

# Hepatitis B management during immunosuppression for haematological and solid-organ malignancies: An Australian consensus statement 2019



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## Contribution and Endorsement

This consensus statement was prepared by an expert panel of medical specialists in infectious diseases, hepatology, haematology, oncology and paediatrics, and representatives from the Australasian Society for Infectious Diseases, the Gastroenterological Society of Australia (Australian Liver Association), the Haematology Society of Australia and New Zealand, the Medical Oncology Group of Australia, and the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine. The Australasian Society for Infectious Diseases, Gastroenterological Society of Australia, Haematology Society of Australia and New Zealand, Medical Oncology Group of Australia, and Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine have endorsed this consensus statement.

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## Acknowledgements

The Consensus Statement Group particularly acknowledge the work of Dr Venessa Pattullo, a dedicated hepatologist who contributed enormously to the practice of hepatology in Australia and was passionate about preventing hepatitis B reactivation in cancer patients. Vanessa passed away during the development of these guidelines and wrote much of the commentary on HBV testing.

## Disclosures of conflicts of interest

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## Executive summary

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Approximately 239,000 Australians are living with chronic hepatitis B virus (HBV) infection; individuals born overseas are more likely to be affected. Individuals with chronic HBV or past exposure to HBV infection are at risk of reactivation during immunosuppressive cancer chemotherapy. The risk of reactivation varies with the degree and duration of immunosuppression, mechanism of action of chemotherapy, underlying HBV disease activity and degree of liver disease. HBV reactivation can lead to liver failure, death or cancer treatment interruption that reduces cancer survival. Oral antiviral therapy for HBV is highly effective and known to prevent reactivation when used appropriately.

Clinical concordance with screening and treatment guidelines is inconsistent in practice. Individualised therapeutic decisions lead to both overuse and underuse of HBV antivirals and potentially increase medication side effects or HBV reactivation risks and increase potential for errors.

International guidelines were developed recently following appraisal of evidence-based practice in this area. There is a need to apply this evidence to the local epidemiology, testing rules under Medicare, and prescribing rules under the Pharmaceutical Benefits Scheme.

This document presents the Australian consensus statement on hepatitis B management during immunosuppression for haematological and solid-organ malignancies. When funded access to testing and treatment are not available under current programs, we suggest that access criteria should be re-evaluated in line with the consensus statement's recommendations.

This is a living document that will be updated as new data emerge. Grading of the levels of evidence for the recommendations is described in the Methodology section.



**ashm**  
Australasian Society for  
HIV, Viral Hepatitis and  
Sexual Health Medicine

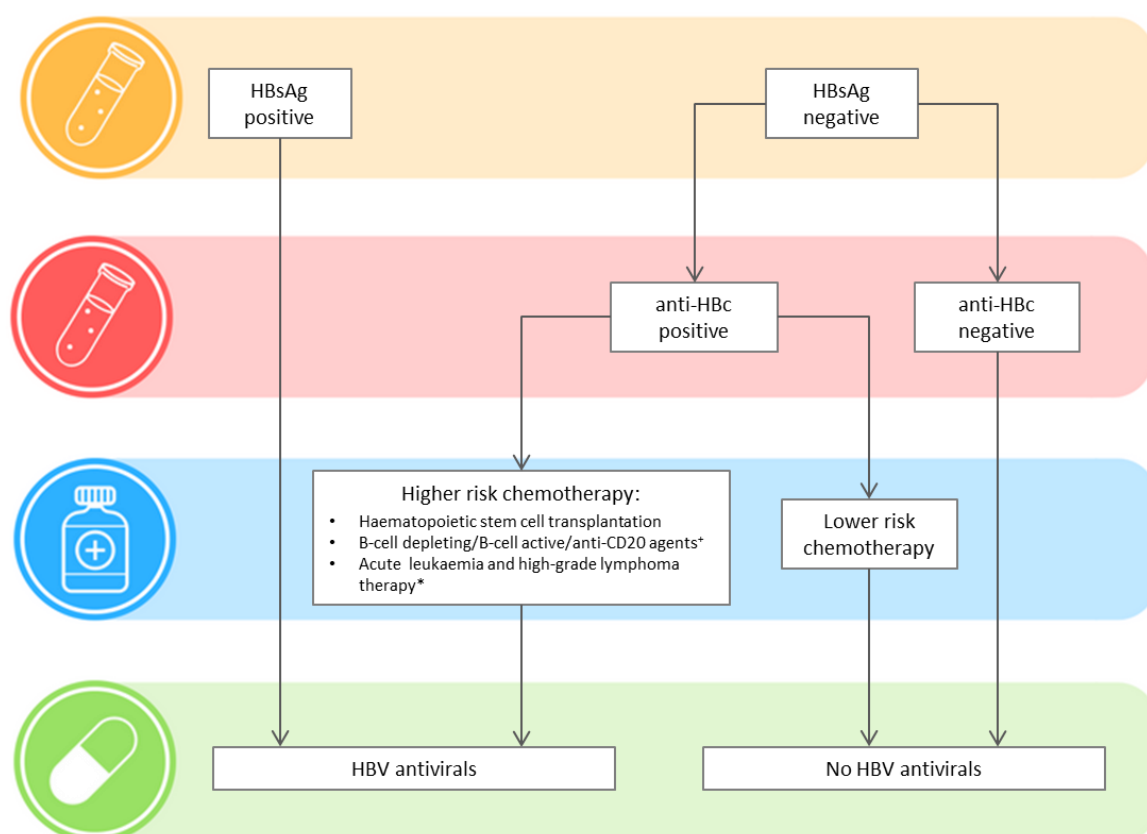


## Recommendations summary

Consensus recommendations	GRADE
<b>1. Who to test for hepatitis B infection</b>	
1.1. We recommend that all patients undergoing therapy for haematological malignancy are tested for hepatitis B infection.	A1
1.2. We recommend that all patients undergoing therapy for solid tumours are tested for hepatitis B infection.	B1
1.3. We suggest that the treating haematologist or medical oncologist prescribing cancer therapy is responsible for hepatitis B testing.	C2
1.4. We recommend that HBsAg, anti-HBc and anti-HBs are performed when testing for hepatitis B infection.	A1
1.5. We recommend hepatitis B testing in children should follow the same approach as for adults.	C1
<b>2. When to start antiviral agents</b>	
2.1. We recommend that all HBsAg positive patients with haematological or solid tumour malignancy undergoing therapy should receive antiviral prophylaxis.	A1
2.2. We recommend that risk for HBV reactivation in patients who are HBsAg negative and anti-HBc positive is determined by the cancer therapy regimen (higher risk vs lower risk).	B1
We make the following recommendations for patients who are HBsAg-negative and anti-HBc positive:	
2.3. Patients undergoing higher risk cancer therapy (haematopoietic stem cell transplantation, B-cell depleting/B-cell active/anti-CD20 agents, acute leukaemia and high-grade lymphoma therapy) should receive antiviral prophylaxis.	B1
2.4. Patients undergoing lower risk cancer therapy do not require antiviral prophylaxis.	C1
2.5. We recommend that patients without evidence of prior HBV exposure (HBsAg negative/anti-HBc negative) do not require antiviral prophylaxis.	C1
We suggest that these patients should be assessed for HBV immunity (using anti-HBs) and offered vaccination if anti-HBs < 10 at 6 months after completion of cancer therapy and when underlying disease is controlled.	C2
2.6. We recommend that antiviral prophylaxis should be commenced as soon as possible relative to the commencement of cancer therapy, but should not delay cancer therapy.	B1

2.7. We recommend the use of potent, high barrier to resistance nucleoside/nucleotide analogues (ie, entecavir or tenofovir) for antiviral prophylaxis.	A1
2.8. We recommend that all HBsAg positive patients should be referred to a viral hepatitis specialist for routine assessment.	C1
2.9. We recommend antiviral prophylaxis for children should follow the same approach as for adults.	C1
<b>3. When to stop antiviral agents</b>	
3.1. We recommend that HBsAg positive patients should be assessed at the start of cancer therapy to determine their phase of disease and ongoing need for hepatitis B treatment after immunosuppression.	C1
3.2. We recommend that patients who fulfil treatment criteria for chronic hepatitis B regardless of their malignancy should remain on therapy and follow standard management guidelines.	A1
3.3. We recommend that patients continue prophylaxis with a nucleoside/nucleotide analogue for 18-24 months after B-cell depleting/B-cell active/anti-CD20 agent or haematopoietic stem cell transplantation therapy provided they DO NOT fulfil criteria for hepatitis B treatment independent of immunosuppression status.	B1
3.4. We recommend that patients continue prophylaxis with a nucleoside/nucleotide analogue for 6–12 months post cessation of cancer therapy (that is not B cell-depleting/B cell-active/anti-CD20 agent or haematopoietic stem cell transplantation therapy; see recommendation 3.3 above) provided they DO NOT fulfil criteria for hepatitis B treatment independent of immunosuppression status.	B1
3.5. We recommend that ALT, HBsAg and HBV DNA level should be tested every 3 months following nucleoside/nucleotide analogue withdrawal for at least 12 months.	B1
3.6. We recommend when to stop antiviral agents in children should follow the same approach as for adults.	C1
<b>4. How to monitor individuals</b>	
4.1. We suggest that patients receiving antiviral prophylaxis during cancer therapy should be seen 3 months after initiating antiviral therapy, and then every 3–6 months.	C2
4.2. We suggest that ALT and HBV DNA should be used to monitor patients receiving antiviral prophylaxis during cancer therapy.	C2
4.3. We suggest that patients' adherence to antiviral prophylaxis should be evaluated throughout therapy.	C2
4.4. We suggest that clinicians should consider hepatitis B infection for any unexplained ALT elevation among patients receiving cancer therapy.	C2

4.5. We recommend that all cases of HBV reactivation should be urgently referred to a viral hepatitis specialist for treatment.	A1
4.6. We recommend all children commenced on antiviral prophylaxis should be monitored using the same approach as for adults, in consultation with a viral hepatitis specialist (ideally with paediatric expertise).	C1



### Flowchart for HBV antiviral prophylaxis in patients undergoing cancer therapy

Notes: “Lower risk” agents are all others not included in “higher risk”; implications for monitoring and duration of antivirals are discussed in the text. +Including rituximab, obinutuzumab, ocrelizumab, ofatumumab and ibrutinib; this is not an exhaustive list as new agents will be introduced and more evidence about the risk of HBV reactivation comes to light. \*Lower level of evidence for risk of HBV reactivation in acute leukaemia and high-grade lymphoma therapy.

## Abbreviations

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ALT	Alanine aminotransferase
CI	Confidence interval
EASL	European Association for the Study of the Liver
eGFR	estimated glomerular filtration rate
anti-EGFR	epidermal growth factor receptor antibodies
GRADE	Grading of Recommendations Assessment, Development and Evaluation
anti-HBc	hepatitis B core antibody
anti-HBe	hepatitis B envelope antibody
anti-HBs	hepatitis B surface antibody
HBeAg	hepatitis B envelope antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HSCT	haematopoietic stem cell transplantation
INR	international normalised ratio
IU	international units
MBS	Medicare Benefits Schedule
mL	millilitre
NHMRC	National Health and Medical Research Council
OR	odds ratio
PBS	Pharmaceutical Benefits Scheme
VEGF	Vascular endothelial growth factor



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## Introduction

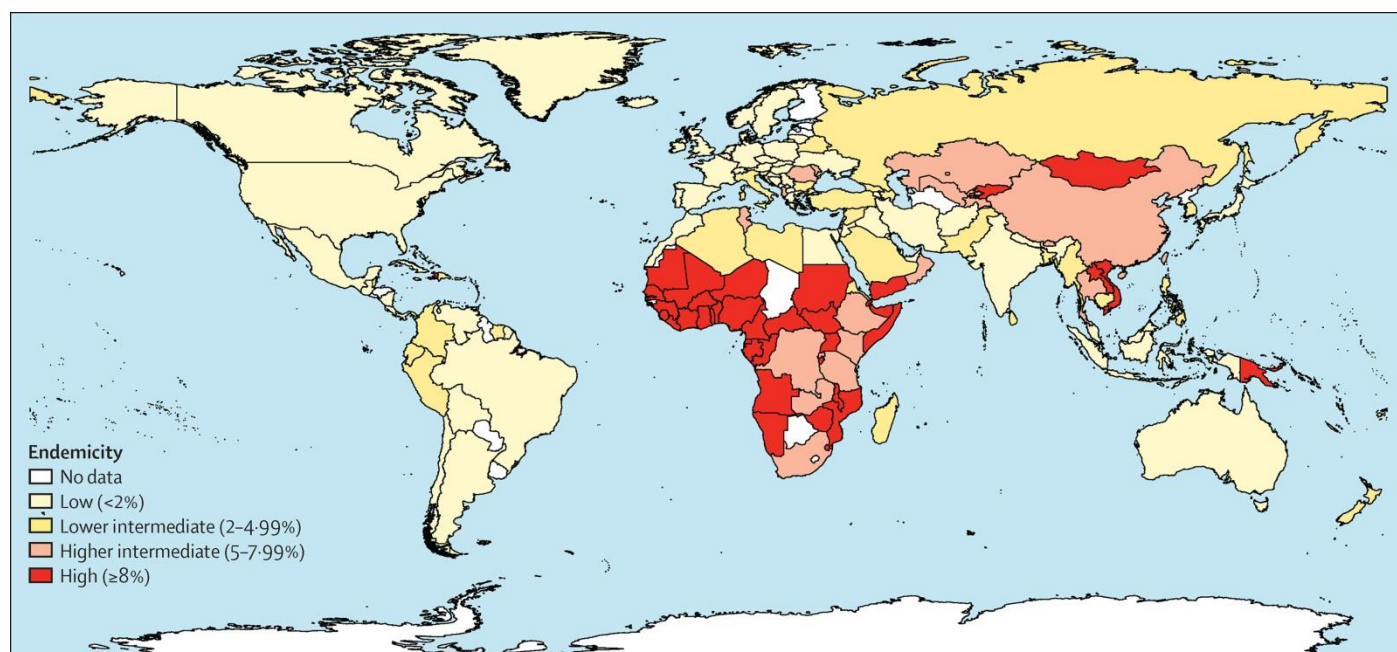
### Epidemiology of hepatitis B in Australia

It is estimated that 239,000 Australians were living with chronic hepatitis B in 2015 (1.0% population prevalence), with the number of people affected steadily increasing (MacLachlan et al., 2018). Of these, only 62% have been diagnosed and 15% are receiving guideline-based care (MacLachlan et al., 2018). In addition, over 10% of all Australians – approximately 2.3 million individuals – are estimated to be hepatitis B core antibody (anti-HBc) positive through previous resolved infection (Cowie et al., 2010).

Most Australians living with chronic hepatitis B were born overseas in endemic areas, particularly Asia and the Pacific, southern Europe and Africa (see Figure 1). In addition, Aboriginal and Torres

Strait Islander peoples, who constitute 2.8% of the total population, are estimated to represent 9% of people living with chronic hepatitis B. Other priority populations include people with a history of injecting drugs, men who have sex with men, and people born in Australia whose parents migrated from endemic areas.

These risk factors lead to substantial heterogeneity in the prevalence of chronic hepatitis B across Australia, with more than 2% of the population estimated to be living with chronic hepatitis B in some areas of Sydney, Melbourne and the Northern Territory, and less than 0.5% of the population affected in other areas (MacLachlan and Cowie, 2016).



**Figure 1. Global HBsAg endemicity (1957–2013)**

Source: Schweitzer et al. (2015). Copyright *The Lancet*, Elsevier 2015; reprinted with permission.

## Hepatitis B virus reactivation during cancer therapy

Haematological and solid tumour malignancies are a major cause of illness in Australia (Australian Institute of Health and Welfare, 2018). Chemotherapy is a common treatment for haematological malignancies and solid tumours. In 2014–15 there were 440,561 hospitalisations for chemotherapy, with many more patients receiving chemotherapy outside hospital (for example, in an outpatient or day centre) (Australian Institute of Health and Welfare, 2018). Individuals undergoing immunosuppressive cancer therapy and with serologic markers for HBV infection are at risk of HBV reactivation. Given the number of people undergoing cancer therapy and the prevalence of HBV in Australia, several thousand people are likely to be at risk of HBV reactivation. Many of these individuals are also likely to be unaware of their HBV status.

HBV reactivation is defined as a tenfold increase in HBV DNA levels from baseline in HBsAg-positive individuals and as seroreversion to HBsAg positivity in HBsAg-negative and anti-HBc-positive individuals (Reddy et al., 2015, European Association for the Study of the Liver, 2017, Lubel and Angus, 2010), although reappearance of HBV DNA often occurs before HBsAg (Mallet et al., 2016).

HBV reactivation has potentially serious consequences including hepatitis flares associated with elevated alanine amino-transferase (ALT), increased mortality due to liver failure, and interruptions to cancer therapy that contribute to poorer curative rates and lower overall survival (Paul et al., 2016, Perrillo et al., 2015).

HBV reactivation during cancer therapy has been reported in many HBsAg-positive patients with

haematological malignancies (Lok et al., 1991, Lau et al., 2003) as well as HBsAg-positive patients with solid tumours such as breast (Yeo et al., 2003, Liu et al., 2017), lung (Lin et al., 2014, Wu et al., 2017), gastrointestinal (Yang et al., 2015), liver (Jang et al., 2006), and head and neck (Yeo et al., 2005, Paul et al., 2016). Patients with resolved or past HBV infection (HBsAg negative/anti-HBc positive) also remain at risk for HBV reactivation (Perrillo et al., 2015), particularly patients with haematological malignancies undergoing therapy with rituximab or other B cell-depleting therapies and novel biological agents (Mozessohn et al., 2015, Yeo et al., 2009).

## Existing international guidelines

Major international organisations, including the American Gastroenterological Association (Reddy et al., 2015), the American Association for the Study of Liver Diseases (Lok and McMahon, 2009, Terrault et al., 2016), the Asian Pacific Association for the Study of the Liver (Sarin et al., 2016), the (European Association for the Study of the Liver, 2017), the European Conference on Infections in Leukaemia (Mallet et al., 2016), and the American Society of Clinical Oncology (Hwang et al., 2015), have produced recommendations for the testing and management of HBV in patients undergoing cancer therapy. These guidelines were developed by expert panels based on reviews of scientific literature and expert opinion and experience. Most guidelines panels evaluated the strength of the recommendation and quality of evidence available using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, while the European Conference on Infections in Leukaemia used the Infectious Diseases Society of America grading system and the American Society of Clinical Oncology did not use a formal grading system.

## Objectives of this consensus statement

The purpose of this consensus statement is to make recommendations for the testing and management of HBV in Australian patients undergoing therapy for haematological and solid tumour malignancies.

This consensus statement is limited to cancer therapy for haematological and solid tumour malignancies. 'Cancer therapy' refers to anti-cancer systemic treatments for haematological and solid tumour malignancies. Such systemic treatments usually fall into the categories of (a) conventional cytotoxic chemotherapy, (b) hormonal agents or (c) targeted therapy or immunotherapy, in contrast to local therapies such as surgery or radiotherapy. Other indications for immunosuppressive therapy such as rheumatologic conditions and solid organ transplantation are beyond the scope of this consensus statement.

This document is intended to be practical and approachable for a broad audience with an interest in the care of patients undergoing cancer therapy and patients with chronic HBV. This includes medical specialists, nurses and pharmacists in cancer or hepatitis services, and general practitioners with a special interest.

The goals of this consensus statement are:

- to prevent HBV reactivation in all patients during and after cancer therapy, and
- for there to be no preventable mortality and no interruptions to cancer therapy due to HBV reactivation.

## Advocacy statement

The recommendations presented in this consensus statement reflect best practice at the time of writing. We advocate for these recommendations to be reflected in the Australian funding structure. The Pharmaceutical Benefits Scheme (PBS) should cover the prescription of new-generation prophylactic HBV antiviral agents for patients identified as at-risk of HBV reactivation during immunosuppressive cancer therapy. The Medicare Benefits Schedule (MBS) should cover regular HBV testing during and after cancer therapy. We acknowledge that the recommendations may not reflect current practice in all cancer and hepatitis services across Australia. We urge health care service administrators and specialists to think about systems and procedures that can enable implementation of the best practice recommendations described in this document.

## Methodology

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This consensus statement was developed by medical specialists with expertise in infectious diseases, gastroenterology, haematology, oncology and paediatrics, and representatives from the Australasian Society for Infectious Diseases, the Gastroenterological Society of Australia (Australian Liver Association), the Haematology Society of Australia and New Zealand, the Medical Oncology Group of Australia, and the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine.

This consensus statement was prepared using a consultative process involving the steering committee and working parties. The recommendations presented in this consensus statement were developed through a review of existing guidelines and published literature, and tailored to the Australian context by referring to local epidemiology and MBS and PBS rules.

Levels of evidence for the recommendations were graded according to the GRADE system (Guyatt et al., 2008). The quality of evidence was classified

as high (A), moderate (B) or low (C). The strength of recommendations was classified as strong (1) or weak (2). Consensus was reached through discussion within each working group. If disagreements arose, further discussion and justification of opinions occurred until a consensus was achieved or the steering committee made a final decision. This final consensus statement was reviewed and endorsed by the following medical societies:

- the Australasian Society for Infectious Diseases (ASID);
- the Gastroenterological Society of Australia/Australian Liver Association (GESA/ALA);
- the Haematology Society of Australia and New Zealand (HSANZ);
- the Medical Oncology Group of Australia (MOGA); and
- the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM).

# 1. Who to test for hepatitis B infection

Consensus recommendations	GRADE
1.1. We recommend that all patients undergoing therapy for haematological malignancy are tested for hepatitis B infection.	A1
1.2. We recommend that all patients undergoing therapy for solid tumours are tested for hepatitis B infection.	B1
1.3. We suggest that the treating haematologist or medical oncologist prescribing cancer therapy is responsible for hepatitis B testing.	C2
1.4. We recommend that HBsAg, anti-HBc and anti-HBs are performed when testing for hepatitis B infection.	A1
1.5. We recommend hepatitis B testing in children should follow the same approach as for adults.	C1

Recommendation 1.1. We recommend that all patients undergoing therapy for haematological malignancy are tested for hepatitis B infection.

**Quality of Evidence:** High

**Strength of Recommendation:** Strong

## Background

Several international and national guidelines provide recommendations as to which patients should be tested for serological markers of HBV infection prior to cancer therapy to identify and manage patients at risk of HBV reactivation. Inconsistencies in these guidelines likely reflect global and regional differences in HBV prevalence, the chemotherapeutic or immunosuppressive therapies used, differences in health systems, and cost effectiveness considerations. In particular, recommendations for testing patients undergoing haematopoietic stem cell transplantation (HSCT) are inconsistent. As much of the literature concerning HBV reactivation in haematology patients is retrospective or in case series, knowledge gaps and limitations to the current evidence base contribute to the inconsistencies.

A “test all” approach is recommended in the Australian National Testing Policy (National

Hepatitis B Virus (HBV) Testing Policy Expert Reference Committee, 2015), the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine “B Positive” monograph (Australasian Society for HIV Medicine, 2014) and local clinical practice guidelines (e.g., Lubel et al. (2007)), and by the Asian Pacific Association for the Study of the Liver (Sarin et al., 2016), the (Gastroenterological Society of Australia, 2010), the European Association for the Study of the Liver (European Association for the Study of the Liver, 2017), and the European Conference on Infections in Leukaemia-5 (Mallet et al., 2016).

A “test high-risk” approach is recommended by the American Gastroenterological Association (Reddy et al., 2015), American Association for the Study of Liver Disease (Terrault et al., 2016, Lok and McMahon, 2009) and American Society of Clinical Oncology (Hwang et al., 2015) to stratify the risk of HBV reactivation according to the individual’s risk of HBV infection (Weinbaum et al., 2008), chemotherapeutic/immunosuppressive drug class to be prescribed or planned HSCT.

Approximately 239,000 Australians are living with chronic hepatitis B, 38% of whom have not yet been diagnosed (MacLachlan et al., 2018). As the



prevalence of HBV is higher in migrants from high-prevalence countries, it is expected that adherence to the “test all” approach will identify a significant burden of HBV within Australian haematology patients requiring HBV prophylaxis during cancer therapy, as well as after therapy has been completed (for those with chronic HBV meeting criteria for long-term therapy).

The cost of serological testing for HBV is covered by the MBS; the Medicare rebate for a full panel of tests (HBsAg, anti-HBs, anti-HBc) is approximately \$35 (item 69481). The cost-effectiveness of universal screening among patients with haematological malignancies has not yet been determined in the Australian context. However, even outside the context of impending immunosuppression, international evidence suggests that screening for hepatitis B may be cost effective down to a population prevalence of 0.3% (Eckman et al., 2011); the estimated prevalence in the Australian population is 1.0% (MacLachlan et al., 2018).

#### *Technical remarks*

1. HBV testing should include patients planned for both curative and non-curative treatment regimens.
2. We suggest that a “test all” approach be incorporated into institutional protocols to ensure that HBV testing is not missed in patients due to receive therapy for haematological malignancy.
3. Testing for HBV should not delay cancer therapy, but ideally should occur prior to the initiation of chemotherapy and be up to date (i.e., within the 12 months prior to cancer therapy) so that HBV prophylaxis may be prescribed concomitant with cancer therapy.

#### *Evidence and rationale*

When considering who to test for HBV prior to cancer therapy, three approaches were considered.

Testing all patients before cancer therapy can identify patients who may benefit from antiviral prophylaxis, allow for assessment of chronic HBV complications and permit contact tracing of family members for chronic HBV infection and link them to care.

A Canadian analysis of pre-treatment HBV serological testing in patients with lymphoma receiving R-CHOP found that a “test all” approach was associated with a tenfold lower rate of HBV reactivation than “test only high risk” or “test none” approaches. The “test all” approach is associated with the highest one-year survival rate and is the most cost effective (Zurawska et al., 2012).

The second approach is to screen only patients at risk of HBV according to Centers for Disease Control “high risk” groups (Weinbaum et al., 2008). This would reduce the number of HBV tests performed, but may miss cases of HBV if risk factors are not identified or considered. Suboptimal testing rates have been observed in pre-treatment oncology patients based on the “test only high-risk” approach (Hwang et al., 2015).

The third approach is to screen only patients who, if serological testing were positive, would be prescribed antiviral prophylaxis. In evaluating this approach, the prevalence of serological markers of HBV amongst patients with haematological malignancy, the reported risk of HBV reactivation, and particular risk factors (patient factors, drug class) could identify haematology patients at higher risk of HBV reactivation; this pathway would then test only these patients at risk of HBV

reactivation. Like the “test high-risk” approach, this has the potential to miss patients, including those who, if not tested for HBV prior to low intensity immunosuppression (i.e., not requiring HBV reactivation prophylaxis), might be missed if cancer therapy was subsequently intensified.

In view of these considerations, a “test all” approach is strongly recommended.

**Recommendation 1.2.** We recommend that all patients undergoing therapy for solid tumours are tested for hepatitis B infection.

**Quality of Evidence:** Moderate

**Strength of Recommendation:** Strong

### *Background*

While less frequent than in haematological malignancy, HBV reactivation has been reported in patients with a variety of solid tumours. Systematic reviews of patients receiving immunosuppressive treatment for common malignancies such as breast cancer (Liu et al., 2017) and lung cancer (Wu et al., 2017) report reactivation rates up to 38%, with significant variation among studies according to population prevalence of HBV. HBV reactivation has also been reported in individuals with a range of underlying malignancies including nasopharyngeal carcinoma, colorectal cancer, gastric cancer, pancreatic cancer and renal cell carcinoma (Voican et al., 2016). As for patients with haematological malignancy, the impact of HBV reactivation includes hepatitis, chemotherapy disruption and mortality from liver failure.

A recommendation for screening all patients for HBV prior to therapy for solid tumours has been controversial based on varying population

prevalence rates, reactivation risks associated with specific therapy regimens and varying conclusions from cost-effectiveness modelling. The Australian National Hepatitis B Testing policy recommends testing all patients prior to undergoing chemotherapy or immunosuppressive therapy (National Hepatitis B Virus (HBV) Testing Policy Expert Reference Committee, 2015). This recommendation is in line with recommendations from the Centers for Disease Control and Prevention, the American Association for the Study of Liver Diseases, the American Gastroenterological Association, the Asian Pacific Association for the Study of the Liver, and the European Association for the Study of the Liver.

The NSW Cancer Institute Cancer Treatment Guidelines recommend screening for all patients with solid tumours receiving curative treatment and those receiving immunosuppressive chemotherapy or high-dose glucocorticoids, but not for patients with incurable solid tumours. It should be noted that even if a tumour is incurable, chemotherapy may prolong life but HBV reactivation may reduce the duration and quality of life significantly.

The American Society of Clinical Oncology recommends screening of patients at high risk for HBV infection. These include people born in a country with a  $\geq 2\%$  HBV prevalence, household or sexual contact with persons with HBV infection, people with a history of injecting drug use, and men who have sex with men. The National Comprehensive Cancer Network also recommends screening high-risk patients but if risk based screening cannot be implemented, then universal screening should be considered.



### *Technical remarks*

1. Patients scheduled to undergo both curative and non-curative treatment regimens should have HBV testing.
2. In patients with very poor prognosis an individualised decision not to undertake screening may be made.
3. A “test all” approach should be incorporated into institutional protocols to ensure that HBV testing is not missed in patients due to receive therapy for solid tumours.
4. Testing for HBV should not delay cancer therapy, but should occur prior to the initiation of cancer therapy (or be up to date within the last 12 months) so that HBV prophylaxis may be prescribed concomitant with cancer therapy.

### *Evidence and rationale*

Multiple cancer therapy regimens have been associated with HBV reactivation. Alkylating agents, anthracyclines, antimetabolites, topoisomerase inhibitors and high-dose glucocorticoids are regarded as being high or moderate-risk therapies for HBV reactivation (Loomba and Liang, 2017). Multikinase inhibitors and mTOR inhibitors have also been associated with HBV reactivation and death. Anti-VEGF (vascular endothelial growth factor), anti-EGFR (epidermal growth factor receptor) and checkpoint inhibitors have not been associated with HBV reactivations to date (Voican et al., 2016).

Clearly some individuals are at higher risk of chronic hepatitis B infection than others. However, it is not possible to identify all those living with chronic hepatitis B based solely on country of birth, racial background, age, perceived risk factors or any other specific variables. As noted earlier, only an estimated 62% of people living with chronic hepatitis B in Australia have been

diagnosed (MacLachlan et al., 2018). The Australian National Testing Policy recommends that all people from priority populations be tested at least once for HBV exposure using HBsAg, anti-HBc and anti-HBs (National Hepatitis B Virus (HBV) Testing Policy Expert Reference Committee, 2015). It cannot be assumed that people at particularly high risk have previously been screened, and for many patients from these populations, the first opportunity for HBV testing may be in the context of screening prior to cancer therapy.

Unless the HBV status of an individual from a priority population is already recorded, it is recommended that all such people be tested for HBV regardless of the underlying malignancy or proposed cancer therapy regimen. Priority populations include people born in an intermediate or high-prevalence country (including countries in the Asia Pacific region, Europe, Africa/Middle East, and South America), Aboriginal or Torres Strait Islander people, and family, sexual or household contacts of a person with HBV infection. The identification of additional risk factors for HBV infection such as injecting drug use, high-risk sexual activity, or previous incarceration should also prompt testing in unvaccinated adults. Furthermore, all people with primary liver cancer and all people with evidence of chronic liver disease should undergo HBV testing.

Limiting HBV testing only to patients with identified risk factors increases the risk of failing to identify HBV-infected patients. A study from France, a country of low HBV endemicity, evaluated the ability of a screening questionnaire to identify patients with solid tumours at risk for HBV (Brasseur et al., 2015). The sensitivity of their risk-based screening questionnaire for identifying

HBV was only 45.5%, leading the authors to conclude that serologic testing should be undertaken in all patients requiring chemotherapy.

The cost-effectiveness of screening all patients undergoing chemotherapy for solid tumours has been modelled for Australia using adjuvant therapy for early breast cancer and palliative therapy for advanced lung cancer. In the Australian health care system, based on 2009 costings, a “test all” (universal) approach was not considered cost effective using an incremental cost-effectiveness ratio threshold of AUD \$50,000 (Day et al., 2011a). Modelling in the adjuvant setting was associated with a 13% probability of being cost-effective, which increased significantly in populations with high rates of undiagnosed HBV and high HBV prevalence. However, this cost-effectiveness study was performed in a higher treatment cost environment (prior to generic HBV antiviral availability) and with a different monitoring approach to that proposed in this document. A study from Singapore evaluated the cost-effectiveness of HBV screening in patients with sarcomas and gastrointestinal stromal tumours (Tan et al., 2016). Modelling was based on a clinical cohort of 485 patients; 5.5% of screened patients were HBsAg positive and 11.8% were HBsAg negative/anti-HBc positive. None of the patients experienced HBV reactivation. The authors determined that a “test all” strategy was not cost effective, except where the risk of death from HBV reactivation was substantial. The success of this strategy, however, relied on close monitoring and prompt treatment of HBV reactivation. If such close monitoring is not undertaken, HBV reactivation may not be promptly diagnosed and treated and a favourable outcome not assured.

In contrast to these negative findings, a modelling study from the United States concluded that population screening for hepatitis B may be cost effective down to a prevalence of 0.3% (Eckman et al., 2011). As noted earlier, the estimated prevalence in the Australian population is 1.0% (MacLachlan et al., 2018).

The disparity in these findings may in part be explained by the fact that studies addressing patients undergoing cancer therapy may limit cost-effectiveness analysis only to the period of cancer treatment, and not consider the long-term benefits for patients diagnosed with chronic hepatitis B who undergo treatment for their condition. Appropriate care for people living with hepatitis B (including monitoring and antiviral treatment where necessary) has been found to be highly cost effective in the Australian setting (Robotin et al., 2009). With only 15% of people living with hepatitis B in Australia estimated to be receiving guideline-based care (MacLachlan et al., 2018), there is significant scope for improvement in identification and linkage to care.

Recommendation 1.3. We suggest that the treating haematologist or medical oncologist prescribing cancer therapy is responsible for hepatitis B testing.

**Quality of Evidence:** Low

**Strength of Recommendation:** Weak

### *Background*

In clinical practice, pre-cancer therapy HBV testing has occurred inconsistently (Leung et al., 2011). This may be due to lack of consensus among treating clinicians (general practitioners, haematologists, medical oncologists, hepatologists) as to who should perform and act on HBV test results, as well as a lack of institutional protocols.

Despite the publication of international guidelines and an Australian National Hepatitis B Testing Policy (National Hepatitis B Virus (HBV) Testing Policy Expert Reference Committee, 2015) recommending screening of all patients prior to undergoing chemotherapy or immunosuppressive therapy, rates of HBV screening remain low in Australia. Policies and guidelines do not clearly state who should be responsible for ensuring that HBV screening occurs.

### *Technical remarks*

1. The treating clinician may delegate testing for HBV infection, providing that institutional systems are in place to ensure that the person responsible for testing acts on the testing recommendations.
2. Pharmacists and nurses can ensure patients undergoing cancer therapy receive hepatitis B testing through documenting performance of testing prior to chemotherapy.
3. If HBV testing has not occurred, we suggest that pharmacy and nursing staff should inform

the treating clinician or person responsible so that testing can be performed.

4. Testing for HBV should not delay chemotherapy.

### *Evidence and rationale*

Multiple studies have indicated that rates of screening prior to cancer therapy in both haematological and solid tumour settings are low around the world. In a recent study of HBV screening undertaken in the USA, only 8.3% of nearly 10,000 patients underwent testing; patients from Asia and those older than 50 years of age were less likely to be screened, despite being at higher risk than younger, non-Asian patients (Kwak et al., 2018). The authors observed that screening rates were higher in university hospital clinics (20%) than in community clinic settings (13%) ( $p < 0.001$ ), and they suggested that the presence of standardised protocols contributed to this higher rate; nonetheless, the overall screening rates were low. In the absence of a standardised protocol for HBV screening at the Mayo Clinic Rochester from 2006–11, only 16% of 8005 patients (52% with haematological malignancy) underwent testing prior to chemotherapy (Wi et al., 2015). This was similar to the reported experience from The University of Texas MD Anderson Cancer Center, where only 16% of 18,688 patients receiving chemotherapy were screened, even after the introduction of international recommendations (Hwang et al., 2013). Even in China, with high HBV prevalence in the general population, fewer than 20% of patients were screened prior to chemotherapy (Wang et al., 2013). In most reports, screening rates for patients with haematological malignancy are much higher than those for patients with solid tumours.

It is recognised that particularly high rates of HBV reactivation occur with rituximab, including in

HBsAg-negative/anti-HBc-positive patients. As a result, all international guidelines, as well as approved product information, recommend HBV screening prior to use of rituximab. An Australian single-centre study reported low rates of pre-treatment HBV screening even in this high-risk group (Leung et al., 2011). Of 355 patients undergoing treatment with rituximab, only 31% underwent HBV screening, and only half were tested prior to introduction of treatment.

An Australian nationwide electronic survey of medical oncologists, conducted in 2009, indicated that only a minority had adopted universal screening for patients undergoing cancer chemotherapy (Day et al., 2011b). When asked why they did not screen, most cited inadequate evidence for a benefit of screening. When they did screen, patient ethnicity was reported as the reason for screening in 82%. However, over one fifth of respondents had observed at least one case of HBV reactivation in their practice, and 30% of those reactivations occurred in Caucasians. Since that time the evidence for universal screening in patients with solid tumours has firmed, and international guidelines have increasingly recommended universal screening. From this survey, it would appear that medical oncologists accepted that it was their responsibility to decide which patients should and should not be screened.

None of the existing guidelines specifies who should be responsible for HBV testing. Our recommendation is based largely on the rationale that someone must be responsible for the overall care of the patient, and that the treating clinician (or their delegate) should also be the one responsible for HBV testing. Testing should be undertaken if the management plan includes prescription of cytotoxic or immunosuppressive chemotherapy, including 'biologics'. This will

avoid confusion of who will request and act on the HBV results, and also avoid testing being missed. The need for HBV testing should be incorporated into patient management protocols.

**Recommendation 1.4.** We recommend that HBsAg, anti-HBc and anti-HBs are performed when testing for hepatitis B infection.

**Quality of Evidence:** High

**Strength of Recommendation:** Strong

### *Background*

The risk of HBV reactivation in the setting of cancer therapy depends on HBV serological status. All current international guidelines recommend hepatitis B surface antigen (HBsAg) testing and the majority recommend hepatitis B core antibody (anti-HBc) testing prior to chemotherapy. Most international guidelines do not specify a recommendation on hepatitis B surface antibody (anti-HBs) testing, or do not recommend it based on a lack of evidence. However evidence is mounting that the presence of anti-HBs in patients who are HBsAg negative/anti-HBc positive is associated with a reduced rate of HBV reactivation in the setting of treatment for haematological malignancy (Paul et al., 2017).

The MBS covers the cost of all three serological tests for hepatitis B (HBsAg, anti-HBc and anti-HBs) performed at the same time. The additional rebate paid for adding a third serologic marker is approximately \$10.

### *Technical remarks*

1. HBsAg and anti-HBc tests should occur prior to initiation of cancer therapy to guide the introduction and duration of antiviral prophylaxis for HBV reactivation.

2. Individual tests should be ordered separately to ensure the laboratory performs the correct test (a request for HBV serology may not provide all required results).
3. When found in the context of HBV screening, a positive HBsAg test indicates a diagnosis of chronic hepatitis B infection. Further testing for HBeAg, anti-HBe, HBV DNA and LFTs should be performed and the patient should be referred to a viral hepatitis specialist for complete assessment and evaluation for long-term treatment and monitoring beyond the period of prophylaxis.
4. Serological patterns can change over time, particularly following periods of immunosuppression. Retesting of HBsAg and anti-HBc should be performed in patients who present with long intervals between cancer therapy treatments (e.g., patients with relapse of underlying haematological malignancy).
5. The presence of an isolated anti-HBc antibody (HBsAg negative/anti-HBc positive/anti-HBs negative) may reflect occult hepatitis B with intermittent or persistent viraemia.
6. The presence of anti-HBs reduces but does not eliminate the risk of HBV reactivation in patients who are HBsAg negative/anti-HBc positive. Patients should therefore still be considered for HBV prophylaxis according to the recommendations of this consensus statement.
7. Even when present prior to cancer therapy, anti-HBs may become undetectable in the context of intensive or myeloablative cancer therapy (e.g., in stem cell transplant recipients). Such patients may be at increased risk of HBV reactivation as anti-HBs titres fall. Re-vaccination against HBV should be considered after immune reconstitution (see recommendation 2.5).
8. The absence of any HBV serological markers (HBsAg negative/anti-HBc negative/anti-HBs

negative) provides an opportunity for HBV vaccination in susceptible individuals (see recommendation 2.5.).

### *Evidence and rationale*

#### **HBsAg**

In a prospective study of 626 consecutive cancer patients who received chemotherapy, the prevalence of HBsAg positivity was 12% (78/568 tested for HbsAg) (Yeo et al., 2000). Patients with lymphoma had the highest prevalence of HBsAg positivity (15/70; 21%) in comparison to leukaemia/myeloma patients (1/17; 6%) and 5-13% with solid tumours. ALT elevation occurred during chemotherapy in 34 of 626 patients; of these, 15 cases (44%) were attributed to HBV reactivation. Six of these HBV reactivations (40%) occurred in lymphoma cases. Overall, this translates to a HBV reactivation rate of 8.6% (6/70) of all lymphoma patients included in the study.

#### **anti-HBc**

Patients with chronic hepatitis B (HBsAg positive) may spontaneously lose HBsAg at an annual rate of 0.5%; this is defined as “spontaneous clearance” (Liaw et al., 2012). Alternatively, patients may have serological evidence of past HBV exposure, both scenarios leading to an HBsAg-negative/anti-HBc-positive state. Globally, these patients by far outnumber those with chronic HBV. The HBV may persist in hepatocytes and other tissues in the form of covalently closed circular DNA. Although the HBV DNA may not be detectable in serum, patients remain at risk of HBV reactivation during some cancer therapy regimens (Bréchot et al., 1985, Chemin et al., 2001).

## anti-HBs

The presence of anti-HBs is not completely protective against HBV reactivation in patients who are HBsAg negative/anti-HBc positive. There is some low-level evidence that an anti-HBs titre of <100 is associated with higher risk of HBV reactivation than those with higher anti-HBs titre (Pei et al., 2012, Cho et al., 2016).

A recent meta-analysis of 20 studies involving 1,672 patients not receiving antiviral prophylaxis concluded that the presence of anti-HBs reduced the risk of HBV reactivation by 79% (pooled OR of 0.21 (95% CI 0.14–0.32)) in patients who were HBsAg negative/anti-HBc positive and receiving chemotherapy for haematological malignancy (Paul et al., 2017). In this analysis, HBV reactivation was observed in 14% with isolated anti-HBc versus 5% with anti-HBc and anti-HBs. The authors were unable to determine if a threshold anti-HBs titre was associated with a reduced rate of HBV reactivation.

As further studies are required, the presence or titre of anti-HBs cannot currently be used to predict or stratify patients as to their risk of HBV reactivation or guide antiviral prophylaxis recommendations.

Testing for anti-HBs in addition to HBsAg and anti-HBc shows whether an individual is immune to HBV. Routine testing of anti-HBs can identify non-immune individuals who are susceptible to HBV infection. Those who are at risk of infection are eligible for government-funded vaccination, although vaccine funding outside the national immunisation schedule may only be provided at the state level. Recommendation 2.5 specifies timing of HBV immunisation in non-immune patients.

Recommendation 1.5. Hepatitis B testing in children should follow the same approach as for adults.

**Quality of Evidence:** Low

**Strength of Recommendation:** Strong

## Background

Most children born in Australia are vaccinated for hepatitis B infection under the universal national immunisation program (National Health and Medical Research Council (NHMRC), 2015). The HBV vaccination rate for Australian-born infants is estimated at over 95% at two years old (Australian Government Department of Health, 2018). Vertical transmission is the most important cause of HBV infection in children, with up to 90% risk of chronic infection in those born to mothers positive for both HBsAg and HBeAg. While the combination of active and passive immunisation at birth is 95% effective in reducing vertical transmission in this population, there remains a small but appreciable risk of infection (Visvanathan et al., 2016).

The prevalence of hepatitis B infection in children with cancer or leukaemia undergoing chemotherapy or HSCT in Australia is unknown and remains an important research gap.

We recommend that all children undergoing cancer treatment or HSCT are tested for hepatitis B infection, with particular attention paid toward patients:

- with no history of hepatitis B vaccination
- born overseas
- of Aboriginal and Torres Strait Islander origin.



## 2. When to start antiviral agents

Consensus recommendations	GRADE
2.1. We recommend that all HBsAg positive patients with haematological or solid tumour malignancy undergoing therapy should receive antiviral prophylaxis.	A1
2.2. We recommend that risk for HBV reactivation in patients who are HBsAg negative and anti-HBc positive is determined by the cancer therapy regimen (higher risk vs lower risk).	B1
We make the following recommendations for patients who are HBsAg-negative and anti-HBc positive:	
2.3. Patients undergoing higher risk cancer therapy (haematopoietic stem cell transplantation, B-cell depleting/B-cell active/anti-CD20 agents, acute leukaemia and high-grade lymphoma therapy) should receive antiviral prophylaxis.	B1
2.4. Patients undergoing lower risk cancer therapy do not require antiviral prophylaxis.	C1
2.5. We recommend that patients without evidence of prior HBV exposure (HBsAg negative/anti-HBc negative) do not require antiviral prophylaxis.	C1
We suggest that these patients should be assessed for HBV immunity (using anti-HBs) and offered vaccination if anti-HBs<10 at 6 months after completion of cancer therapy and when underlying disease is controlled.	C2
2.6. We recommend that antiviral prophylaxis should be commenced as soon as possible relative to the commencement of cancer therapy, but should not delay cancer therapy.	B1
2.7. We recommend the use of potent, high-barrier-to-resistance nucleoside/nucleotide analogues (i.e., entecavir or tenofovir) for antiviral prophylaxis.	A1
2.8. We recommend that all HBsAg positive patients should be referred to a viral hepatitis specialist for routine assessment.	C1
2.9. We recommend antiviral prophylaxis for children should follow the same approach as for adults.	C1

Recommendation 2.1. We recommend that all HBsAg positive patients with haematological or solid tumour malignancy undergoing therapy should receive antiviral prophylaxis.

**Quality of Evidence:** High

**Strength of Recommendation:** Strong

### Background

Most international guidelines recommend antiviral prophylaxis for HBsAg positive patients undergoing chemotherapy (European Association for the Study of the Liver, 2017, Sarin et al., 2016, Lok and McMahon, 2009, Hwang et al., 2015). The American Gastroenterology Association uses a risk-based approach recommending prophylaxis

for HBsAg-positive patients at high and moderate risk of HBV reactivation (Reddy et al., 2015).

### *Evidence and rationale*

Reactivation of HBV replication with increase in serum HBV DNA and ALT levels has been reported in 16–80% of hepatitis B carriers undergoing chemotherapy (Lok et al., 1991, Levy et al., 1990). The hepatitis flares are often asymptomatic; however, icteric hepatitis, clinical hepatic decompensation and death have been reported. HBV reactivation is well documented in patients with haematological malignancies, in particular those treated with rituximab-based chemotherapy (Evens et al., 2011, Dong et al., 2013).

Several prospective, randomised controlled trials (Hwang et al., 2012, Huang et al., 2013, Lau et al., 2003, Hsu et al., 2008, Jang et al., 2006) and multiple published case series have demonstrated the effectiveness of antiviral prophylaxis (therapy started prior to or at the same time as starting cancer therapy), predominantly using lamivudine in preventing HBV reactivation in HBsAg-positive patients receiving cancer therapy.

A systematic review (Loomba et al., 2008) of the effect of prophylactic lamivudine on HBV reactivation during chemotherapy of HBsAg-positive patients included 14 studies with 275 patients receiving lamivudine prophylaxis and 485 control patients who were not given lamivudine. Prophylactic lamivudine therapy decreased HBV reactivation and HBV-related hepatitis by 80–100% and eliminated HBV-related hepatic failure. Cancer-related mortality was decreased in the lamivudine treated patients, probably by reducing the need for delay or interruption of cancer therapy.

The risk of HBV reactivation is also substantial in patients with solid tumours. A recent review of HBV reactivation in solid tumours (Paul et al., 2016) included 19 studies with 1751 HBsAg positive patients of whom 774 received prophylaxis (14 studies with lamivudine, two studies with lamivudine or entecavir, one study with entecavir, and one study with lamivudine or adefovir). HBV reactivation in HBsAg-positive patients without antiviral prophylaxis ranged from 4% to 68% (median 25%) (Paul et al., 2016). Most included studies – sub-grouped by chemotherapy class or tumour type – reported a greater than 10% risk of HBV reactivation. In HBsAg-positive patients, antiviral prophylaxis substantially reduced the odds of HBV reactivation by 88% (OR 0.12, 95% CI 0.06–0.22), HBV-related hepatitis by 82% (OR 0.18, 95% CI 0.10–0.32), and chemotherapy interruption by 90% (OR 0.10, 95% CI 0.04–0.27) (Paul et al., 2016).

**Recommendation 2.2.** We recommend that risk for HBV reactivation in patients who are HBsAg negative and anti-HBc positive is determined by the cancer therapy regimen (higher risk vs lower risk).

**Quality of Evidence:** Moderate

**Strength of Recommendation:** Strong

### *Background*

Recommendations for prophylaxis in HBsAg-negative/ anti-HBc-positive patients undergoing cancer therapy vary across international guidelines. Various factors are used to recommend antiviral prophylaxis, including chemotherapy regimen, presence of HBV DNA, presence of anti-HBs, and underlying disease. The European Association for the Study of the Liver and the Asian Pacific Association for the Study of the Liver



guidelines recommend that HBsAg-negative/anti-HBc-positive patients with detectable HBV DNA should be treated similarly to HBsAg-positive patients (i.e., should receive HBV antiviral prophylaxis) (European Association for the Study of the Liver, 2017, Sarin et al., 2016). European Association for the Study of the Liver and Asian Pacific Association for the Study of the Liver guidelines also suggest prophylaxis in all HBsAg-negative/anti-HBc-positive patients with undetectable HBV DNA who receive rituximab (anti-CD20) and/or combined regimens for haematological malignancy, if they are anti-HBs negative and/or if close monitoring of HBV DNA is not guaranteed (European Association for the Study of the Liver, 2017, Sarin et al., 2016). The American Association for the Study of Liver Diseases does not make a specific recommendation for prophylaxis in HBsAg-negative/anti-HBc-positive patients due to insufficient evidence. The American Gastroenterological Association's risk-based approach includes prophylaxis for HBsAg-negative/anti-HBc-positive patients treated with B-cell-depleting agents such as rituximab and suggests prophylaxis for HBsAg-negative/anti-HBc-positive patients undergoing treatment that places them at moderate risk (e.g., tumour necrosis factor alpha inhibitors, tyrosine kinase inhibitors, prolonged or high-dose corticosteroids) (Reddy et al., 2015). The American Society of Clinical Oncology and European Conference on Infections in Leukaemia recommend prophylaxis for HBsAg-negative/anti-HBc-positive patients with high risk of reactivation (e.g., rituximab or HSCT) (Hwang et al., 2015, Mallet et al., 2016).

## *Evidence and rationale*

### **Higher vs lower-risk cancer therapy**

In this consensus statement, higher-risk cancer therapy for HBsAg-negative/anti-HBc-positive patients refers to HSCT, B cell-depleting/B cell-active/anti-CD20 agents (including rituximab, obinutuzumab, ocrelizumab, ofatumumab and ibritinib) and acute leukaemia and high-grade lymphoma therapy (see Figure 2). Some combinations of cancer therapies may also elevate reactivation risk and should be considered on an individual basis.

HBsAg-negative/anti-HBc-positive patients receiving rituximab-containing chemotherapy remain at risk of HBV reactivation (Hsu et al., 2014, Mozessohn et al., 2015, Yeo et al., 2009). Studies of HBsAg-negative/anti-HBc-positive patients with haematological malignancy who underwent treatment with rituximab have found that even patients with undetectable HBV DNA at baseline are at risk for HBV reactivation (Huang et al., 2013, Hsu et al., 2014).

Due to the profound immune suppression associated with chemotherapy conditioning before HSCT, HBsAg-negative/anti-HBc-positive patients undergoing HSCT are at high risk of HBV reactivation (Hammond et al., 2009, Mallet et al., 2016). The risk of reactivation may be higher in allogeneic HSCT than in autologous HSCT (Yoo et al., 2015).

Evidence for HBV reactivation in HBsAg-negative/anti-HBc-positive acute leukaemia and high-grade lymphoma receiving therapy that does not contain B cell-depleting/B cell-active/anti-CD20 agents is limited. Studies with HBsAg-negative/anti-HBc-positive patients receiving chemotherapy without rituximab for acute

leukaemia and high-grade lymphoma reported rates of HBV reactivation of 2.0–12.5% (Paul et al., 2017, Totani et al., 2015, Chen et al., 2015a, Lok et al., 1991).

There is limited evidence on the risk of HBV reactivation in HBsAg-negative/anti-HBc-positive patients not receiving higher-risk cancer therapy. A prospective study of 32 HBsAg-negative/anti-HBc-positive patients with solid tumours undergoing non-B cell-depleting chemotherapy (for example, cyclophosphamide, methotrexate, docetaxel) reported no HBV reactivation in the follow-up period (up to 36 months) (Federico et al., 2017). This study suggests that the risk of reactivation is low in this patient group, but further research is required.

Emerging classes of immunotherapy or targets agents, for example checkpoint inhibitors and tyrosine kinase inhibitors have been reported to cause HBV reactivation with uncertain mechanisms (Voican et al., 2016, Chang et al., 2017, Bui and Wong-Sefidan, 2015). In studies of novel immunotherapies, patients with HBV exposure (anti-HBc positive) have been required to be on suppressive HBV antivirals making it difficult to determine reactivation risks currently. Immune stimulating drugs can also cause immune-mediated hepatitis (independent of HBV) or other organ inflammation, sometimes requiring the use of other immune suppressing medications like steroids. While contributing to HBV reactivation in some circumstance, tyrosine kinase inhibitors have not been classified as high risk in previous systematic reviews (Perrillo et al., 2015).

At this stage, novel immunotherapies and targeted therapies are not consider high-risk drugs when used alone. HBsAg-positive individuals should be given prophylaxis (as with all other cancer therapies), but their use should not prompt

prophylaxis in HBsAg-negative, anti-HBc positive individuals. All anti-HBc-positive individuals receiving novel immunotherapies and targeted therapies should be monitored closely, particularly when used in combination with other immune suppressing agents

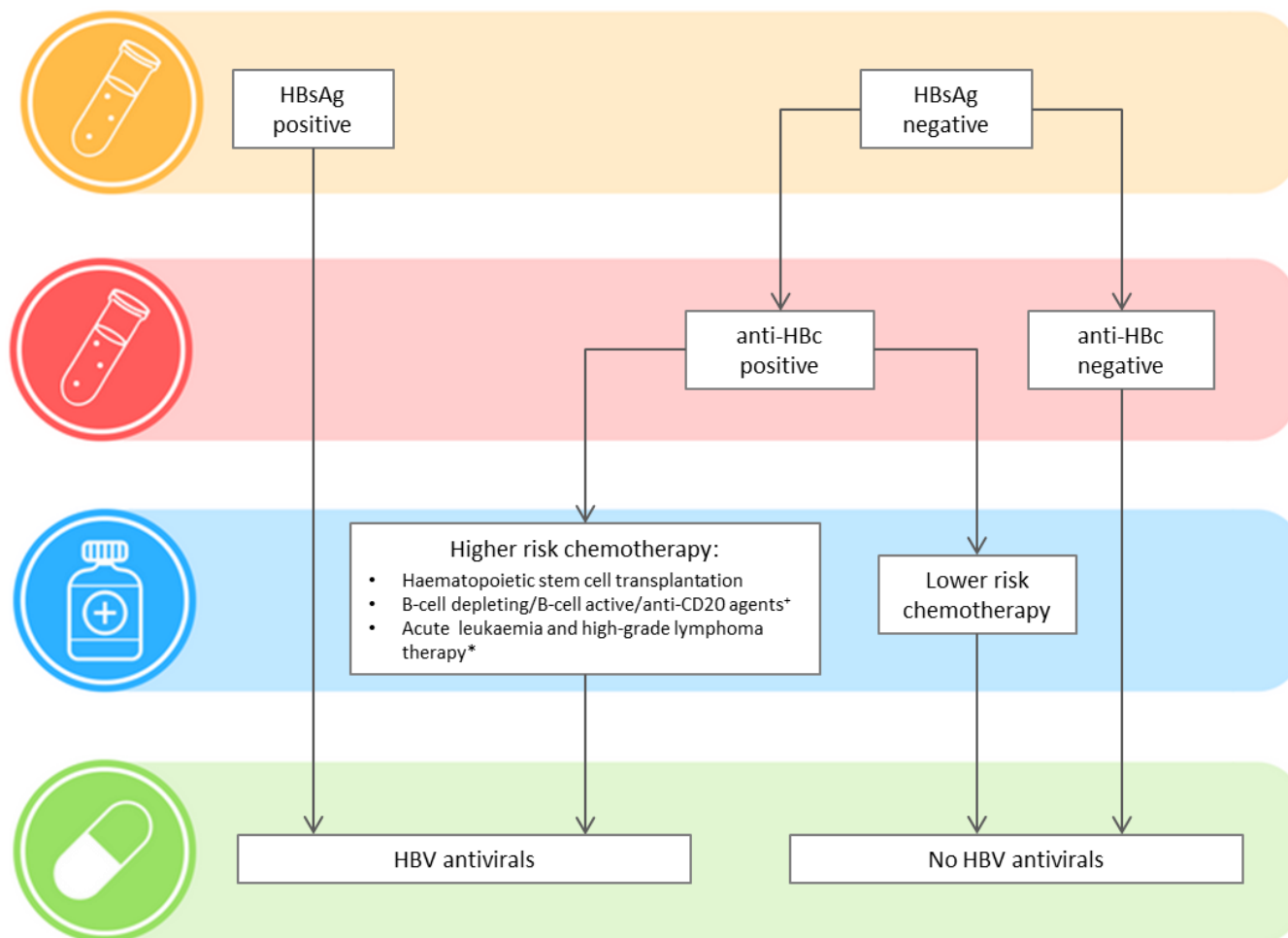
## **HBV DNA**

Most international guidelines recommend HBV DNA testing when HBsAg and/or anti-HBc are positive (Sarin et al., 2016, European Association for the Study of the Liver, 2017, Mallet et al., 2016, Reddy et al., 2015, Terrault et al., 2016, Lok and McMahon, 2009, Hwang et al., 2015). The presence of HBV DNA in HBsAg-negative/anti-HBc-positive patients indicates occult HBV infection. Patients with isolated anti-HBc (HBsAg negative/anti-HBs negative) may have occult HBV with detectable viraemia and be at increased risk of HBV reactivation. An Australian study with 1,451 patients found that prevalence of occult HBV infection was 0.69% (Martinez et al., 2015), suggesting that it is rare in Australia. Given this rare occurrence of HBV DNA, universal HBV DNA testing for all HBsAg-negative/anti-HBc-positive patients is not cost effective and would detect HBV DNA in very few individuals. However, if patients are already known to have occult infection, it is reasonable to treat them as similar to HBsAg-positive patients and prescribe antiviral prophylaxis.

## **anti-HBs**

There is insufficient evidence about the role of anti-HBs in protecting against HBV reactivation in HBsAg-negative/anti-HBc-positive patients (see recommendation 1.4.). Meta-analyses have explored the protective role of anti-HBs, finding 79% lower odds of reactivation among people with anti-HBs compared to without anti-HBs (both anti-

HBc positive) (Paul et al., 2017). Nevertheless, there were still reactivations among those with otherwise detectable anti-HBs titres (Paul et al., 2017).



**Figure 2: Flowchart for HBV antiviral prophylaxis in patients undergoing cancer therapy**

Notes: “Lower risk” agents are all others not included in “higher risk”; implications for monitoring and duration of antivirals are discussed in the text. +Including rituximab, obinutuzumab, ocrelizumab, ofatumumab and ibrutinib; this is not an exhaustive list as new agents will be introduced and more evidence about the risk of HBV reactivation comes to light. \*Lower level of evidence for risk of HBV reactivation in acute leukaemia and high-grade lymphoma therapy.

Recommendation 2.3. We recommend that HBsAg-negative/anti-HBc positive patients undergoing higher risk cancer therapy (haematopoietic stem cell transplantation, B-cell depleting/B-cell active/anti-CD20 agents, acute leukaemia and high-grade lymphoma therapy) should receive antiviral prophylaxis.

**Quality of Evidence:** Moderate

**Strength of Recommendation:** Strong

#### *Evidence and rationale*

Given the ongoing risk of HBV reactivation in HBsAg-negative/anti-HBc-positive patients undergoing higher-risk cancer therapy, we recommend that these patients should receive antiviral prophylaxis. Some studies used a method of monthly HBV DNA monitoring followed by pre-emptive antiviral therapy (Kusumoto et al., 2015, Seto et al., 2014). However, the practical and resource limitations associated with frequent and active monitoring means that this procedure is unlikely to be effective or practical for clinicians in real-world practice (outside well-funded research studies). HBV DNA monitoring could have serious consequences if the re-emergence or elevation of HBV DNA is not detected in time.

As discussed above (section 2.2), the level of evidence for acute leukaemia and high-grade lymphoma is lower.

There is a need to keep up to date as new agents are introduced and evidence about their potential for HBV reactivation comes to light.

Recommendation 2.4. We recommend that HBsAg-negative/anti-HBc positive patients undergoing lower risk cancer therapy do not require antiviral prophylaxis.

**Quality of Evidence:** Low

**Strength of Recommendation:** Strong

There is no evidence to recommend prophylaxis in HBsAg-negative/anti-HBc-positive patients undergoing lower-risk cancer therapy; the risk of HBV reactivation in these patients may be low (Federico et al., 2017). Therefore, prophylactic antivirals are not clinically indicated, and we suggest monitoring these patients (see recommendation 4.4).

Recommendation 2.5. We recommend that patients without evidence of prior HBV exposure (HBsAg negative/anti-HBc negative) do not require antiviral prophylaxis.

**Quality of Evidence:** Low

**Strength of Recommendation:** Strong

We suggest that these patients should be assessed for HBV immunity (using anti-HBs) and offered vaccination if anti-HBs < 10 at 6 months after completion of cancer therapy and when underlying disease is controlled.

**Quality of Evidence:** Low

**Strength of Recommendation:** Weak

#### *Background*

Hepatitis B vaccination is recommended for Australians at risk of hepatitis B infection, including adults with weakened immune function (National Health and Medical Research Council (NHMRC), 2015). With high immunosuppression, HBV antibodies are likely to be depleted during cancer therapy. Vaccination should be considered after immune function has improved following chemotherapy immunosuppression.

### *Evidence and rationale*

In general, it is recommended to wait six months after completion of cancer therapy and until underlying disease is controlled to improve the effectiveness of HBV vaccination, although HBV vaccination is safe during immunosuppression and can be administered if HBV transmission risks are present (National Health and Medical Research Council (NHMRC), 2015).

Recommendation 2.6. We recommend that antiviral prophylaxis should be commenced as soon as possible relative to the commencement of cancer therapy, but should not delay cancer therapy.

**Quality of Evidence:** Moderate

**Strength of Recommendation:** Strong

### *Evidence and rationale*

HBV antivirals should be commenced as soon as possible at the same time as the start of cancer therapy. HBV reactivation may occur at any time during or after cancer therapy, although there is typically a delay between the initiation of therapy and HBV reactivation (Lau et al., 2003, Seto et al., 2014). A study with HBsAg-positive patients receiving chemotherapy for lymphoma reported a median delay of 16 weeks (range 4–36 weeks) after the initiation of chemotherapy (Lau et al., 2003). Another study with HBsAg-negative/anti-HBc-positive patients undergoing rituximab-based chemotherapy for haematological malignancy reported a median delay of 23 weeks (range 4–100 weeks) after the commencement of rituximab treatment (Seto et al., 2014). To ensure optimal cancer treatment outcomes, we recommend that cancer therapy initiation should not be delayed due to antiviral prophylactic therapy.

Recommendation 2.7. We recommend the use of potent, high-barrier-to-resistance nucleoside/nucleotide analogues (i.e., entecavir or tenofovir) for antiviral prophylaxis.

**Quality of Evidence:** High

**Strength of Recommendation:** Strong

### *Background*

Much of the literature reports the use of lamivudine for HBV prophylactic therapy in chemotherapy patients, because it was the mainstay of HBV treatment prior to entecavir and tenofovir entering the market. Existing international guidelines also support the use of HBV antiviral drugs with a high barrier to resistance in HBsAg-positive patients, with less evidence in HBsAg-negative/anti-HBc-positive patients (European Association for the Study of the Liver, 2017, Reddy et al., 2015, Mallet et al., 2016).

In Australia, prescription of HBV antiviral agents for prophylaxis of HBV reactivation in the setting of cancer therapy (when no other HBV indication exists) is not currently funded under the PBS. The PBS currently subsidises HBV antiviral agents for patients with chronic HBV infection, with elevated HBV DNA and evidence of chronic liver injury.

### *Evidence and rationale*

Lamivudine is associated with a high rate of drug resistance, particularly when used beyond one year. Lamivudine resistance rates in non-immunocompromised patients are reported at 20% and 30% at 1 and 2 years, respectively (Lok et al., 2003). These rates are likely to be higher in patients receiving immunosuppressive treatment. Patients with solid tumour or haematological malignancy often undergo therapy regimens of

unpredictable and potentially long duration with multiple cycles, which may place them at greater risk of lamivudine drug resistance. Third-generation nucleoside/nucleotide analogues such as entecavir or tenofovir have a much lower mutation rate (Tenney et al., 2009) and are superior to lamivudine in preventing HBV reactivation in immunosuppressed patients (Huang et al., 2014, Chen et al., 2015b). With generic access to entecavir and tenofovir, these high-barrier-to-resistance agents are also similarly priced. A prospective randomised study of entecavir versus lamivudine prophylaxis in 121 patients with lymphoma undergoing rituximab-based chemotherapy showed that prophylactic entecavir resulted in a significantly lower incidence of HBV reactivation (6.6% vs 30%), delayed HBV-related hepatitis (0 vs 13.3%) and chemotherapy disruption (1.6% vs 18.3%) (Huang et al., 2014). A retrospective analysis of 213 patients with solid tumours undergoing chemotherapy also found significantly lower rates of HBV reactivation and chemotherapy disruption among patients who received prophylactic entecavir rather than lamivudine (0% vs 7.0%, and 2.9% vs 9.7% respectively) (Chen et al., 2015b). Serious medication side effects of tenofovir (including renal impairment, osteoporosis) and entecavir (including lactic acidosis) are rare, but they can influence choice of medication, require monitoring during prolonged therapy, and highlight the need for specialist referral for people found to have chronic HBV.

We recommend the use of potent, high-barrier-to-resistance nucleoside/nucleotide analogues (i.e., entecavir or tenofovir) over lamivudine for prophylactic antiviral therapy in patients undergoing cancer therapy. In line with our recommendation, we advocate for HBV reactivation prophylaxis for patients undergoing

chemotherapy to be included as a standalone indication for antiviral medication prescription with a PBS subsidy.

**Recommendation 2.8.** We recommend that all HBsAg-positive patients should be referred to a viral hepatitis specialist for routine assessment.

**Quality of Evidence:** Low

**Strength of Recommendation:** Weak

*Technical remarks:*

1. HBsAg-positive patients should be referred to a viral hepatitis specialist for assessment.
2. If the treating clinician is unsure of appropriate management for a patient who is HBsAg negative/anti-HBc positive, they should consult a viral hepatitis specialist for guidance.

*Evidence and rationale*

Positive HBsAg indicates a diagnosis of chronic hepatitis B infection. Due to the complex nature of chronic hepatitis B infection during immunosuppression, we recommend that all HBsAg-positive patients are referred to a viral hepatitis specialist for assessment. Assessment follows existing guidelines for the assessment and management of patients with chronic HBV including further testing for HBeAg, anti-HBe, HBV DNA, LFTs, blood borne virus serology (Hepatitis A, C, D and HIV), and potential complications of chronic HBV such as liver cirrhosis and hepatocellular carcinoma (European Association for the Study of the Liver, 2017, Terrault et al., 2016, Reddy et al., 2015, Sarin et al., 2016). HBV DNA testing will identify viraemic patients who may meet criteria for long-term antiviral therapy according to guidelines for the management of chronic hepatitis B.



HBsAg-negative/anti-HBc-positive patients do not routinely need to be referred to a viral hepatitis specialist, although we suggest that a specialist is consulted for advice in planning treatment and monitoring of these patients, particularly if the treating clinician is unsure of appropriate management. Consultation pathways and protocols may vary depending on the service capacity of individual hospitals.

Recommendation 2.9. We recommend antiviral prophylaxis for children should follow the same approach as for adults.

**Quality of Evidence:** Low

**Strength of Recommendation:** Strong

*Technical remarks:*

1. All HBsAg-positive and all HBsAg-negative/anti-HBc-positive children undergoing cancer therapy should be referred to a viral hepatitis specialist, ideally with paediatric expertise, for routine assessment.
2. All HBsAg-positive children requiring cancer therapy should receive antiviral prophylaxis.
3. Antiviral prophylaxis should be considered for HBsAg-negative/anti-HBc-positive children undergoing higher-risk cancer therapy (HSCT, B cell-depleting/B cell-active/anti-CD20 agents, acute leukaemia and high-grade lymphoma therapy).
4. HBsAg-negative/anti-HBc-positive children undergoing lower-risk cancer therapy can be followed and treated upon reactivation of HBV infection if it occurs.
5. Nucleoside/nucleotide analogues with high genetic barriers to resistance (entecavir, tenofovir) should be used for antiviral prophylaxis in children.
6. Prescribers should seek advice from a viral hepatitis specialist, ideally one with paediatric expertise, and refer to product information and prescribing guidelines for dosing.

*Evidence and rationale*

There is very limited evidence available to inform the treatment and management of HBV in immunosuppressed children. HBV reactivation has been reported in children who received liver transplantation and were subsequently treated with lamivudine (Shapira et al., 2001). However, we were unable to identify any studies of HBV reactivation in children undergoing therapy for haematological or solid organ malignancy.

The European Society of Pediatric Gastroenterology, Hepatology and Nutrition guidelines for management of HBV in immunocompromised children are largely based on expert opinion, a few case reports and extrapolation from evidence in adult patients (Sokal et al., 2013). The Society recommends that the following children should receive antiviral prophylaxis: HBsAg-positive children requiring immunosuppressive therapy; HBsAg-negative/anti-HBc-positive children receiving rituximab or combined regimens for haematological malignancies or undergoing bone marrow or stem cell transplantation; and HBsAg-negative/anti-HBc-positive children with detectable HBV DNA (Sokal et al., 2013).

Randomised controlled trials have demonstrated the safety and efficacy of entecavir (Jonas et al., 2016) and tenofovir (Murray et al., 2012) in children with chronic hepatitis B. In this study of tenofovir in adolescents, tenofovir was associated with a loss of bone density, although the possible long-term clinical implications are unclear (Murray et al., 2012). Australian regulations (as at

July 2018) allow for entecavir prescription and PBS reimbursement for children over the age of two years, and tenofovir for children over age 12 years.



### 3. When to stop antiviral agents

Consensus recommendations	GRADE
3.1. We recommend that HBsAg positive patients should be assessed at the start of cancer therapy to determine their phase of disease and ongoing need for hepatitis B treatment after immunosuppression.	C1
3.2. We recommend that patients who fulfil treatment criteria for chronic hepatitis B regardless of their malignancy should remain on therapy and follow standard management guidelines.	A1
3.3. We recommend that patients continue prophylaxis with a nucleoside/nucleotide analogue for 18–24 months after B cell-depleting/B cell-active/anti-CD20 agent or haematopoietic stem cell transplantation therapy provided they DO NOT fulfil criteria for hepatitis B treatment independent of immunosuppression status.	B1
3.4. We recommend that patients continue prophylaxis with a nucleoside/nucleotide analogue for 6–12 months post cessation of cancer therapy (that is not B cell-depleting/B cell-active/anti-CD20 agent or haematopoietic stem cell transplantation therapy, see recommendation 3.3 above) provided they DO NOT fulfil criteria for hepatitis B treatment independent of immunosuppression status.	B1
3.5. We recommend that ALT, HBsAg and HBV DNA level should be tested every 3 months following nucleoside/nucleotide analogue withdrawal for at least 12 months.	B1
3.6. We recommend when to stop antiviral agents in children should follow the same approach as for adults.	C1

Recommendation 3.1. We recommend that HBsAg positive patients should be assessed at the start of cancer therapy to determine their phase of disease and ongoing need for hepatitis B treatment after immunosuppression.

**Quality of Evidence:** Low

**Strength of Recommendation:** Strong

#### *Evidence and rationale*

Due to the complex nature of chronic hepatitis B infection, we recommend that all HBsAg-positive patients be assessed by a viral hepatitis specialist to determine disease stage and need for treatment. This includes assessment for complications of chronic HBV infection, including liver cirrhosis and hepatocellular carcinoma, and commencement of ongoing preventive health

strategies as described in international guidelines for the management of chronic HBV infection (European Association for the Study of the Liver, 2017, Terrault et al., 2016, Reddy et al., 2015, Sarin et al., 2016). Assessment prior to cancer therapy will help determine who will require ongoing HBV treatment after immunosuppression.

Recommendation 3.2. We recommend that patients who fulfil treatment criteria for chronic hepatitis B regardless of their malignancy should remain on therapy and follow standard management guidelines.

**Quality of Evidence:** High

**Strength of Recommendation:** Strong

### *Evidence and rationale*

Management of all HBsAg-positive patients should follow international evidence-based guidelines and the Australian guidelines (European Association for the Study of the Liver, 2017, Terrault et al., 2016, Reddy et al., 2015, Gastroenterological Society of Australia, 2010, Sarin et al., 2016). All HBsAg-positive people who fulfil criteria for HBV treatment should be maintained on treatment irrespective of their immunosuppression status.

Recommendation 3.3. We recommend that patients continue prophylaxis with a nucleoside/nucleotide analogue for 18–24 months after B cell-depleting/B cell-active/anti-CD20 agent or haematopoietic stem cell transplantation therapy provided they DO NOT fulfil criteria for hepatitis B treatment independent of immunosuppression status.

**Quality of Evidence:** Moderate

**Strength of Recommendation:** Strong

### *Background*

Anti-CD20 monoclonal antibody, B cell-depleting or B cell-active agents cause profound suppression of antibody production due to almost complete depletion of B cells peripherally and significant depletion in bone marrow (Yeo et al., 2009, Pei et al., 2010). Loss of anti-HBs and HBsAg seroreversion is described in 25–40% of anti-HBc-positive patients on rituximab (Yeo et al., 2009, Pei et al., 2010). HBV reactivation is common, with pooled estimates of HBV reactivation in anti-HBc-positive patients of approximately 16.9% (Perrillo et al., 2015). Importantly, HBV reactivation has been reported at least 12 months after cessation of immunosuppressive therapy, including in HBsAg-

negative/anti-HBc-positive patients (Pei et al., 2012, Perrillo et al., 2015). HBV reactivations can be severe, leading to liver failure and the need for transplantation (Sperl et al., 2013).

### *Technical remarks:*

1. Cessation of prophylaxis after 18–24 months should only occur if no further immunosuppressive therapy is planned.

### *Evidence and rationale*

There is strong evidence for HBV prophylaxis reducing the risk of HBV reactivation in patients on rituximab (Buti et al., 2017, Huang et al., 2013), but the optimal duration of prophylaxis is controversial and international guidelines differ in their recommendations. Evidence from randomised double-blinded controlled trials of both entecavir and tenofovir prophylaxis in HBsAg-negative/anti-HBc-positive patients on rituximab show that 12 months of therapy significantly reduces the risk of HBV reactivation and that HBV reactivation may occur up to 12 months after immunosuppression cessation (Buti et al., 2017, Huang et al., 2013, Perrillo et al., 2015). Based on these data, guidelines recommend 12 months of therapy after B cell-depleting/B cell-active/anti-CD20 agent or haematopoietic stem cell transplantation therapy (Reddy et al., 2015), but the recent 2017 European guidelines suggest a more conservative timeline of 18 months (based on expert opinion) to ensure all cases of reactivation are captured (European Association for the Study of the Liver, 2017).

For the Australian context, the expert panel recommends 18–24 months duration of HBV prophylaxis after B cell-depleting/B cell-active/anti-CD20 agent or haematopoietic stem cell transplantation therapy. This is based on (1)

recognition that timely testing and review may not occur immediately after 12 months, therefore 18–24 months represents a safety window to detect all late HBV reactivation events; and (2) B cell-depleting therapies are rarely used in isolation and risks are likely to be compounded by use in combination with other immunosuppressive therapies (such as occurs in non-Hodgkin's lymphoma treatment), therefore 18–24 months represents a conservative timeframe to identify and treat virtually all HBV reactivation events. Similarly, HSCT is associated with profound immunosuppression and B cell failure, therefore a similar approach to HBV prophylaxis is recommended for this group (Perrillo et al., 2015).

Though the barrier of viral resistance to current nucleoside/nucleotide analogues is high, frequent stopping and starting of HBV prophylaxis with changing immunosuppressive regimens poses a risk for inadequate prophylaxis leading to HBV reactivation. We therefore recommend maintaining HBV prophylaxis until all planned immunosuppressive therapy is completed, in accordance with other international guidelines (European Association for the Study of the Liver, 2017, Mallet et al., 2016, Reddy et al., 2015).

Recommendation 3.4. We recommend that patients continue prophylaxis with a nucleoside/nucleotide analogue for 6–12 months post cessation of cancer therapy (that is not B cell-depleting/B cell-active/anti-CD20 agent or haematopoietic stem cell transplantation therapy, see recommendation 3.3 above) provided they DO NOT fulfil criteria for hepatitis B treatment independent of immunosuppression status.

**Quality of Evidence:** Moderate

**Strength of Recommendation:** Strong

*Technical remarks:*

1. Cessation of prophylaxis after 6–12 months should only occur if no further immunosuppressive therapy is planned.

*Evidence and rationale*

Use of HBV prophylaxis for six months after cessation of moderate/high-risk non-B cell-depleting immunosuppression is supported by several randomised controlled trials of lamivudine use for HBV prophylaxis (Perrillo et al., 2015, Hsu et al., 2008, Lau et al., 2003, Long et al., 2011). Results from these studies have been extrapolated for the use of third-generation nucleoside/nucleotide analogues (Perrillo et al., 2015). The recommended duration of prophylaxis after cessation of cancer therapy varies in international guidelines. The American Gastroenterological Association recommends six months (Reddy et al., 2015), while the European Association for the Study of the Liver recommends 12 months (European Association for the Study of the Liver, 2017). There is limited evidence on the differences between continuing prophylaxis for 6 or 12 months.

Recommendation 3.5. We recommend that ALT, HBsAg and HBV DNA level should be tested every 3 months following nucleoside/nucleotide analogue withdrawal for at least 12 months.

**Quality of Evidence:** Moderate

**Strength of Recommendation:** Strong

*Evidence and rationale*

There is good evidence that most HBV reactivation events in patients who receive HBV prophylaxis

occur after withdrawal of nucleoside/nucleotide analogue therapy (Buti et al., 2017, Hsu et al., 2008, Pei et al., 2012), particularly within six months of cessation (Hsu et al., 2008). Therefore, monitoring with ALT, HBsAg and HBV DNA levels every three months is recommended following nucleoside/nucleotide analogue withdrawal for at least six months after cessation of HBV prophylaxis. It is important to note that currently there is no funding for three-monthly monitoring in patients receiving HBV prophylaxis whilst on immunosuppression.

There are several key areas in which published data are of insufficient quality to guide recommendations. There is minimal evidence to establish the ideal frequency for monitoring of HBV DNA and transaminases during and after HBV prophylaxis (Perrillo et al., 2015) in order to maximise cost-effectiveness, particularly in the Australian setting. Similarly, to date no studies have systematically compared whether 12 months or 18 months duration of HBV prophylaxis for patients on B cell-depleting therapies maximises cost-effectiveness. There is limited data on the effect of cancer treatment interruption or cessation due to HBV reactivation on survival outcomes in malignancy (Perrillo et al., 2015).

Finally, there is a paucity of evidence for optimal HBV prophylaxis duration in children (Perrillo et al., 2015).

Recommendation 3.6. Decisions about when to stop antiviral agents in children should follow the same approach as for adults.

**Quality of Evidence:** Low

**Strength of Recommendation:** Strong

There are no studies to guide the optimal duration of antiviral treatment in children with HBV and cancer or haematological malignancy. Until further evidence is available, we recommend that the decision to stop antiviral agents should follow the same approach as for adults. Monitoring of children receiving antiviral therapy should be in consultation with a viral hepatitis specialist (ideally with paediatric expertise).

## 4. How to monitor individuals

Consensus recommendations	GRADE
4.1. We suggest that patients receiving antiviral prophylaxis during cancer therapy should be seen 3 months after initiating therapy, and then every 3–6 months.	C2
4.2. We suggest that ALT and HBV DNA should be used to monitor patients receiving antiviral prophylaxis during cancer therapy.	C2
4.3. We suggest that patients' adherence to antiviral prophylaxis should be evaluated throughout therapy.	C2
4.4. We suggest that clinicians should consider hepatitis B infection for any unexplained ALT elevation among patients receiving cancer therapy.	C2
4.5. We recommend that all cases of HBV reactivation should be urgently referred to a viral hepatitis specialist for treatment.	A1
4.6. We recommend all children commenced on antiviral prophylaxis should be monitored using the same approach as for adults, in consultation with a viral hepatitis specialist (ideally with paediatric expertise).	C1

Recommendation 4.1. We suggest that patients receiving antiviral prophylaxis during cancer therapy should be seen 3 months after initiating therapy, and then every 3–6 months.

**Quality of evidence:** Low

**Strength of recommendation:** Weak

### *Evidence and rationale*

The objectives of monitoring are: (1) to detect primary treatment failure, which is rare and often related to non-adherence, (2) to detect virological and biochemical breakthrough, and (3) to assess adverse effects. There is limited evidence on the optimal frequency of monitoring patients on antiviral prophylaxis undergoing cancer therapy. We suggest that on-treatment monitoring for patients undergoing cancer therapy should be similar to monitoring of antiviral treatment in chronic hepatitis B management guidelines (Gastroenterological Society of Australia, 2010, Mallet et al., 2016). We suggest that patients should be monitored three months after commencement of antivirals until undetectable and then every

three to six months. The frequency of monitoring may be decreased to six monthly once treatment adherence is confirmed, as the risk of reactivation is expected to be low with effective treatment and ongoing monitoring at three-monthly intervals may not be feasible.

Recommendation 4.2. We suggest that ALT and HBV DNA should be used to monitor patients receiving antiviral prophylaxis during cancer therapy.

**Quality of evidence:** Low

**Strength of recommendation:** Weak

### *Evidence and rationale*

There is limited evidence about the optimal monitoring strategy for antiviral prophylaxis among patients during cancer therapy. We suggest that the tests used for on-treatment monitoring should be similar to existing guidelines for monitoring antiviral treatment among chronic hepatitis B patients (Gastroenterological Society of Australia, 2010, Mallet et al., 2016). We suggest that



patients receiving antiviral prophylaxis should be monitored using ALT and HBV DNA. HBsAg testing is optional in HBsAg-negative/anti-HBc-positive patients, as seroreversion is not expected to occur on antiviral prophylaxis. Individuals with liver cirrhosis require additional monitoring for complications whilst on antiviral treatment, including clinical review for features of decompensation; liver function tests, platelets, eGFR and international normalised ratio (INR) monitoring for decompensation; and liver ultrasound and alpha-fetoprotein (aFP) screening for hepatocellular carcinoma surveillance.

**Recommendation 4.3.** We suggest that patients' adherence to antiviral prophylaxis should be evaluated throughout therapy.

**Quality of evidence:** Low

**Strength of recommendation:** Weak

*Evidence and rationale*

As adherence to treatment is the key determinant of the success of this strategy, early and ongoing review, including discussion of optimising adherence and overcoming barriers to adherence is recommended. Patient adherence may be established by clinical assessment. Measurement of HBV DNA may be useful in detecting non-adherence (Gastroenterological Society of Australia, 2010), although primary treatment failure cannot be determined until week 12 of treatment.

**Recommendation 4.4.** We suggest that clinicians should consider hepatitis B infection for any unexplained ALT elevation among patients receiving cancer therapy.

**Quality of evidence:** Low

**Strength of recommendation:** Weak

*Evidence and rationale*

*Among HBsAg negative/anti-HBc positive patients only:*

Several existing guidelines recommend a close monitoring strategy with pre-emptive treatment for HBsAg-negative/anti-HBc-positive patients receiving cancer therapy (Gastroenterological Society of Australia, 2010, Mallet et al., 2016, Sarin et al., 2016). These recommendations are supported by low-quality evidence and are largely based on studies of patients receiving agents with high risk of reactivation (i.e., HSCT and rituximab). We recommend HBsAg-negative/anti-HBc-positive patients undergoing higher-risk cancer therapy receive antiviral prophylaxis; therefore, only HBsAg-negative/anti-HBc-positive patients receiving lower-risk cancer therapy will not be prescribed antiviral prophylaxis routinely (see "When to start" section). There is insufficient evidence to inform an optimal monitoring strategy in this lower-risk patient group. One small prospective cohort study of 32 HBsAg-negative/anti-HBc-positive patients receiving chemotherapy for solid tumours tested ALT and HBsAg every three months; however, none of the 32 patients had HBV reactivation (Federico et al., 2017). We suggest monitoring ALT at three-month intervals and investigating HBV if there is any unexpected rise in ALT.

*Among all patients receiving cancer therapy:*

Clinicians should consider hepatitis B infection if there is an unexplained elevation of ALT for any patients on cancer therapy regardless of their prior HBV serologic testing status. As a proportion of individuals with occult hepatitis B infection will not be diagnosed by standard serological testing, particularly if there is a prolonged period between infection, HBsAg clearance and immunosuppressive therapy, it is important to consider re-testing individuals for active hepatitis B infection if they develop ALT flares during cancer therapy.

Recommendation 4.5. We recommend that all cases of HBV reactivation should be urgently referred to a viral hepatitis specialist for treatment.

**Quality of evidence:** High

**Strength of recommendation:** Strong

*Background*

AASLD defines HBV reactivation in HBsAg-positive, anti-HBc-positive patients as one of the following:

- (1) a 2 log (100-fold) increase in HBV DNA compared to the baseline level;
- (2) HBV DNA 3 log (1,000) IU/mL in a patient with previously undetectable level; or
- (3) HBV DNA 4 log (10,000) IU/mL if the baseline level is not available (Terrault et al., 2018).

For HBsAg-negative/anti-HBc-positive patients, HBV reactivation is defined as:

- (1) HBV DNA is detectable or

- (2) reverse HBsAg seroconversion occurs (reappearance of HBsAg) (Terrault et al., 2018).

*Evidence and rationale*

HBV reactivation is usually initially asymptomatic and manifests with re-emergence of HBsAg and/or HBV DNA. Clinical flares of HBV are associated with morbidity and mortality, including disruption of the chemotherapeutic regimen and potentially worse oncologic outcomes, therefore detection of reactivation whilst asymptomatic, with commencement of pre-emptive therapy, is the preferred strategy. Antiviral therapy should be commenced urgently if HBsAg re-emerges or if HBV DNA becomes detectable (Gastroenterological Society of Australia, 2010, Mallet et al., 2016, Sarin et al., 2016).

Recommendation 4.6. We recommend all children commenced on antiviral prophylaxis should be monitored using the same approach as for adults, in consultation with a viral hepatitis specialist (ideally with paediatric expertise).

**Quality of Evidence:** Low

**Strength of Recommendation:** Strong

There are no studies to guide HBV monitoring in children with cancer or haematological malignancy. All children with documented HBV infection should be monitored during and after completion of cancer therapy following the same approach as for adults, in consultation with a viral hepatitis specialist (ideally with paediatric expertise).

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