancet 2011;378:73-85.
18. Shadur B, Maclachlan J, Cowie B. Hepatitis D Virus in Victoria 2000-2009. Intern Med 2013;43:1081-7.
19. Davies J, Tong SYC, Davis JS. Hepatitis D is rare or non-existent in hepatitis B virus-infected Indigenous Australians in the Northern Territory. Aust NZ J Public Health 2013;37:188-9.
20. Wedemeyer H. Re-emerging interest in hepatitis delta: new insights into the dynamic interplay between HBV and HDV. J Hepatol 2010;52:627-9.
21. Bazinet M, Pantea V, Cebotarescu V, Cojuhari L, Jimbei P, Albrecht J, et al. Safety and efficacy of REP 2139 and pegylated interferon alfa-2a for treatment-naive patients with chronic hepatitis B virus and hepatitis D virus co-infection (REP 301 and REP 301-LTF): a non-randomised, open-label, phase 2 trial. Lancet Gastroenterol Hepatol 2017;2:877-89.
22. MacLachlan J, Allard N, Carville K, Haynes K, Cowie B. Mapping progress in chronic hepatitis B: geographic variation in prevalence, diagnosis, monitoring and treatment, 2013-15. AustNZ J Public Health 2018;42:62-8.
23. Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). National HBV Testing Policy [internet]. Available at: http://testingportal.ashm.org.au/hbv (last accessed 2 July 2018).
24. Tsutsumi Y, Ogasawara R, Miyashita N, Tanaka J, Asaka M, Imamura M. HBV reactivation in malignant lymphoma patients treated with rituximab and bendamustine. Int J Hematol. 2012;95:588-91.
25. Lalazar G, Rund D, Shouval D. Screening, prevention and treatment of viral hepatitis B reactivation in patients with haematological malignancies. Br J Haematol 2007;136:699-712.
26. Lopez-Serrano P, de la Fuente Briongos E, Alonso EC, Perez-Calle JL, Rodriguez CF. Hepatitis B and immunosuppressive therapies for chronic inflammatory diseases: when and how to apply prophylaxis, with a special focus on corticosteroid therapy. World J Hepatol 2015;7:539-47.

Authors

Nicole Allard - General Practitioner, cohealth, Footscray and WHO Collaborating Centre for Viral Hepatitis, Victorian Infectious Diseases Reference Laboratory, Doherty Institute, Melbourne VIC

Benjamin Cowie - WHO Collaborating Centre for Viral Hepatitis, Doherty Institute, Royal Melbourne Hospital, and Department of Medicine, University of Melbourne, Melbourne VIC