ASCO special articles

Hepatitis B Virus Screening and Management for Patients With Cancer Prior to Therapy: ASCO Provisional Clinical Opinion Update

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abstract

PURPOSE This Provisional Clinical Opinion update presents a clinically pragmatic approach to hepatitis B virus (HBV) screening and management.

PROVISIONAL CLINICAL OPINION All patients anticipating systemic anticancer therapy should be tested for HBV by 3 tests—hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc) total immunoglobulin (Ig) or IgG, and antibody to hepatitis B surface antigen—but anticancer therapy should not be delayed. Findings of chronic HBV (HBsAg-positive) or past HBV (HBsAg-negative and anti-HBc–positive) infection require HBV reactivation risk assessment.

Patients with chronic HBV receiving any systemic anticancer therapy should receive antiviral prophylactic therapy through and for minimum 12 months following anticancer therapy. Hormonal therapy alone should not pose a substantial risk of HBV reactivation in patients with chronic HBV receiving hormonal therapy alone; these patients may follow noncancer HBV monitoring and treatment guidance. Coordination of care with a clinician experienced in HBV management is recommended for patients with chronic HBV to determine HBV monitoring and long-term antiviral therapy after completion of anticancer therapy.

Patients with past HBV infection undergoing anticancer therapies associated with a high risk of HBV reactivation, such as anti-CD20 monoclonal antibodies or stem-cell transplantation, should receive antiviral prophylaxis during and for minimum 12 months after anticancer therapy completion, with individualized management thereafter. Careful monitoring may be an alternative if patients and providers can adhere to frequent, consistent follow-up so antiviral therapy may begin at the earliest sign of reactivation. Patients with past HBV undergoing other systemic anticancer therapies not clearly associated with a high risk of HBV reactivation should be monitored with HBsAg and alanine aminotransferase during cancer treatment; antiviral therapy should commence if HBV reactivation occurs.

Additional information is available at www.asco.org/supportive-care-guidelines.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

In 2010, ASCO published a Provisional Clinical Opinion (PCO) on hepatitis B virus (HBV) infection screening in patients receiving anticancer therapy for the treatment of malignant diseases.[1] PCOs are based on a rigorous, evidence-based approach and are designed to offer timely clinical direction to ASCO membership following publication or presentation of potentially practice-changing information.

PCOs are updated periodically based on review of recently published data. ASCO published an updated PCO on this topic in 2015 that introduced a risk-adaptive clinical algorithm to help clinicians identify and treat patients with HBV infection to reduce their risk of HBV reactivation from anticancer therapy.[2] This 2020 PCO update presents a clinically pragmatic approach to HBV screening and management that calls for universal HBV serologic testing of patients at the onset of anticancer therapy.

STATEMENT OF THE CLINICAL ISSUES

Largely due to limited data, there has been an historical lack of agreement regarding the preferred approach to HBV serologic testing in individuals with

THE BOTTOM LINE

Hepatitis B Virus Screening and Management for Patients With Cancer Prior to Therapy: ASCO Provisional Clinical Opinion Update

Target Population

Newly diagnosed patients receiving anticancer therapy.

Target Audience

Medical oncologists, hematologists, oncology nurses, oncology pharmacists, and other health care professionals who care for patients with cancer, and patients with cancer.

Methods

A search for new evidence on HBV screening in individuals with cancer was conducted to identify relevant studies published since the 2015 ASCO PCO.

Provisional Clinical Opinion

- All patients with cancer anticipating systemic anticancer therapy should be tested for hepatitis B virus (HBV) by 3 tests—hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc) total immunoglobulin (Ig) or IgG, and antibody to hepatitis B surface antigen (anti-HBs)—prior to, or at the beginning of, systemic anticancer therapy. Anticancer therapy should not be delayed for the results of these screening tests. Findings of chronic HBV (HBsAg-positive) or past HBV (HBsAg-negative and anti-HBc–positive with either negative or positive anti-HBs) infection require further action (Type of recommendation: evidence based, benefits outweigh harms; Strength of recommendation: strong).
- Patients with chronic HBV receiving any systemic anticancer therapy should receive antiviral prophylactic therapy for the duration of anticancer therapy, as well as for at least 12 months after receipt of the last anticancer therapy. Monitoring recommendations include checking alanine aminotransferase (ALT) and HBV DNA level at baseline prior to or at the beginning of their anticancer therapy, as well as every 6 months during antiviral therapy. Hepatitis flares, presenting as elevated ALT levels, can occur after the discontinuation of antiviral therapy. As such, ALT levels should be monitored frequently, at least monthly for the first 3 months after the cessation of antiviral therapy and every 3 months thereafter. Coordination of care with a clinician experienced in HBV management is highly recommended for patients with chronic HBV, especially to monitor for withdrawal flares, determine monitoring and antiviral therapy after the cessation of anticancer therapy, and evaluate for advanced liver disease such as cirrhosis or liver cancer (Type: informal consensus, benefits outweigh harms; Strength of recommendation: strong).
- Hormonal therapy without systemic anticancer therapy is unlikely to increase the risk of HBV reactivation in patients with chronic or past HBV. Antiviral therapy and management for these patients should follow national HBV guidelines, independent of cancer therapy, including management by a clinician experienced in HBV management for prevention of liver disease such as cirrhosis or liver cancer. Should their anticancer treatment regimen change beyond hormonal therapy alone, the risk of HBV reactivation based on their new anticancer therapy should be reassessed (Type: informal consensus, benefits outweigh harms; Strength of recommendation: moderate).
- Patients with past HBV receiving anticancer therapies associated with an established high risk of HBV reactivation, such as anti-CD20 monoclonal antibodies or stem-cell transplantation, should be started on antiviral prophylaxis at the beginning of anticancer therapy and continued on antiviral therapy for at least 12 months after the cessation of anticancer therapy. HBV DNA should be obtained at baseline and followed every 6 months during antiviral therapy. Patients with a negative anti-HBs may be at higher risk of HBV reactivation than patients who have a positive anti-HBs. An alternative pathway is careful monitoring with HBsAg and HBV DNA every 3 months, with immediate antiviral therapy at the earliest sign of HBV reactivation (appearance of HBsAg or HBV DNA $\geq$ 1,000 IU/mL), so long as patients and providers are able to adhere to frequent and consistent follow-up during anticancer therapy and for up to 12 months after last anticancer therapy (as delayed HBV reactivation may occur years after cessation of anticancer therapy). If HBV DNA is quantifiable but $<$ 1,000 IU/mL, then repeat testing at monthly intervals may be indicated. Hepatitis flares, presenting as elevated ALT levels, can occur after the discontinuation of antiviral therapy. As such, ALT levels should be monitored frequently, at least monthly for the first 3 months after the cessation of antiviral therapy and every 3 months thereafter (Type: informal consensus, benefits outweigh harms; Strength of recommendation: strong).
- Patients with past HBV undergoing anticancer therapies that are not clearly associated with a high risk of HBV reactivation (eg, regimens that do not include anti-CD20 monoclonal antibodies or stem-cell transplantation) should be followed carefully during cancer treatment, with HBsAg and ALT testing every 3 months (with subsequent HBV DNA

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THE BOTTOM LINE (CONTINUED)

testing if a hepatitis flare develops) with initiation of antiviral therapy only if HBsAg becomes positive or HBV DNA exceeds 1,000 IU/mL in the setting of a hepatitis flare. Follow-up testing after the cessation of anticancer therapy is likely not necessary (Type: informal consensus, benefits outweigh harms; Strength of recommendation: strong).

Additional Resources

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

cancer, and, as a result, HBV testing has been suboptimal.[3-5] A range of strategies has been previously recommended.[2,6,7] These include a universal screening approach in which all patients with cancer are tested, or a risk-adaptive approach that tests only those patients with cancer with risk factors for HBV infection or who would be treated with anticancer therapies associated with a high risk of HBV reactivation. Table 1 offers a summary of contemporary HBV screening guidelines.

ASCO's first PCO on this topic in 2010 recommended that clinicians consider screening patients belonging to groups at heightened risk for chronic HBV infection or if highly immunosuppressive therapies, such as rituximab or stem-cell transplantation, were planned.[1] In 2015,[2] ASCO's updated PCO recommended that clinicians test patients for HBV infection before starting anti-CD20 therapy or stem-cell transplantation and that providers also test patients with risk factors for HBV infection. However, the 2015 updated PCO highlighted that current evidence at that time was insufficient to support HBV testing for patients who had neither HBV risk factors nor anticipated anticancer therapy that was not associated with a high risk of reactivation. Notably, 2 panel members in 2015 offered a minority viewpoint, namely, a strategy of universal HBsAg and selective anti-HBc testing.

However, recent data have called into question the utility of risk-adaptive models for HBV screening. In a multicenter, prospective cohort study of HBV status among individuals newly diagnosed with cancer (n = 3,051), Ramsey et al[8] found that 21% of patients with chronic HBV had no known risk factors for HBV infection. Hwang et al[3] conducted a large prospective observational cohort study of 2,124 patients with cancer to develop various HBV screening strategies prior to the initiation of systemic anticancer therapy. In the latter study, authors reported that, regardless of the number of questions, about 90% of patients had at least one of the significant risk variables of HBV infection and thus would have needed serologic testing, making selective screening inefficient and impractical.

The results of these 2 studies suggest that a universal screening approach, its potential harms (eg, patient and clinician anxiety about management, financial burden associated with antiviral therapy) notwithstanding,[2,9] is the most efficient, clinically pragmatic approach to HBV screening in persons anticipating systemic anticancer treatment. Universal HBV testing could identify all patients with cancer at risk for HBV reactivation.[3] Risk-based screening approaches, by contrast, are difficult to implement—many oncologists may be unfamiliar with the risk factors for HBV infection or lack time to conduct a complete HBV risk assessment—and HBV screening rates are low.[10] These issues are discussed in more detail below in the Clinical Considerations section.

ASCO 2020 PROVISIONAL CLINICAL OPINION

Key elements of the 2020 HBV Update are listed below and in Figure 1.

- All patients with cancer anticipating systemic anticancer therapy should be tested for hepatitis B virus (HBV) by 3 tests—hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc) total immunoglobulin (Ig) or IgG, and antibody to hepatitis B surface antigen (anti-HBs)—prior to, or at the beginning of, systemic anticancer therapy. Anticancer therapy should not be delayed for the results of these screening tests. Findings of chronic HBV (HBsAg-positive) or past HBV (HBsAg-negative and anti-HBc–positive with either negative or positive anti-HBs) infection require further action (Type of recommendation: evidence-based, benefits outweigh harms; Strength of recommendation: strong).
- Patients with chronic HBV receiving any systemic anticancer therapy should receive antiviral prophylactic therapy for the duration of anticancer therapy, as well as for at least 12 months after receipt of the last anticancer therapy. Monitoring recommendations include checking alanine aminotransferase (ALT) and HBV DNA level at baseline prior to or at the beginning of their anticancer therapy, as well as every 6 months during antiviral therapy. Hepatitis flares, presenting as elevated ALT levels, can occur after the

TABLE 1. Selected Guidance Documents With Recommendations for Hepatitis B Screening and Management

Recommending Body	Patient Population/Screening Recommendation	Serological Tests	Prophylaxis
American Association for the Study of Liver Diseases (2018)[17]	Screening recommended in all persons needing any immunosuppressive or immunomodulatory therapy, including cancer chemotherapy before initiation of treatment	HBsAg and anti-HBc	HBsAg-positive, anti-HBc–positive patients should initiate anti-HBV prophylaxis before immunosuppressive or cytotoxic therapy.
			HBsAg-negative, anti-HBc–positive patients could be carefully monitored with ALT, HBV DNA, and HBsAg with the intent for on-demand therapy, except for patients receiving anti-CD20 antibody therapy (eg, rituximab) or undergoing stem-cell transplantation, for whom anti-HBV prophylaxis is recommended.
			When indicated, anti-HBV prophylaxis should be initiated as soon as possible before or, at the latest, simultaneously with the onset of immunosuppressive therapy. Once started, anti-HBV prophylaxis should continue during immunosuppressive therapy and for at least 6 months (or for at least 12 months for patients receiving anti-CD20 therapies) after completion of immunosuppressive therapy.
			Anti-HBV drugs with a high resistance barrier (entecavir, TDF, or TAF) should be preferred over low-barrier agents.
			For patients being monitored without prophylaxis, HBV-DNA levels should be obtained every 1-3 months. Patients should be monitored for up to 12 months after cessation of anti-HBV therapy.
Australian Consensus Statement: Hepatitis B Management During Cancer Therapy Consensus Statement Group[13]	All patients undergoing cancer treatment prior to start of therapy	HBsAg, anti-HBc, anti-HBs	Patients with chronic HBV infection (HBsAg-positive) or past exposure (HBsAg-negative and anti-HBc–positive) who are receiving higher-risk chemotherapy require antiviral prophylaxis with tenofovir or entecavir.
Centers for Disease Control and the American College of Physicians High Value Care Task Force (2017)[14]	Clinicians should screen all patients receiving chemotherapy, immunosuppressive therapy, or direct-acting antivirals.	HBsAg, anti-HBc, anti-HBs	Clinicians should provide or refer all patients identified with HBV (HBsAg-positive) for post-test counseling and HBV-directed care.
European Society for Medical Oncology (2016)[15]	Follicular lymphoma/HBV screening is required.	HBsAg and anti-HBc	In patients with positive hepatitis B serology, including occult carrier (HBsAg-negative and anticore-positive), prophylactic antiviral medication and regular monitoring of HBV DNA are strongly recommended.

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TABLE 1. Selected Guidance Documents With Recommendations for Hepatitis B Screening and Management (continued)

Recommending Body	Patient Population/Screening Recommendation	Serological Tests	Prophylaxis
Indian National Association for Study of the Liver[16]	All patients (both adult and pediatric) with hematologic or nonhematologic malignancies who are candidates for chemotherapy, immunosuppressive therapy, or HSCT	HBsAg and anti-HBc	Preemptive antiviral prophylaxis with ETV, TDF, or TAF is recommended for patients when HBsAg or HBV DNA is positive.
			Treatment should be continued for at least 12 months after discontinuation of chemotherapy or immunosuppressive therapy (18 months for rituximab-based regimens and HSCT).
			Patients who have only isolated anti-HBc positivity should be monitored with HBsAg, ALT, and HBV DNA testing every 3 months during therapy and up to 6 months after.
			Preemptive antiviral therapy with ETV, TDF, or TAF should be started immediately on detection of HBsAg or HBV DNA positivity.
			Preemptive antiviral therapy in patients with isolated anti-HBc–positive (with HBsAg and HBV DNA negative) can be initiated in high-risk groups such as patients with lymphoma under a rituximab-containing regimen or those undergoing HSCT.
			In children, the following drugs should be used for preemptive prophylaxis or therapy: ETV for children > 2 years of age and ETV or TDF for children > 12 years of age.
National Comprehensive Cancer Network Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma (2020)	HBV testing indicated due to risk of reactivation during treatment (eg, immunotherapy, chemoimmunotherapy, chemotherapy, targeted therapy)	HBsAg and anti-HBc for patients with no risk factors	Prophylactic antiviral therapy with entecavir recommended for HBsAg-positive patients undergoing antilymphoma therapy
	Screen all patients receiving anti-CD20 antibody therapy.	Add e-antigen if risk factors or history of HBV; if positive, check viral load and consult with gastroenterologist.	Adefovir, telbivudine, and tenofovir are acceptable alternative antiviral agents. Avoid lamivudine due to resistance.
		HBsAg and anti-HBc testing recommended for all patients receiving anti-CD20 antibody-based regimens.	Monitor viral load with PCR monthly through treatment and every 3 months after treatment completion.
			Consult with hepatologist for duration of therapy in patients with active HBV.
National Comprehensive Cancer Network Prevention and Treatment of Cancer-Related Infections (2020)	Consider screening all patients for HBV prior to induction of chemotherapy or immunosuppressive therapy.	HBsAg, anti-HBc, anti-HBs	For patients with HBV, consult with treatment expert to determine possible antiviral prophylaxis. If active infection, consider delayed transplantation.
	Any patient expected to receive immunosuppressive therapy or chemotherapy should be screened.		Antiviral therapy with entecavir (preferred), tenofovir (preferred) or lamivudine
	Implementation of universal screening should be considered.		Surveillance for at least 6-12 months after conclusion of antiviral treatment

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TABLE 1. Selected Guidance Documents With Recommendations for Hepatitis B Screening and Management (continued)

Recommending Body	Patient Population/Screening Recommendation	Serological Tests	Prophylaxis
American Gastroenterological Association Institute (2015)[6]	Patients who will be treated with immunosuppressive therapy. Screen patients at high risk for HBV infection or moderate or high risk of HBV reactivation.	HBsAg and anti-HBc	Antiviral prophylaxis in high- and moderate-risk patients; recommend against routine antiviral prophylaxis in low-risk patients. Antivirals with high barrier to resistance are recommended over lamivudine. Treatment should be continued for 6 months after discontinuation of immunosuppressive therapy.
ASCO (2020)	All patients with cancer anticipating systemic anticancer therapy should be tested for HBV.	HBsAg, anti-HBc, and anti-HBs	All patients anticipating systemic anticancer therapy should be tested for HBV by 3 tests—HBsAg, anti-HBc total immunoglobulin (Ig) or IgG, and antibody to hepatitis B surface antigen—but anticancer therapy should not be delayed.
			Patients with chronic HBV receiving any systemic anticancer therapy should receive antiviral prophylactic therapy through and for minimum 12 months following anticancer therapy.
			Coordination of care with a clinician experienced in HBV management is recommended for patients with chronic HBV to determine HBV monitoring and long-term antiviral therapy after completion of anticancer therapy.
			Hormonal therapy alone should not pose a substantial risk of HBV reactivation in patients with chronic HBV receiving hormonal therapy alone; these patients may follow noncancer HBV monitoring and treatment guidance.
			Patients with past HBV infection undergoing anticancer therapies associated with a high risk of HBV reactivation, such as anti-CD20 monoclonal antibodies or stem-cell transplantation, should receive antiviral prophylaxis during and for minimum 12 months after anticancer therapy completion, with individualized management thereafter. Careful monitoring may be an alternative if patients and providers can adhere to frequent, consistent follow-up so antiviral therapy may begin at the earliest sign of reactivation.
			Patients with past HBV undergoing other systemic anticancer therapies not clearly associated with a high risk of HBV reactivation should be monitored with HBsAg and ALT during cancer treatment; antiviral therapy should commence if HBV reactivation occurs.

Abbreviations: ALT, alanine aminotransferase; anti-HBc, hepatitis B core antibody; anti-HBs, antibody to hepatitis B surface antigen; ETV, entecavir; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HSCT, hematopoietic stem-cell transplantation; PCR, polymerase chain reaction; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

discontinuation of antiviral therapy. As such, ALT levels should be monitored frequently, at least monthly for the first 3 months after the cessation of antiviral therapy and every 3 months thereafter. Coordination of care with a clinician experienced in HBV management is highly recommended for patients with chronic HBV, especially to monitor for withdrawal flares, determine monitoring and antiviral therapy after the cessation of anticancer therapy, and evaluate for advanced liver disease such as cirrhosis or liver cancer (Type of recommendation: informal consensus, benefits outweigh harms; Strength of recommendation: strong).

- Hormonal therapy without systemic anticancer therapy is unlikely to increase the risk of HBV reactivation in patients with chronic or past HBV. Antiviral therapy and management for these patients should follow national HBV guidelines, independent of cancer therapy, including management by a clinician experienced in HBV management for prevention of liver disease such as cirrhosis or liver cancer. Should their anticancer treatment regimen change beyond hormonal therapy alone, the risk of HBV reactivation based on their new anticancer therapy should be reassessed (Type of recommendation: informal consensus, benefits outweigh harms; Strength of recommendation: moderate).
- Patients with past HBV receiving anticancer therapies associated with an established high risk of HBV reactivation, such as anti-CD20 monoclonal antibodies or stem-cell transplantation, should be started on antiviral prophylaxis at the beginning of anticancer therapy and continued on antiviral therapy for at least 12 months after the cessation of anticancer therapy. HBV DNA should be obtained at baseline and followed every 6 months during antiviral therapy. Patients with a negative anti-HBs may be at higher risk of HBV reactivation than patients who have a positive anti-HBs. An alternative pathway is careful monitoring with HBsAg and HBV DNA every 3 months, with immediate antiviral therapy at the earliest sign of HBV reactivation (appearance of HBsAg or HBV DNA $>$ 1,000 IU/mL), so long as patients and providers are able to adhere to frequent and consistent follow-up during anticancer therapy and for up to 12 months after last anticancer therapy (as delayed HBV reactivation may occur years after cessation of anticancer therapy). If HBV DNA is quantifiable but $<$ 1,000 IU/mL, then repeat testing at monthly intervals may be indicated. Hepatitis flares, presenting as elevated ALT levels, can occur after the discontinuation of antiviral therapy. As such, ALT levels should be monitored frequently, at least monthly for the first 3 months after the cessation of antiviral therapy and every 3 months thereafter (Type of recommendation: informal consensus, benefits outweigh harms; Strength of recommendation: strong).
- Patients with past HBV undergoing anticancer therapies that are not clearly associated with a high risk of HBV reactivation (eg, regimens that do not include anti-CD20 monoclonal antibodies or stem-cell transplantation) should be followed carefully during cancer treatment, with HBsAg and ALT testing every 3 months (with subsequent HBV DNA testing if a hepatitis flare develops), with initiation of antiviral therapy only if HBsAg becomes positive or HBV DNA exceeds 1,000 IU/mL in the setting of a hepatitis flare. Follow-up testing after the cessation of anticancer therapy is likely not necessary (Type of recommendation: informal consensus, benefits outweigh harms; Strength of recommendation: strong).

METHODS

ASCO PCOs are updated by an Expert Panel on the basis of periodic review and analysis of new information on the topic. The members of the Expert Panel are listed in Appendix Table A1 (online only). This guidance product was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff with health research methodology expertise. The Expert Panel met via teleconference and webinar, and the group corresponded through e-mail. Based on the consideration of the evidence, the authors were asked to contribute to the development of the PCO, to provide critical review, and to finalize the provisional opinion. The PCO was sent for an open comment period of 2 weeks, allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the opinion. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the PCO, which was then circulated for external review and submitted to *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidance products are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee prior to publication. All funding for the administration of the project was provided by ASCO.

Guideline Disclaimer

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PCO and Conflict of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

LITERATURE SEARCH STRATEGY AND RESULTS

ASCO staff conducted a search for new evidence on HBV screening in individuals with cancer to identify relevant randomized controlled trials (RCTs) that have been published since the 2015 ASCO PCO. The PubMed database was searched from January 2014 to January 2020 (Data Supplement).

A medical librarian at The University of Texas MD Anderson Cancer Center supplemented the search for RCTs with a broad search of the literature to identify studies on screening and management of hepatitis B infection among patients with cancer receiving systemic anticancer therapy, including immunotherapies or chemotherapies, and studies on prevention of HBV reactivation after anticancer therapy. Controlled vocabulary supplemented with key words was used to search Ovid Medline, Ovid Embase, and PubMed from January 2009 through January 2020 (Data Supplement).

Articles were selected for inclusion in the review of the evidence if they were phase III randomized controlled trials (HBV screening question) or studies of prevalence HBV infection, predictive models of HBV infection, or HBV reactivation. Articles were excluded from the review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, news articles, case reports, narrative reviews, or studies of children; and (3) published in a non-English language.

As expected, the search conducted to identify RCTs of HBV screening in patients with cancer yielded no relevant records. The search, in combination with articles identified by individual Panel members, identified several practice guidelines that had been published since the 2015 PCO.[6,11-16] The recommendations for HBV screening, use of serological tests, and antiviral prophylaxis from selected national and international guidelines are summarized in Table 1. Articles identified by individual Panel members, combined with results from the formal searches, informed the Panel's consensus opinions.

CLINICAL CONSIDERATIONS

Absent evidence from RCTs on the comparative utility of risk-based HBV screening versus universal screening strategies or on the predictors of HBV reactivation, especially the risk caused by a myriad of anticancer therapies, the Panel outlined several clinical considerations to support and amplify the recommendations offered in the PCO and associated clinical algorithm (Fig 1).

Uniformity of Definitions

The definition of HBV reactivation has been inconsistent, which has contributed to imprecise estimates of risk and incidence of reactivation. The Expert Panel supports the American Association for the Study of Liver Diseases definition of HBV reactivation and adverse clinical liver-associated outcomes as outlined in the 2018 HBV Guidance[17] and summarized in Table 2. In our PCO (Fig 1), we use a simplified cut-off threshold of HBV DNA $>$ 1,000 IU/mL to assist and guide oncology providers with respect to the threshold above which further management is warranted in patients with past HBV infection. Asymptomatic rises in HBV DNA are very different from clinical hepatitis flares and thus should be interpreted with caution depending on the definitions used.

Chronic HBV infection refers to patients who are HBsAg-positive regardless of anti-HBc status, although most will be anti-HBc–positive. Past HBV infection refers to patients who have a negative HBsAg with positive anti-HBc, regardless of anti-HBs status; HBV DNA is usually

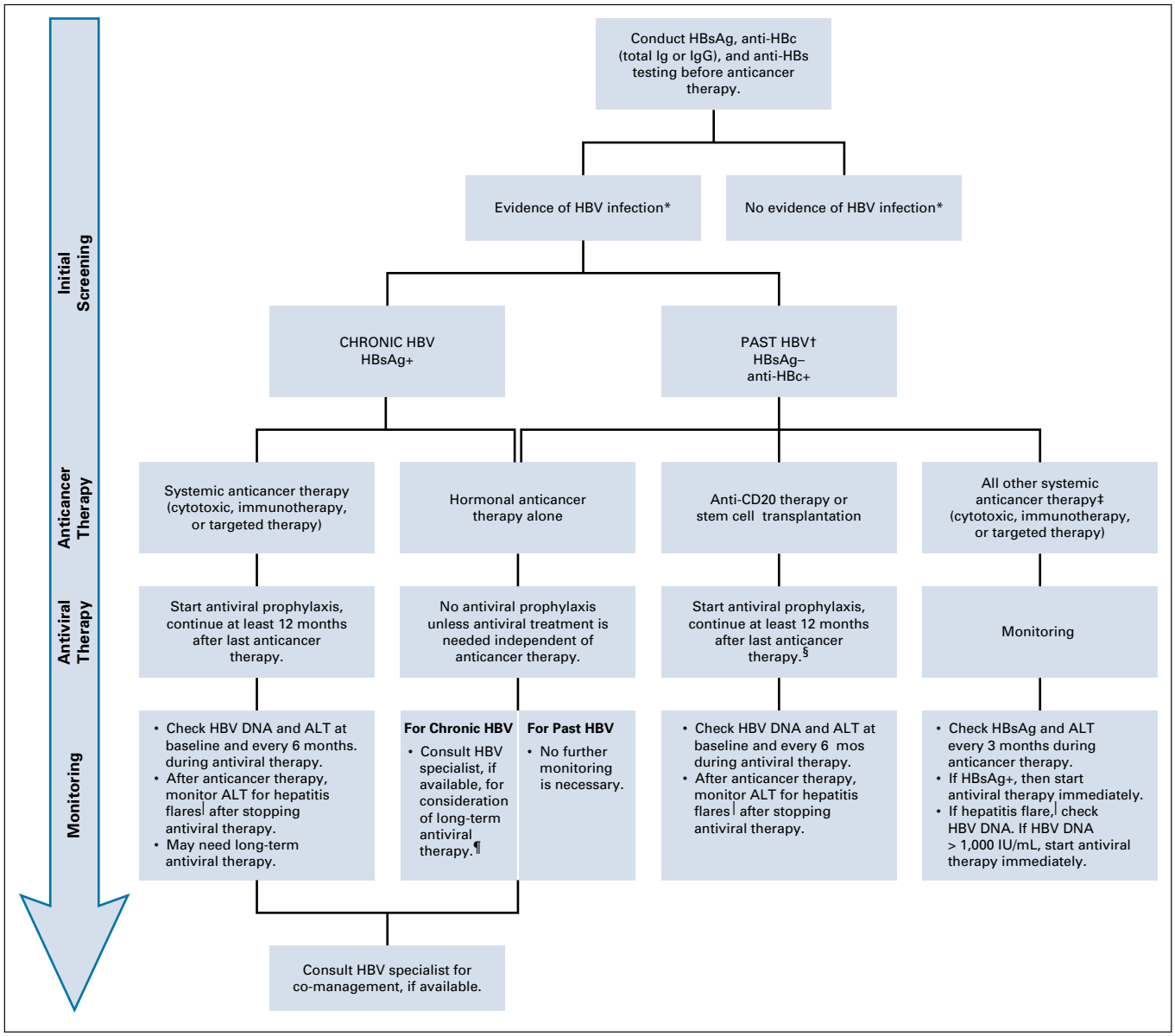

FIG 1. (*) Evidence of hepatitis B virus (HBV) infection refers to hepatitis B surface antigen (HBsAg)–positive or hepatitis B core antibody (HBc)–positive (either total immunoglobulin [Ig] or IgG; do not order IgM unless acute HBV infection is suspected). If evidence of HBV infection, do not delay anticancer therapy while obtaining further testing or referrals. See Table 3 for details for serologic interpretation of HBV screening tests. (†) Past HBV: HBsAg-negative, anti-HBc–positive, regardless of anti-HBs status. A positive anti-HBs test likely attenuates the risk of reactivation in patients with past HBV infection (see text for details). (‡) All other systemic anticancer therapy besides anti-CD20 therapy or stem-cell transplantation. Due to the lack of strong data, the risk of HBV reactivation is unclear for specific anticancer drugs besides anti-CD20 therapy or stem-cell transplantation. It is possible that these anticancer therapies have a low risk of reactivation for patients with past HBV infection and may not require routine monitoring. (§) An alternative pathway is careful monitoring with HBsAg and HBV DNA every 3 months with immediate antiviral therapy at the earliest sign of HBV reactivation so long as patients and providers are able to adhere to frequent and consistent follow-up during and for up to 12 months after last anticancer therapy (see text for details). (‖) Hepatitis flare: alanine aminotransferase (ALT) > 100 U/mL and 3 times baseline.[17] (¶) Long-term antiviral therapy management for patients with cancer after the cessation of anticancer therapy should follow national hepatology recommendations for all patients with chronic HBV.[11,17] An HBV specialist is a clinician experienced in HBV management.

undetectable. Among patients with past HBV, if the anti-HBs is positive, then this is considered resolved HBV infection; if the anti-HBs is negative, then this is considered isolated anti-HBc–positive. See Table 3 for details of the HBV conditions based on screening test results.

Universal HBV Screening

Since the Panel's 2015 PCO,[2] there has been a series of informative and independent studies to clarify the optimal HBV screening approach. Randomized clinical trials of universal HBV screening compared with HBV risk-based or

TABLE 2. Definitions of HBV Reactivation and Related Outcomes[17]

Outcome	Definition
Virologic outcome	
HBV reactivation	
Chronic HBV	≥ 2 log (100-fold) increase in HBV DNA compared with baseline, or
	HBV DNA ≥ 3 log (1,000) IU/mL if previously undetectable HBV DNA, or
	HBV DNA ≥ 4 log (10,000) IU/mL if baseline HBV DNA not available
Past HBV	HBV DNA detectable
	Reverse HBsAg seroconversion (HBsAg-negative to HBsAg-positive)
Hepatitis flare	ALT increase > 3 × baseline and > 100 U/L
Clinical outcomes	
HBV-associated hepatitis flare	HBV reactivation plus hepatitis flare
HBV-associated liver failure	Impaired synthetic function (total bilirubin > 3 mg/dL or INR > 1.5), or
	Ascites, or
	Encephalopathy
Death attributed to HBV reactivation	Following HBV-associated liver failure

Abbreviations: ALT, alanine aminotransferase; HBV, hepatitis B virus; INR, international normalized ratio.

no HBV screening are considered unethical to conduct, as patients with known HBV risk factors might be not tested. However, the following large, prospective cohort studies[3,8,18] provide strong, albeit indirect, evidence that supports universal HBV screening in patients with cancer.

In 2015, Brasseur et al[18] published a study of 388 patients with a solid tumor who completed a brief survey about potential risks for HBV infection—including birth place in high HBV-prevalence area, drug use, and transfusions, among others—and who had HBV testing over a 14-month period of time during 2012-2013 in Reims, France. The investigators found that the sensitivity and specificity of the HBV risk factor questions were 46% and 56%, respectively. However, this study's resultant poor positive predictive value (9%) of this selective tool discourages use of an HBV risk factor approach to screening patients with cancer for HBV.

TABLE 3. Interpretation of HBV Test Results

HBV Status	HBsAg	Anti-HBc[a]	Anti-HBs
Chronic HBV infection	+	+	−
Past HBV infection			
Resolved	−	+	+
Isolated core	−	+	−

Abbreviations: anti-HBc, hepatitis B core antibody; anti-HBs, antibody to hepatitis B surface antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

(+) refers to a reactive (or positive) test result; (−) refers to a nonreactive (or negative) test result.

[a]Anti-HBc should be total immunoglobulin (Ig) or IgG test (not IgM, which if positive would indicate acute HBV infection). Although the sensitivity and specificity of the anti-HBc test exceeds 99%, positive anti-HBc test results may, in rare cases, indicate a false-positive result (eg, after administration of intravenous Ig). As such, clinical assessment and evaluation may be warranted.

In 2019, Ramsey et al[8] published a study of HBV, hepatitis C virus (HCV), and HIV screening among 3,051 patients with a hematologic malignancy or a solid tumor awaiting any anticancer therapy over a nearly 42-month period of time during 2013-2017 among 18 institutions within the SWOG Cancer Research Network, a member of the National Clinical Trials Network. Participants completed a survey about viral risk factors drawn from the National Health Interview Survey and the Centers for Disease Control and Prevention (CDC) and had serologic testing for HBV, HCV, and HIV. Among the patients with chronic HBV (prevalence, 0.6%; 19/3,050), 21% (n = 4) had no known HBV risk factors. Among patients with past HBV (prevalence, 6.5%; 197/3,050), 27% (n = 54) had no known HBV risk factors. HBV risk factors for this study did not include age or race/ethnicity, which could explain the difference in prevalence of HBV risk factors in this study compared with the study below.[3] In summary, this study by Ramsey et al does not support HBV risk-based screening, given that a large portion of patients with chronic or past HBV did not have known HBV risk factors, contributing to the evidence that indirectly supports universal HBV testing in patients with cancer prior to anticancer therapy.

In another prospective study, Hwang et al[3] explored a broader set of HBV risk factors in a study of 2,124 patients with a hematologic malignancy or a solid tumor awaiting systemic anticancer therapy over a 17-month period during 2013-2014 in Houston, Texas. Study participants were tested for HBV and completed a 19-item HBV risk survey based on the CDC hepatitis risk assessment that was modified to include ethnicity/race variables. Using bootstrapping methods, the investigators developed various models to determine the most efficient number and type of HBV risk questions to minimize the false-negative rate so

that patients with HBV would not be missed, as this would be potentially devastating after anticancer therapy. Brief risk tools of 5-7 items were developed, which yielded high sensitivities of 99%-100%. However, the specificities of the brief tools were low (< 15%), likely due to the high prevalence of having at least one of the significant risk variables in the models—for instance, 76% of the participants were > 50 years of age. As such, nearly 90% of the patients who completed a survey would need serologic testing for HBV infection, making selective HBV screening impracticable among patients with cancer.[3]

In view of these recent studies, the Panel recommends HBsAg and anti-HBc testing in all patients with cancer prior to systemic anticancer therapy to determine HBV status (Table 3) and appropriate HBV management to prevent HBV reactivation (see HBV Management section).

An alternative approach to screening using both HBsAg and anti-HBc tests would be to advise HBsAg testing in all patients with cancer, regardless of treatment regimen, and to limit anti-HBc testing to those receiving cancer therapy for which there is an appreciable risk of reactivation, thus requiring surveillance and/or antiviral therapy. However, the major challenge with such an approach is the rapid evolution of cancer therapy and the unknown reactivation risk for many regimens. It is clear that for anti-HBc–positive patients receiving high-risk anticancer therapies like anti-CD20 monoclonal antibodies or stem-cell transplantation, the risk of reactivation is substantial and either close monitoring or preemptive antiviral therapy is recommended. In contrast, for lower-risk anticancer therapies—likely most standard solid tumor regimens—the reactivation risk may be very low and surveillance or antiviral therapy may not be required. However, operationalizing such an alternative, universal HBV screening strategy may be difficult.

The Panel further recommends anti-HBs be performed as part of the screening panel. It is not only the standard of care for HBV screening aligned with public health guidelines,[12] but a positive anti-HBs likely attenuates the risk of HBV reactivation in patients with past HBV infection.[17] In a meta-analysis of 20 studies involving 1,672 patients with hematologic malignancies, the reactivation risk was 14% in 388 patients who were anti-HBc–positive and anti-HBs–negative and 5% in 1,284 patients who were anti-HBc–positive and anti-HBs–positive.[19] Other studies have shown that the timing and presence of anti-HBs at baseline before anticancer therapy,[20] as well as a high titer of anti-HBs,[21] is protective against HBV reactivation among patients with hematologic malignancies. A positive anti-HBs alone (with negative HBsAg and anti-HBc) indicates vaccine-induced protective immunity and would not require further testing or management.

The interpretation of HBV test results may be complicated in patients who have received intravenous immunoglobulin (IVIG) known to produce passive transfer of anti-HBc, leading to false-positive anti-HBc test results. To further complicate matters, patients with cancer who receive IVIG usually have a hematologic malignancy and could also be receiving anticancer therapies that pose a high risk of HBV reactivation, such as B cell–depleting strategies or stem-cell transplantation. In one retrospective study conducted in a single institution during 2004-2011,[22] the rate of passive transfer of anti-HBc after IVIG was 15%, and the probability of positive anti-HBc decreased with time after IVIG administration. As such, anti-HBc testing after IVIG should be interpreted with caution. Universal HBV screening before the initiation of IVIG administration in patients with cancer would, however, mostly obviate this diagnostic challenge.

Implementation of Universal HBV Screening

Systems-based approaches have been used to address barriers to the implementation of universal HBV screening in primary care populations. Most published efforts use electronic health records (EHR). In primary care–based HBV screening, an EHR alert in Epic Systems was shown to significantly increase HBsAg testing in a high-risk patient population in a group of providers using alerts compared with a control group (odds ratio, 2.64; 95% CI, 1.88 to 3.73; $P < .001$).[23] In another study, a simple alert system was used to promote the referral of HBsAg patients to hepatologists through EHR, increasing referrals from 28% (5/18) to 73% (11/15; $P = .009$).[24]

HBV screening and linkage to care using EHR in the cancer population. In one study, a multidisciplinary team of clinicians, pharmacists, and public health professionals prospectively studied HBV screening and antiviral use among patients in the Veterans Health Administration receiving anti-CD20 therapy.[25] Using a comprehensive set of multimodal interventions, which included pharmacy staff checking for HBV screening and treatment prior to anti-CD20 therapy and an electronic medication order review to assess appropriate HBV testing and antiviral treatment before anti-CD20 therapy, investigators found that HBV screening prior to anti-CD20 therapy increased national rates of HBV testing to > 90% and antiviral prophylaxis to > 80%.

In another study of 965 patients with cancer at a single hospital in Taiwan from 2011 to 2012 who received systemic anticancer therapy and were not previously screened for HBV, a computer-assisted system was used to send reminders to oncology providers to order HBsAg testing prior to ordering anticancer therapy and, if the test was positive, to start antiviral therapy and refer to hepatology.[26] HBV screening increased from a baseline of 8% to an overall rate of 86% (825/965), without significant differences according to cancer type. However, the overall antiviral prophylactic rate was only 46% (61/134). The rates of antiviral prophylaxis were lower for doctors treating lung, breast, and colorectal cancers than for those treating

hematologic malignancies (all $P < .05$). The rate of HBV reactivation was lower in patients who received antiviral prophylaxis than in those who did not (1.6% *v* 15.1%; $P < .01$).

HBV Management

Chronic HBV infection. Chronic HBV infection, as part of its natural course, may lead to cirrhosis, liver failure, and/or hepatocellular carcinoma (HCC). The risks vary according to patient factors (eg, immune competence, sex, age, family history), viral factors (eg, viral load, genotype), as well as environmental factors (eg, concurrent viral infections, alcohol use, metabolic syndrome).[11] Patients with hematologic malignancies and chronic HBV are at high risk of HBV reactivation (approximately 50%) and associated adverse liver outcomes, and, as such, they should receive antiviral prophylaxis to prevent HBV reactivation.[17,27,28] Similarly, patients with HCC due to underlying chronic HBV should be continued or treated with antiviral therapy due to the high risk of reactivation—up to 30% after various systemic anticancer therapies including combined chemoradiation.[29,30] Antiviral therapy also reduces the risk of HCC recurrence after potentially curative HCC therapy. Patients with chronic HBV with solid tumors other than HCC are also at heightened risk for HBV reactivation and thus would need antiviral therapy. However, in this latter group, the optimal timing for the antiviral initiation is not yet clear, as strong data about the risk of HBV reactivation due to various anticancer therapies are not available. Until such data are available, our Panel recommends that HBsAg-positive patients with solid tumors should be initiated on antiviral prophylaxis before and continue through systemic anticancer therapy. In summary, patients with chronic HBV receiving any systemic anticancer therapy should be started on antiviral prophylaxis for the duration of anticancer therapy, as well as for at least 12 months after receipt of the last anticancer therapy, and they should have a baseline HBV DNA prior to or at the beginning of their anticancer therapy, as well as every 6 months during antiviral therapy.

One exception may be the HBsAg-positive patient receiving hormonal therapy alone. Based on unpublished analyses of data from the National Cancer Database (L. Nogueira, personal communication, January 2020), an estimated 12% of newly diagnosed patients with cancer in 2016 received single-agent hormonal therapy as first-line treatment. This group included about 43% of patients diagnosed with breast cancer and 23% of patients diagnosed with prostate cancer. However, hormonal therapy with steroids such as used with abiraterone plus low-dose prednisone[31] could confer a higher risk of HBV reactivation than hormonal therapy alone, and these patients may need a personalized management plan including antiviral prophylaxis or close monitoring.

Past HBV infection. Regardless of whether patients with past HBV infection have resolved HBV infection or isolated anti-HBc positivity (Table 3), it is important to note that covalently closed circular DNA remains and is capable of replicating in the liver of individuals with this serologic profile. It is believed that such replication is inhibited by a host's strong immune control, and thus HBV reactivation occurs only with potent immunosuppression. Patients with past HBV with hematologic malignancies anticipating anti-CD20 or stem-cell transplantation have a high risk of HBV reactivation. These patients should start antiviral prophylaxis prior to anticancer therapy and continue it at least 12 months after the end of anticancer therapy and even longer, as their cumulative risk of reactivation increases until nearly 2 years after the cessation of anticancer therapy. The risk of HBV reactivation is higher in patients with negative anti-HBs than in those who are anti-HBs–positive, supporting anti-HBs testing in these patients. In one study of 63 HBsAg-negative and anti-HBc–positive patients with lymphoma, undetectable anti-HBs at baseline prior to rituximab-containing anticancer therapy was a significant predictor of HBV reactivation (hazard ratio, 3.51; 95% CI, 1.37 to 8.98; $P = .009$).[20]

An alternative approach to antiviral prophylaxis among patients with past HBV and a hematologic malignancy was evaluated by Seto et al[32] but requires commitment to careful clinical and laboratory monitoring. In this study, 83 HBsAg-negative and anti-HBc–positive patients with a hematologic malignancy receiving anti-CD20 therapy were followed with frequent laboratories every 4 weeks without antiviral therapy. The rate of reactivation, defined as appearance of HBV DNA at any level, was 25%, and, once reactivation developed, the follow-up frequency increased to every 2 weeks. All patients who developed HBV reactivation and had evidence of active HBV disease (defined in this study as reverse HBsAg seroconversion from HBsAg-negative to HBsAg-positive or an increase in ALT > twice upper limit of normal) received antiviral therapy, and all had normalization of ALT with return of HBV DNA to undetectable levels. There were no cases of clinical hepatitis, liver failure, or death.

Antiviral therapy. Currently, there are 7 antihepatitis B antiviral therapies, and, among these, 3 are preferred medications—entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide—due to their higher potency and high viral resistance barrier.[17] These 3 antiviral therapies are recommended to be used in the prophylaxis or treatment of HBV reactivation and are recommended to be given concomitantly with anticancer therapy, although only the efficacy of entecavir has been established in a randomized clinical trial with the less potent antiviral lamivudine.[33] All of these antiviral therapies suppress HBV replication but do not eliminate the viral genome from the liver and thus require long-term therapy. It is important to test for HIV prior to starting entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide in patients with HBV, since these medications have anti-HIV properties, and HIV monotherapy is not recommended

for patients with HIV. Newer anti-HBV antiviral therapies are in development that may allow a functional cure or sustained HBsAg clearance and undetectable viral levels.[34]

Risk Factors for HBV Reactivation

Cancer types. We have described the patient population at risk for HBV reactivation in the 2015 PCO.[2] In brief, HBV reactivation has been well characterized among patients with HBV with a hematologic malignancy, where the risk of reactivation ranges from 48% among patients with chronic HBV to 18% among those with past HBV.[35,36] HBV reactivation has been studied less frequently among patients with HBV with a solid tumor,[37] where the risk of reactivation has been estimated to be approximately 25% among those with chronic HBV and 3% among those with past HBV.

Anticancer therapies. Currently, there is a lack of data to accurately ascertain the risk of HBV reactivation by anticancer class or specific drug, apart from the established high risk after anti-CD20 monoclonal antibodies or stem-cell transplantation. Multi-agent regimens, varied duration of therapy, and effects of prior lines of therapy preclude precise estimates of HBV reactivation, as the risk by drug or class would be unclear. We highlight several anticancer therapies where data are evolving and treatment options are expanding.

Immunotherapy. Of concern is the recent signal of potential complications from HBV after checkpoint blockade immunotherapy. Previous immunotherapy clinical trials excluded patients with HBV; however, a few case reports of HBV reactivation have been published.[38,39] Recently, a prospective study followed 129 HBsAg-positive patients after PD-1 blockade.[40] Among those who had undetectable HBV DNA and had not been on antiviral therapy at baseline, the rate of HBV reactivation was 21% (5/24). Specific challenges with checkpoint blockade include the known risks of immune-related hepatitis and further immune suppression and risk of HBV reactivation if patients receive high-dose steroids for immune-related adverse events. HBV DNA contains a transcriptional regulatory element that has been shown to be activated by glucocorticoids.[41]

Radiation therapy and transarterial chemoembolization. The risk of reactivation among HBsAg-positive patients with HCC has been reported to be 6% after radiation therapy and 20% after radiation therapy and transarterial chemoembolization in one large retrospective study of 133 patients.[42] In another study that included 109 HBsAg-negative/anti-HBc–positive patients with HCC,[43] the risk of reactivation was 14% after radiation therapy and transarterial chemoembolization among patients with HCC with past HBV.

Other B-cell agents. The reactivation risk identified from rituximab has been extended to other anti-CD20 therapies, including obinutuzumab and ofatumumab. We anticipate other agents such as blinatumomab and inotuzumab producing B-cell aplasia to have high HBV reactivation risks; however, studies of these agents have excluded patients with HBV. Similarly, CD19 chimeric antigen receptor T cells (CAR-T) represent a unique high-risk group based on biology that aims to cause B-cell aplasia. Most of these patients have received highly immunosuppressive lymphodepleting regimens and prior anti-CD20 exposure. Case reports of HBV reactivation have been reported after CAR-T therapy in patients with known HBV infection.[44,45] Taken together, regimens producing profound B-cell aplasia may warrant careful monitoring and may require HBV prophylaxis. For B cell–modulating agents such as Bruton tyrosine kinase inhibitors (eg, ibrutinib), cases of HBV reactivation have been reported, but the degree of risk has not yet been clearly established.[46,47]

Special Situations

The decision for oncologists to screen aging patients with cancer who are debilitated or frail and whose life expectancy is limited warrants consideration of risks and benefits of screening and antiviral therapy. This could be explored using geriatric assessments to improve patient-centered communication about cancer care and management of comorbid conditions, as well as aging concerns.[48]

Future Directions

The risk of HBV reactivation among patients with solid tumors—who make up the majority of patients with cancer—is very likely lower than for patients with hematologic malignancies. However, because these patients have not been well studied, large randomized studies are needed to determine optimal management strategies. In addition, patients with past HBV, especially those who are not receiving anti-CD20 therapy or stem-cell transplantation, have a lower risk of HBV reactivation than those with chronic HBV; studies should be conducted to elucidate optimal clinical care paths for these patients.

Future studies will be needed to make universal HBV screening and linkage to care efficient and systematic, likely based in EHR systems. Ongoing studies of HBV tests such as ultrasensitive HBsAg,[49] HBV RNA, and hepatitis B core antigen,[50] are being studied and may be useful in predicting risk of HBV reactivation.

Identifying the mechanism and risks of reactivation due to specific types of anticancer drugs has been problematic. While prospective studies are needed, they would likely be impractical; thus, large, multicenter retrospective studies with long-term follow-up may be a preferred option. Specifically, patients with cancer and past HBV infection, who represent a significant proportion of the cancer patient population (about 7%),[3,8] could be at risk for adverse liver outcomes from newer anticancer therapies such as immunotherapy and should be systematically monitored. Our Panel specifically identified a research gap of HBV reactivation risks for the growing list of agents that deplete or modulate B cells.

TABLE 4. Summary of Recent (2015-2020) Cost-Effectiveness Analyses of Screening for Hepatitis B Virus Infection in Patients With Cancer

Authors (year)	Primary Objective	Study Population	Screening Strategies	Results and Conclusions
Crespo et al (2017)[64]	To estimate HBV screening cost effectiveness in Spain	Hypothetical cohort of 1,000 patients with hematologic malignancies screened before rituximab-based chemotherapy	No HBV screening *v* HBV screening and prophylaxis with tenofovir disoproxil fumarate	HBV screening would prevent a total of 7.36 reactivations during an 18-month period. Antiviral prophylaxis based on screening decreases HBV reactivation rate and HBV associated mortality.
Hwang et al (2019)[63]	To conduct cost-effectiveness analyses to identify optimal HBV screening strategies	Hypothetical cohorts of patients with cancer anticipating a 12-month course of systemic anticancer therapy considered to be associated with high or lower risk of HBV reactivation	No HBV screening *v* universal screening *v* selective screening based on use of an HBV infection risk tool	Universal HBV screening was cost effective for patients receiving anticancer therapy with a high risk of HBV reactivation but not for patients receiving therapy with a low risk of HBV reactivation.
Konijeti et al (2019)[65]	To analyze cost effectiveness of different HBV screening approaches	Adults in the United States who started chemotherapy for a solid tumor	Screen all patients *v* screen only high-risk patients *v* screen none	Screening all patients for HBV infection found to be most cost effective in a Markov model analysis.
Tan et al (2016)[66]	To evaluate cost effectiveness of universal screening before systemic therapy for sarcomas, including GISTs	274 evaluable patients with sarcomas and 211 patients with GISTs who were starting neoadjuvant, adjuvant, or palliative chemotherapy	Screen-all *v* screen-none strategies	Universal HBV screening in patients with sarcomas or GISTs receiving anticancer therapy was not cost-effective.
Tsou et al (2020)[68]	To compare cost effectiveness between prophylactic antiviral therapy and HBV DNA monitoring for the prevention of HBV-related complications	Patients with resolved HBV infection and newly diagnosed with diffuse large B-cell lymphoma treated with rituximab-CHOP as first-line chemotherapy	Prophylactic antiviral therapy *v* regular HBV DNA monitoring	Prophylactic antiviral therapy more cost effective than regular HBV DNA monitoring in most settings. Antiviral prophylaxis for anti-HBs negative patients with past HBV—a higher HBV reactivation risk group—has the best cost effectiveness.
Wong et al (2015)[67]	To estimate the health and economic effects of HBV screening	Women with breast cancer receiving adjuvant chemotherapy	(1) No screening, (2) screen-and-treat to prevent reactivation (screen all) with either lamivudine/tenofovir or entecavir, and (3) screen-and-treat high-risk only	Screen-all was most cost effective; screen high risk was inferior in all scenarios evaluated. HBV screening before breast cancer adjuvant therapy would prevent HBV reactivations, would extend patients' lives, and is moderately cost effective.

Abbreviations: anti-HBs, antibody to hepatitis B surface antigen; CHOP, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone; GIST GI stromal tumor; HBV, hepatitis B virus.

Anti-HBs testing allows for assessing immunity. Individuals who are negative for HBsAg and anti-HBc, as well as anti-HBs, have never been exposed to HBV, are not immune, and thus are susceptible to HBV infection. Vaccination can be recommended, taking into consideration a patient's clinical situation and timing. Insufficient data exist to recommended vaccination specifically for immunocompromised individuals, but cancer survivors who are not immunocompromised may fall into one of the other groups for whom vaccination is recommended.[51] Some recommendations suggest waiting 3-6 months after cessation of anticancer treatment.[52] Because anticancer therapy can dampen immunogenicity of HBV vaccination, higher doses or more intensive vaccination regimens may be needed to achieve protective levels of anti-HBs. If immunocompromised patients receive vaccination, post-vaccination serology testing has been suggested.[51] Future work is needed to determine optimal timing and best practices.

Among patients who have isolated anti-HBc–positive with negative HBsAg and anti-HBs, studies have shown that protective levels of anti-HBs can decrease risk of HBV reactivation,[19-21] Thus, future research should assess the

efficacy of HBV vaccination to achieve protective anti-HBs levels,[53] which could decrease risk of HBV reactivation.[19-21]

In the United States, the rise in the acute HBV infection due to the opioid crisis[54] may be shifting national HBV screening and vaccination practices to expand. A universal HBV screening strategy would be aligned with national universal screening guidelines for HCV[55]and for HIV.[56] Furthermore, universal HBV screening before anticancer therapy may ultimately be pre-empted by universal population-based HBV screening and management.

EXTERNAL REVIEW AND OPEN COMMENT

The draft statements were released to the public for open comment from February 10, 2020, through February 24, 2020. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed statement, and 25 written comments were received. A total of 7 of the 10 respondents either agreed or agreed with slight modifications with the recommendations, and 3 of the respondents disagreed with at least one of the recommendations. Panel members reviewed comments from all sources and determined whether to maintain original draft statements, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated prior to Clinical Practice Guidelines Committee review and approval.

PATIENT AND CLINICIAN COMMUNICATION

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[57] Communication topics of particular relevance to HBV screening and management are briefly discussed below:

- Patients should be informed of their HBV testing results.
- Patients who are found to have chronic HBV infection should be informed of their status. These patients should be referred to and managed in collaboration with a clinician experienced in HBV management, which could include a hepatologist, an infectious disease clinician, a gastroenterologist, or a primary care provider with HBV experience. Even if HBV treatment is not indicated during their cancer treatment, it is important for them to receive ongoing care for their HBV, including assessment for long-term antiviral therapy based on standard HBV guidelines and evaluation for HCC screening. Patients with a positive HBsAg test should be counseled that they are potentially infectious to others through blood-borne, perinatal, and sexual transmission as well as through close household contact.[7,17] Screening and vaccination of partners and household contacts is recommended.
- Patients who have isolated anti-HBc may need further work-up because the HBV management for these patients depends on the type of anticancer therapy administered. These patients are not at risk for transmission through sexual or close personal contact.[17]
- Patients with a detectable anti-HBs but who are negative for HBsAg and anti-HBc can be counseled that they have protective levels of antibody from previous vaccination.
- Patients who are positive for anti-HBc and anti-HBs have resolved hepatitis B infection and should be counseled that they are at risk, albeit lower than if they had a negative anti-HBs, of HBV reactivation.
- Patients who are negative for all HBV screening tests (negative HBsAg, anti-HBc, and anti-HBs) are considered not to be immune to HBV, have never been exposed to HBV, and may benefit from HBV vaccination,[14] taking into consideration a patient's clinical situation and timing of anticancer therapy.

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial/ethnic minorities suffer disproportionately from comorbidities such as HBV infection and could experience more substantial obstacles to receiving care. They face barriers due to language and culture, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans. Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have ≥ 2 such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials, whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating

constraints for expert groups to make recommendations for care in this heterogeneous patient population.

We lack evidence in patients with MCC. Important factors to consider are if concurrent medical conditions further amplify HBV reactivation risks (eg, immunosuppression for other conditions), drug interactions with antiviral therapy, and patient goals. Accounting for these factors will promote shared decision making.

COST CONSIDERATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[58,59] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[60,61] Discussion of cost can be an important part of shared decision making.[62]

The targeted literature search conducted for this cost section yielded 59 abstracts, of which 6 were considered relevant to the topic of HBV screening and management in patients with cancer anticipating systemic anticancer therapy.[63-68] Excluded from consideration by ASCO are cost-effectiveness analyses that lack contemporary cost data and agents that are not currently available in the United States and/or are industry sponsored.

Table 4 summarizes the methods and results of the 6 cost-effectiveness analyses identified by the targeted literature search. The consistency of the results from studies estimating the cost effectiveness of different screening or prophylaxis approaches varies depending on the population studied. Universal HBV screening[63] and antiviral prophylaxis approaches[64,68] were found to be cost effective in studies of patients with hematologic malignancies at high risk of HBV reactivation. Studies of patients with solid tumors, by contrast, at lower risk of HBV reactivation due to the treatments received, have been less consistent. Universal HBV screening before the start of anticancer therapy for patients with solid tumors was found to be cost effective in analyses conducted by Konijeti et al[65] and by Wong et al[67] but not cost effective in analyses conducted by Hwang et al[63] and Tan et al.[66] Additional research is needed on HBV screening to address cost effectiveness more definitively, particularly in patients with solid tumors for whom adequate data on the reactivation risk of commonly used anticancer treatments are lacking.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Integration of Palliative Care Into Standard Oncology Care: American Society of Clinical Oncology Clinical Practice Guideline Update (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

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EDITOR'S NOTE

Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/supportive-care-guidelines.

EQUAL CONTRIBUTION

J.P.H. and A.S.A. were Expert Panel co-chairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.20.01757.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

TABLE A1. Hepatitis B Virus Screening Expert Panel Membership

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Jessica P. Hwang, MD, MPH (co-chair)	The University of Texas MD Anderson Cancer Center, Houston, TX	Internal Medicine/Health Services Research
Devena E. Alston-Johnson, MD	Upstate Oncology Associates, Greenville, SC	Medical Oncology
Donna R. Cryer, JD (patient pepresentative)	American Liver Foundation, Washington, DC	Patient Advocacy
Jordan J. Feld, MD, MPH	Toronto Centre for Liver Disease, University Health Network, University of Toronto, Toronto, Ontario	Hepatology
Sarah P. Hammond, MD	Dana Farber Cancer Institute, Boston, MA	Infectious Disease
Dawn L. Hershman, MD, MS	Herbert Irving Comprehensive Cancer Center at Columbia University, New York, NY	Medical Oncology/Health Services Research
Andrew P. Loehrer, MD	Dartmouth-Hitchcock Medical Center, Lebanon, NH	Surgical Oncology
Anita L. Sabichi, MD	Baylor College of Medicine, Houston, TX	Medical Oncology
Banu E. Symington, MD (Practice Guidelines Implementation Network representative)	Memorial Hospital of Sweetwater County, Rock Springs, WY	Medical Oncology
Norah Terrault, MD, MPH	Keck School of Medicine, University of Southern California, Los Angeles, CA	Hepatology
Su H. Wang, MD, MPH	Saint Barnabas Medical Center, Florham Park, NJ	Internal Medicine
Melisa L. Wong, MD	Division of Hematology/Oncology University of California San Francisco, San Francisco, CA	Thoracic Oncology/Geriatrics
Mark R. Somerfield, PhD	American Society of Clinical Oncology, Alexandria, VA	ASCO Practice Guidelines Staff (health research methods)