*Open Forum Infectious Diseases*

BRIEF REPORT

# Acute Hepatitis B Surge: Opioid Epidemic Implication and Management Challenges

**Erik D. Johansson[1] and Marina Nunez[2]**

[1]Wake Forest School of Medicine, Winston-Salem, North Carolina, USA, and [2]Section on Infectious Diseases, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA

We recognized a surge in acute hepatitis B at our institution and a link to the opioid epidemic since 2017. Among barriers to optimal management, we identified frequent deviations from national recommendations and patient noncompliance with follow-up.

**Keywords.** acute hepatitis B; hepatitis B; opioid epidemics.

Hepatitis B virus (HBV) infection declined in the United States after implementing an effective vaccination protocol in the early 1990s. However, a recent national uptick in acute hepatitis B has coincided with an epidemic of opioid abuse [1]. We aimed to assess the impact of this trend on our practice and the readiness of our health care workforce to address it. We examined the outcomes and the epidemiological factors of patients with acute hepatitis B, as this information can aid vaccination efforts. Additionally, we examined the diagnosis and management of acute hepatitis B at our institution to determine clinician preparedness as the opioid epidemic proceeds.

## METHODS

We performed a retrospective study in accordance with the Declaration of Helsinki and with institutional review board approval. The primary objective was to examine the number of patients with acute HBV infection managed at the Wake Forest Baptist Medical Center–Winston Salem campus (WFBH-WS) from January 1, 2015, to December 31, 2018, as well as their characteristics and serological and clinical outcomes. A secondary objective was to evaluate the diagnosis and treatment at the institution, based on national standards.

We identified all patients managed at WFBH-WS with a diagnosis of acute hepatitis B during the study period using the institutional infection prevention information system (TheraDoc) database. Then we evaluated each case using electronic health records (EHRs; Epic 2017 HYPERSPACE) for access to internal and external clinical data. Based on the 2012 Centers for Disease Control and Prevention's case definition, we defined a case of acute hepatitis B with the following criteria: (1) a positive hepatitis B surface antigen (HBsAg) and (2) either jaundice or elevated alanine aminotransferase (ALT) levels >100 IU/L without alternative explanation and (3) either (a) an acute illness with a discrete onset of any sign or symptom consistent with acute viral hepatitis (eg, fever, headache, malaise, anorexia, nausea, vomiting, diarrhea, and abdominal pain) without alternative explanation or (b) a documented negative HBsAg within the prior 6 months or (c) a positive hepatitis B core (HBc) IgM antibody [2]. We excluded patients with chronic hepatitis B or with insufficient clinical data for a conclusive diagnosis.

Outcome measures included clinical course, use of anti-HBV treatment, and progression to chronic infection, using the American Association for the Study of Liver Diseases (AASLD) criteria [3, 4]. A protracted–severe course was defined as either >4 weeks of an elevated INR (≥1.5) or total bilirubin >3 mg/dL (or direct >1.5 mg/dL) or clinical evidence of encephalopathy or ascites. The lack of these criteria defined an uncomplicated course. Following AASLD guidelines, indications for anti-HBV treatment included protracted–severe course, and acute liver failure was defined as an elevated INR (≥1.5) with evidence of altered sensorium in a patient without preexisting cirrhosis. HBsAg positivity for at least 6 months after the initial HBsAg-positive result defined chronic HBV infection.

We recorded demographics (age, ethnicity, sex, ZIP code, and health insurance status), HBV risk factors (a sexual or injection drug exposure as recorded by providers in the EHR), psychiatric comorbidities, emergency room visits to WFBH in the 12 months before presentation, and anti-HBV treatment provided during the course of acute infection. Laboratory data included ALT and total bilirubin levels, international normalized ratio (INR), hepatitis C virus (HCV) antibodies, HBsAg, HBc IgM, and HBV DNA. We used Microsoft Excel to record data. We reported data using absolute numbers and proportions for categorical variables and mean and range for quantitative variables.

## RESULTS

We identified 36 cases of acute HBV during the study period, 8 in 2015–2016 and 28 in 2017–2018 (Figure 1; Supplementary Data). Twenty-eight (78%) patients had available HBc IgM

Received 18 February 2020; editorial decision 11 May 2020; accepted 19 May 2020.

Correspondence: Marina Nunez, MD, PhD, Infectious Diseases, Wake Forest Baptist Medical Center, Medical Center Boulevard, Winston Salem, NC 27157 (mnunez@wakehealth.edu).

**Open Forum Infectious Diseases®**



DOI: 10.1093/ofid/ofaa190

**Table 1. Patient Characteristics, Clinical Management, and Outcomes**

| A, Patient Characteristics | No. | % |
|---|---|---|
| Age group | | |
| 19–29 y | 6 | 17 |
| 30–39 y | 8 | 22 |
| 40–49 y | 9 | 25 |
| 50–59 y | 8 | 22 |
| 60–69 y | 4 | 11 |
| 70+ y | 1 | 3 |
| Male sex | 28 | 78 |
| Race | | |
| White | 29 | 81 |
| Black | 6 | 17 |
| American Indian | 1 | 3 |
| Health insurance | | |
| Medicaid | 5 | 14 |
| Medicare | 8 | 22 |
| Commercial | 14 | 39 |
| Veterans Administration | 1 | 3 |
| Uninsured | 8 | 22 |
| Prior HBV vaccination | 2 | 6 |
| Psychiatric comorbidities | 20 | 56 |
| HCV Ab positive | 8 | 22 |
| HCV RNA | | |
| Positive | 5 | 14 |
| Negative | 8 | 22 |
| Unknown | 23 | 64 |
| HIV status | | |
| Positive | 1 | 3 |
| Negative | 26 | 72 |
| Unknown | 9 | 25 |
| Prior emergency room visits[a] | | |
| None | 25 | 69 |
| 1–2 | 6 | 17 |
| 3+ | 5 | 14 |
| HBV risk factor | | |
| Sexual | 13 | 36 |
| IVDU | 8 | 22 |
| Other/undisclosed | 15 | 42 |
| B, Clinical Management and Outcomes | | |
| Clinical course | | |
| Uncomplicated | 34 | 94 |
| Acute liver failure | 0 | 0 |
| Protracted–severe | 2 | 6 |
| Anti-HBV treatment | | |
| Yes, indicated[b] | 2 | 6 |
| Yes, not indicated[b] | 6 | 17 |
| No | 28 | 78 |
| Progression to chronic HBV | | |
| Yes | 1 | 3 |
| No | 16 | 44 |
| Unknown | 19 | 53 |

Abbreviations: AASLD, American Association for the Study of Liver Diseases; HBV, hepatitis B virus; HCV, hepatitis C virus; IVDU, intravenous drug use.

[a]Within the prior 12 months.

[b]By AASLD guidelines.

serology (1 also had a negative HBsAg within the previous 6 months). The remaining 8 (22%) were diagnosed via a viral hepatitis syndrome without alternative explanation.

Table 1A summarizes the characteristics of the patients. The majority were male and of white ethnicity. The mean age (range) was 43 (19–81) years. A history of intravenous drug use (IVDU) was identified in 8 (22%) patients, and all of these had acute hepatitis B in 2017 and 2018 (Figure 1; Supplementary Data). Forty-two percent did not disclose HBV risk factors. More than half of patients had a psychiatric comorbidity listed in the EHR. One patient was infected with HIV before the HBV infection. Eight (22%) patients were seropositive for HCV antibody, and 5 (14%) had detectable HCV RNA at the time of acute HBV infection. About one-third of the patients had at least 1 unrelated emergency room visit within the prior 12 months. Two patients (6%) reported vaccination against HBV several years before the infection. One of them was vaccinated upon diagnosis of HIV infection. Out of the 5 patients born after 1991, when the recommendation for universal HBV child vaccination was issued, only 1 confirmed having been vaccinated.

Table 1B summarizes clinical course and management. Two (6%) patients, ages 69 and 81, had a protracted–severe course, while the mean age of patients with an uncomplicated course was 42 years. Eight (22%) patients received treatment with entecavir or tenofovir, and only 2 of these met AASLD criteria for treatment due to a protracted–severe course.

More than half of patients did not follow up after diagnosis of acute HBV, and therefore their clearance status could not be determined. Seventeen patients had follow-up HBsAg testing, and 1 (6%) developed chronic HBV infection. This patient was co-infected with HIV, and his antiretroviral regimen included lamivudine as the only drug active against HBV. One patient with Crohn's disease, who was on treatment with mesalamine at the time of the infection, cleared the HBsAg by the 14th month after acute illness.

## DISCUSSION

Our data suggest that IVDU has contributed to an increase in acute hepatitis B cases in our community at least since 2017. This coincides with a national uptrend in drug abuse, an epidemic ongoing for more than a decade [5]. Most patients were white, consistent with national data with regards to both acute HBV and IVDU [6–8]. The majority were male, unlike the current opioid epidemic, but consistent with national data on acute HBV [1, 8]. This is not surprising, as sexual transmission, in particular among men who have sex with men, is the most frequent HBV infection route in the United States [1]. A recent national study highlighted the high prevalence of undetectable immunity against HBV among adults at high risk [9]. In the HBV vaccination efforts, new ways of identifying individuals at high risk and additional venues to deliver the vaccine could be considered. On this regard, in our study one-third of the patients had used the hospital emergency room within the prior year, and more than half had psychiatric disease.

Limited vaccine effectiveness constitutes another barrier in the fight against HBV. Thus, 2 of our patients became infected

despite prior vaccination, 1 of whom was HIV-positive. As HIV infection is not only a well-recognized risk factor for poorer response to the HBV vaccine but also for developing chronic infection, including tenofovir as part of the HIV treatment can confer additional protection [10, 11].

Anti-HBc IgM was not available for all patients, despite the Centers for Disease Control and Prevention recommendation for case confirmation [2]. It should be noted, however, that it is not rare to encounter positive IgM anti-HBc in patients with chronic HBV and acute exacerbation [12]. We carefully evaluated each case and based the diagnosis of acute HBV infection on multiple pieces of information. We also observed divergences from national recommendations, as anti-HBV therapy was most often prescribed without indication per the AASLD guidelines. Overtreatment of HBV subjects patients to medication side effects and added costs.

Most subjects (53%) were lost to follow-up after the initial encounter, indicating that patients at risk for HBV pose challenges for adequate medical care. For those with follow-up data, 95% cleared the infection, which is consistent with reported clearance rates in adults [13]. The patient who developed chronic HBV was infected with HIV, an association that is well recognized, with an estimated risk up to 6 times higher than non-HIV hosts [14]. Interestingly, we observed spontaneous HBsAg clearance after 6 months in 1 patient with Crohn's disease. It is unclear if this delay was related to Crohn's in the absence of immunosuppressive therapy. It suggests, though, that some patients may require monitoring beyond the 6-month hallmark before diagnosing chronic infection. Although our sample was small, age did not affect the elimination of HBsAg, contrary to a prior report [15]. Additional studies would help to investigate this, as well as the possibly more severe clinical course in elderly patients suggested by our data.

This study has several limitations. As it is retrospective, some relevant data were missing, which could have caused the exclusion of uncertain cases, and potentially underestimation. It also adds an element of subjectivity that could affect sample validity. Lastly, it is a small sample size from a single medical center, and therefore may not be representative of other practices.

In summary, our study confirms that the IVDU epidemic is implicated in the surge of HBV cases in our community, and it highlights the importance of additional efforts for vaccination targeting at-risk individuals at all possible levels of care. We identified opportunities to inform and prepare our health care providers while the opioid epidemic continues in order to better align the diagnosis and management of acute HBV with national guidelines.

## Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Acknowledgments

We thank Tammy Bischoff , BSN, MPH, from Infection Prevention for her invaluable help in the identification of cases.

***Financial support.*** This research has been possible thanks to the 2019 Medical Student Research Program, supported through the Wake Forest University School of Medicine and the Kulynych Endowed Interdisciplinary Cancer Research Fund.

***Potential conflicts of interest.*** The authors do not have conflicts of interest. Both authors: no reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

## References

1. Centers for Disease Control and Prevention. Surveillance for viral hepatitis – United States, 2017. Available at: https://www.cdc.gov/hepatitis/statistics/2017surveillance/index.htm. Accessed 4 February 2020.
2. Centers for Disease Control and Prevention. National Notifiable Diseases Surveillance System—hepatitis B, acute 2012 case definition. Available at: https://wwwn.cdc.gov/nndss/conditions/hepatitis-b-acute/case-definition/2012. Accessed 3 March 2019.
3. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology **2018**; 67:1560–99.
4. Terrault NA, Bzowej NH, Chang KM, et al; American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. Hepatology **2016**; 63:261–83.
5. National Institutes of Health, National Institute on Drug Abuse. Nationwide trends. Available at: https://www.drugabuse.gov/publications/drugfacts/nationwide-trends. Accessed 3 February 2020.
6. Harris AM, Iqbal K, Schillie S, et al. Increases in acute hepatitis B virus infections—Kentucky, Tennessee, and West Virginia, 2006–2013. MMWR Morb Mortal Wkly Rep **2016**; 65:47–50.
7. Comer M, Matthias J, Nicholson G, et al. Notes from the field: increase in acute hepatitis B infections—Pasco County, Florida, 2011–2016. MMWR Morb Mortal Wkly Rep **2018**; 67:230–1.
8. QuickStats: Age-adjusted rates of drug overdose deaths involving heroin, by Race/Ethnicity† — National Vital Statistics System, United States, 1999–2017. MMWR Morb Mortal Wkly Rep **2019**; 68:810.
9. Yeo YH, Le MH, Chang ET, et al. Prevalence of undetectable vaccine-induced immunity against hepatitis B virus in US adults at high risk for infection. Hepatology **2019**; 69:1385–97.
10. Rech-Medeiros AF, Marcon PDS, Tovo CDV, de Mattos AA. Evaluation of response to hepatitis B virus vaccine in adults with human immunodeficiency virus. Ann Hepatol **2019**; 18:725–9.
11. Chun HM, Fieberg AM, Hullsiek KH, et al; Infectious Disease Clinical Research Program HIV Working Group. Epidemiology of hepatitis B virus infection in a US cohort of HIV-infected individuals during the past 20 years. Clin Infect Dis **2010**; 50:426–36.
12. Park JW, Kwak KM, Kim SE, et al. Differentiation of acute and chronic hepatitis B in IgM anti-HBc positive patients. World J Gastroenterol **2015**; 21:3953–9.
13. Liang TJ. Hepatitis B: the virus and disease. Hepatology **2009**; 49:S13–21.
14. Bodsworth NJ, Cooper DA, Donovan B. The influence of human immunodeficiency virus type 1 infection on the development of the hepatitis B virus carrier state. J Infect Dis **1991**; 163:1138–40.
15. McKeating C, Cadden I, McDougall N, et al. Progression from acute to chronic hepatitis B is more common in older adults. Ulster Med J **2018**; 87:177–80.