Hepatitis B Virus Variants

Disease Agent:

- Hepatitis B virus (HBV) precore, core promoter, and S gene variants

Disease Agent Characteristics:

- Family: *Hepadnaviridae*; Genus: *Hepadnavirus*
- Virion morphology and size: Enveloped, icosahedral nucleocapsid symmetry, spherical particles, 42-47 nm in diameter
- Nucleic acid: Relaxed circular, partially duplex DNA, ~3.2 kb in length
- Physicochemical properties: Stability of HBV (and presumably its variants) does not always coincide with that of its envelope protein, HBsAg; immunogenicity and antigenicity are retained after exposure to ether, acid (pH 2.4 for at least 6 h), and heat (98°C for 1 min or 60°C for 10 h); exposure of HBsAg to 0.25% sodium hypochlorite for 3 minutes destroys antigenicity; infectivity in serum is lost after direct boiling for 2 minutes, autoclaving at 121°C for 20 minutes, dry heat at 160°C for 1 hour, exposure to sodium hypochlorite (500 mg of free chlorine/L) for 10 minutes, 0.1-2% aqueous glutaraldehyde, Sporicidin, 70% isopropyl alcohol, 80% ethyl alcohol at 11°C for 2 minutes, Wescodyne diluted 1:123, or combined β-propiolactone and ultraviolet irradiation; HBV retains infectivity when stored at 30-32°C for at least 6 months and when frozen at –20°C for 15 years.

Disease Name:

- Precore, core promoter, and S gene variants of hepatitis B

Priority Level:

- Scientific/Epidemiologic evidence regarding blood safety: Very low in the US and other countries where testing for antibody to the hepatitis B core antigen (anti-HBc) is performed.
- Public perception and/or regulatory concern regarding blood safety: Absent
- Public concern regarding disease agent: Absent

Background:

- There is very little information concerning the natural history and transmissibility of HBV mutants, and it is assumed that these events will be similar to nonmutated HBV. Conversely, mutations in the precore, core promoter, and S gene regions of the HBV genome could alter the natural history or transmissibility of the virus.
- HBV variants are either emergent or potentially emergent because of evolutionary pressures caused by an increase in vaccination, hepatitis B immune globulin (HBIG), and antiviral use and because HBV genomes lack a proofreading function to correct mismatched nucleotides.
- Mutations in the HBV genome could modulate both natural and induced immunity, resulting in antiviral resistance and, most critically for transfusion medicine, loss of detection by serologic and NAT donor-screening assays.

Common Human Exposure Routes:

- Percutaneous transmission: Injection-drug use (IDU), contaminated needles and syringes, transfusions or transplants from infected donors, and household exposure to infected contacts via skin abrasions (e.g., biting)
- Sexual transmission
- Mother-to-infant transmission

Likelihood of Secondary Transmission:

- Yes, via common exposure routes

At-Risk Populations:

- Injection-drug users
- Sex partners of infected persons
- Infants born to HBV-infected mothers in the absence of an infant immunization program
- Susceptible health-care professionals

Vector and Reservoir Involved:

- None identified

Blood Phase:

- If similar to nonmutant HBV, viremia is first detected 2-5 weeks postinfection. In immunocompetent adults, about 96-99% will remain viremic for ~6 months, whereas ~1-4% will develop chronic viremia.

Survival/Persistence in Blood Products:

- Indefinite persistence in plasma and cellular components that have not been subjected to viral inactivation and/or removal procedures.

Transmission by Blood Transfusion:

- HBV variants have been demonstrated to be transmitted similar to wild-type HBV.

Cases/Frequency in Population:

- Related to ethnicity, place of birth, and HBV genotypes
- In Scottish blood donors, frequencies of precore mutations were 10%, 88%, 25%, and 74% for genotypes A, B, C, and D, respectively.

- Precore and core promoter mutations were detectable in 27% and 44% of patients with chronic HBV infection in the US.

Incubation Period:

- Exposure to detection of HBV DNA: 2-5 weeks
- Exposure to symptoms: 6-8 weeks

Likelihood of Clinical Disease:

- In persons ≥5 years old: 30-50%
- In children <5 years old: 10%
- In general, similar for variants and wild type; however, some HBV core and precore variants appear to be more frequently associated with acute liver failure.

Primary Disease Symptoms:

- Flu-like symptoms
- Jaundice
- Fulminant hepatitis

Severity of Clinical Disease:

- Sometimes associated with substantial morbidity, especially in neonates

Mortality:

- Rare, primarily from acute fulminant hepatitis

Chronic Carriage:

- Unclear, but probably similar to that observed in HBV-infected patients without pre-core or core promoter variants who have a low viral burden (e.g., 1-4% in adults and <30% in children). However, lower levels of the precore and core promoter variant HBV DNA circulating in individuals infected with HBV variants could be a factor in reducing the risk of natural transmission and chronicity.

Treatment Available/Efficacious:

- Several FDA-approved and investigational drugs available
- Efficacy depends on the particular drug or drug combination, length of treatment, and the definition of success. For example, suppression of HBV DNA during treatment occurs in 60-90%, but sustained suppression 1 year after treatment is 30-40% after interferon but 20-30% with nucleotide or nucleoside analogs. Extending treatment duration with the oral agents, often indefinitely, can lead to HBV DNA suppression in 70-90% although HBeAg seroconversion remains comparable to that occurring with interferon (21-27%).
- Development of resistant HBV possible

Agent-Specific Screening Question(s):

- None specifically for hepatitis B variants; however, questions from the Donor History Questionnaire concerning a history of clinical hepatitis and possible exposure to hepatitis viruses are relevant. These specific questions are as follows: Have you ever had hepatitis after the age of 11 years? Have you ever used needles to take drugs? In the past 12 months, have you had sexual contact with a person who had hepatitis? In the past 12 months, have you lived with a person who has hepatitis?

Laboratory Test(s) Available:

- A variety of FDA-licensed blood donor screening assays are currently available in the US for the detection of HBsAg and anti-HBc. Licensed HBV DNA (NAT) assays also are available in the US and are used to a variable extent.
- There is evidence that some HBsAg assays will not detect all S gene variants of HBV. However, donors in the US are universally screened for both HBsAg and anti-HBc; this makes it likely that a mutant strain of HBV would be detected in the US. An exception might be an individual with an S gene variant who presents in the early stages of acute hepatitis prior to the development of anti-HBc although NAT should detect all S gene, and other variants.
- Precore and core promoter mutants are detected by currently available HBsAg and anti-HBc assays.

Currently Recommended Donor Deferral Period:

- FDA requires an indefinite deferral for a clinical history of viral hepatitis after the age of 11 years (regardless of the specific viral agent) and a permanent deferral if an individual tests positive for HBsAg, whether infected with wild-type or variant HBV.

Impact on Blood Availability:

- Agent-specific screening question(s): Questions are already in place.
- Laboratory test(s) available: Tests are already in place.

Impact on Blood Safety:

- Agent-specific screening question(s): Questions are already in place.
- Laboratory test(s) available: HBsAg tests currently in use may not detect all variants; however, prevalence of variant strains is low. Therefore, the impact of a newer test would be minimal. NAT should detect all mutants.

Leukoreduction Efficacy:

- No effect anticipated

Pathogen Reduction Efficacy for Plasma Derivatives:

- All validated inactivation measures for nonmutant HBV (which are highly efficacious) are likely to be similarly effective for HBV variants.

Other Preventive Measures:

- Universal immunization of infants
- Vaccination of populations at high-risk of infection; however, 5-15% of individuals may not respond to the vaccine. This nonresponse rate is considerably higher in immunocompromised individuals.
- Postexposure prophylaxis (hepatitis B immune globulin and vaccination) following exposure to HBV parentally, sexually, inadvertently, or as a household contact.

Suggested Reading:

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