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# Reactivation of Hepatitis B During Immunosuppressive Therapy: Potentially Fatal Yet Preventable

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Reactivation of hepatitis B virus (HBV) replication, an abrupt increase or reappearance of serum HBV DNA in a patient with chronic or past HBV infection, is a known complication of immunosuppressive therapy. This condition can lead to hepatocellular injury, elevated alanine aminotransferase levels, symptoms of acute hepatitis, liver failure, and even death (1). Many physicians who regularly prescribe immunosuppressive therapy unfortunately do not recognize this potentially fatal condition.

Hepatitis B virus reactivation has been best studied in patients receiving chemotherapy for hematologic cancer, but it has also been reported during treatment of solid tumors (2). In addition, reactivation can occur in patients receiving antirejection treatment, long-term corticosteroid therapy, and tumor necrosis factor-$\alpha$ inhibitors (3, 4). Most cases of HBV reactivation occur in patients who are hepatitis B surface antigen (HBsAg)–positive, but it has also been reported in patients who are HBsAg-negative/hepatitis B core antibody (anti-HBc)–positive, particularly when rituximab is used (5).



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A systematic review of 14 studies (including 2 randomized, controlled trials) evaluated 550 HBsAg-positive patients receiving cancer chemotherapy. In patients who did not receive prophylactic antiviral therapy, 36.8% had HBV reactivation, 33.4% had HBV-related hepatitis, 13% had liver failure, and 5.5% died (6). Prophylactic use of lamivudine decreased the risk for HBV reactivation and HBV-related hepatitis by 79% to 100%, and no cases of HBV-related liver failure occurred. Furthermore, patients who received prophylactic lamivudine had less interruption of chemotherapy and lower rates of cancer-related, as well as all-cause, mortality.

By contrast, anti-HBV treatment initiated after the onset of hepatitis has been shown to be less effective. Randomized trials of prophylactic versus deferred lamivudine (that is, lamivudine therapy initiated after an increase in HBV DNA or alanine aminotransferase level) showed that severe HBV-related hepatitis occurred in 0% versus 13% to 36% (7).

The Centers for Disease Control and Prevention (CDC) recommends testing patients for HBsAg, anti-HBc, and hepatitis B surface antibody before they receive immunosuppressive therapy (8). The Practice Guidelines of the American Association for the Study of Liver Diseases (AASLD) and the 2008 National Institutes of Health Consensus Development Conference on Hepatitis B also recommend HBV screening before beginning immunosuppressive therapy (9, 10).

Current assays for HBsAg and anti-HBc are sensitive, specific, and inexpensive, and the results can be available in 1 to 2 days. In the United States, all positive HBsAg test results must be confirmed before the result is reported. Commercially available anti-HBc assays claim to have diagnostic specificity and sensitivity of 99%. However, false-positive results may occur, particularly in low-prevalence groups. When anti-HBc is the only marker present, experts recommend confirmation with strength of the reaction in the anti-HBc test, repeated testing with a different assay, or testing for HBV DNA (11).

The AASLD guidelines recommend prophylactic anti-viral therapy for patients who are HBsAg-positive (9). Patients who are HBsAg-negative/anti-HBc–positive should be monitored by measuring aminotransferase and HBV DNA levels, and antiviral therapy should be initiated at the first sign of HBV-related hepatitis.

Although the evidence is less compelling, it is reasonable to consider prophylactic antiviral therapy if HBsAg-negative/anti-HBc–positive patients will be receiving potent immunosuppressive therapies, such as chemotherapy for hematologic cancer or rituximab-containing regimens (12). Outcomes are best if antiviral therapy is initiated before the start of immunosuppressive therapy. If this method is not feasible, clinicians should aim to start antiviral therapy concurrent with or as soon as possible after the initiation of immunosuppressive therapy.

Despite the CDC recommendations to test for HBV before starting immunosuppressive therapy, surveys of oncologists have found that only 13% to 19% routinely test patients before initiating immunosuppressive therapy (13, 14). The low rate of HBV screening is related to lack of awareness, uncertainty about who should be screened, and the cost of testing. A 2010 Institute of Medicine report (15) recognized lack of awareness and knowledge about hepatitis B among the public and health care providers as a barrier to HBV prevention.

Oncologists cite the lack of evidence from randomized, controlled trials as a reason for not screening their patients for HBV. This need for data is reflected in the American Society of Clinical Oncology's Provisional Clinical Opinion, which states that the evidence is insufficient to determine the net benefits and harms of routine screening for HBV infection

in persons who are about to receive cytotoxic or immunosuppressive therapy (16). The American Society of Clinical Oncology recommends HBV screening for patients with increased risk for chronic HBV infection or if highly immunosuppressive therapy is planned and states that antiviral therapy may be considered in patients with chronic infection.

The American College of Rheumatology recommends screening for HBV in high-risk patients receiving leflunomide or methotrexate therapy (17). “High risk” is defined by risk behavior or occupation but does not include birth in endemic areas, and there is no recommendation for HBV screening before starting biologic disease-modifying antirheumatic drug (DMARD) therapy. A survey of rheumatologists in the United States found that 42% reported routinely screening for HBV before beginning nonbiologic DMARD therapy and 69% screened patients for HBV before beginning biologic DMARD therapy (18).

Because 7% of the rheumatologists surveyed had witnessed HBV reactivation with biologic DMARDs, the next iteration of the American College of Rheumatology guidelines provides an opportunity to strengthen recommendations about HBV screening. The AASLD's position, supported by the CDC's guidelines, is that the potential benefit of HBV screening and prophylactic antiviral therapy in infected persons warrants a stronger recommendation.

Although screening patients at high risk for HBV infection would be a more cost-effective strategy than universal screening, targeted screening is difficult to implement and can miss infected patients who do not recognize or report risk factors. One study of pregnant women in the United States found that fewer than 60% of those who tested positive for HBsAg had a positive response to any of the questions on risks for HBV (19). These findings led to the current policy of universal prenatal screening. The Institute of Medicine committee estimated that only 35% of persons with chronic HBV infection in the United States have been diagnosed (15).

Compelling data indicate that reactivation of HBV in patients receiving immunosuppressive therapy can cause severe hepatitis and even death. Screening for HBV and a once-daily oral antiviral medication can prevent this complication. Because an estimated 800 000 to 1.4 million Americans have chronic HBV infection (15), the problem of HBV reactivation deserves serious consideration. We agree with the American Society of Clinical Oncology that more robust data are needed and that studies should be conducted to determine the incidence and predictive factors for HBV reactivation and optimal duration of prophylactic antiviral therapy. These studies should be done not only in patients receiving cancer chemotherapy but also in those receiving other immunosuppressive therapies or biologic agents.

Because the prevalence of anti-HBc (4.7%) in the United States is higher than that of HBsAg (0.27%) (20), these data are particularly important for HBsAg-negative/anti–HBc-positive patients, in whom false-positive test results can occasionally occur and screening and management are more controversial. Collaboration of multidisciplinary medical specialists and public health experts can facilitate these studies. To begin this process, the AASLD and CDC are partnering to establish a registry of cases of reactivated hepatitis B. Both organizations look forward to collaborating with primary care physicians, oncologists, gastroenterologists, rheumatologists, dermatologists, and other spe cialists to conduct prospective studies that will provide more definitive data.

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