

## 14 | HEPATITIS B VIRUS VARIANTS (AND HEPATITIS DELTA)

### 14.1 | Disease agent

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

### 14.2 | 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 min destroys antigenicity; infectivity in serum is lost after direct boiling for 2 min, autoclaving at 121°C for 20 min, dry heat at 160°C for 1 h, exposure to sodium hypochlorite (500 mg of free chlorine/L) for 10 min, 0.1%–2% aqueous glutaraldehyde, Sporidicin, 70% isopropyl alcohol, 80% ethyl alcohol at 11°C for 2 min, Wescodyne diluted 1:123, or combined  $\beta$ -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.

### 14.3 | Disease name

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

### 14.4 | Priority level

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

### 14.5 | Background

- There is little information concerning the natural history and transmissibility of HBV mutants; while these events may be similar to nonmutated HBV, 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.

### 14.6 | Common human exposure routes

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

### 14.7 | Likelihood of secondary transmission

- High, via common exposure routes

### 14.8 | At-risk populations

- Infants born to mothers with hepatitis B
- People born in certain countries where hepatitis B is common
- People born in the United States not vaccinated as infants whose parents were born in countries with high rates for hepatitis B
- People with hepatitis C
- People who have been incarcerated
- People who inject drugs or share needles, syringes, and other types of drug equipment
- Sex partners of people with hepatitis B
- People who have sexually transmitted infections
- People with HIV infection

- Men who have sex with men
- People who live with someone who has hepatitis B
- Health care and public safety workers exposed to blood on the job
- People on dialysis
- People who have elevated levels of certain liver enzymes

#### 14.9 | Vector and reservoir involved

- Infected primates

#### 14.10 | 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.

#### 14.11 | Survival/persistence in blood products

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

#### 14.12 | Transmission by blood transfusion

- HBV variants transmitted similar to wild-type HBV.

#### 14.13 | 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.
- In a study including 583 US donors with recent (anti-HBc negative) and occult HBV infection (OBI), five of 10 sequenced OBI donors were identified with S-gene escape mutants and nine with defects in HBsAg secretion including one variant each of P120K, P120T, C121G, M133I, D144G, G145R, and C147Y, and two with D144E. No such S-gene mutations were found for 40 sequenced donors with recent HBV infection.

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

#### 14.14 | Incubation period

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

#### 14.15 | 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.

#### 14.16 | Primary disease symptoms

- Flu-like symptoms
- Jaundice
- Fulminant hepatitis

#### 14.17 | Severity of clinical disease

- Sometimes associated with substantial morbidity, especially in neonates

#### 14.18 | Mortality

- Rare, primarily from acute fulminant hepatitis

#### 14.19 | Chronic carriage

- The risk of chronic infection with variants is probably similar to that with wild type virus, but 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.

#### 14.20 | 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.

#### 14.21 | Agent-specific screening question(s)

- None specifically for hepatitis B variants; however, questions from the AABB Donor History Questionnaire (DHQ) concerning possible exposure to hepatitis viruses are relevant. These specific questions are as follows:
  - In the past 3 months, have you had sexual contact with a person who had hepatitis?
  - In the past 3 months, have you lived with a person who has hepatitis?

#### 14.22 | Laboratory test(s) available

- A variety of FDA-licensed blood donor screening assays are recommended in the United States for the detection of HBV DNA (NAT), HBsAg and anti-HBc.
  - The 2023 FDA guidance agenda includes consideration of rescinding the recommendation for donor screening using HBsAg.
- There is evidence that some HBsAg assays will not detect all S-gene variants of HBV. However, donors in the United States are universally screened for HBV DNA and anti-HBc; this makes it highly unlikely that an S-gene mutant would not be detected in the United States.
- Precore and core promoter mutants are detected by currently available HBsAg and anti-HBc assays.

#### 14.23 | Currently recommended donor deferral period

- FDA requires a permanent deferral if an individual tests positive for HBV DNA and/or confirmed HBsAg, whether infected with wild-type or variant HBV.
- Donors with a history or recent HBV vaccination (the vaccines contain HBsAg) and no other markers of infection can be requalified.

- Donors who are repeatedly reactive for anti-HBc on more than one occasion in the absence of HBsAg or DNA are deferred but can be reentered following demonstration of test negativity after a deferral period of 56 days; versus 56 days for reentry of false positives for HBsAg and 180 days for HBV DNA.

#### 14.24 | Impact on blood availability

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

#### 14.25 | 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. NAT would detect all mutants.

#### 14.26 | Leukoreduction efficacy

- No effect anticipated

#### 14.27 | 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.

#### 14.28 | 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.

#### 14.29 | Other comments

- As a “parasite” of HBV, it is important to mention Hepatitis D virus (HDV). HDV, also known as

- deltavirus (its genus) is a very small (35-nm diameter), defective, hepatotropic pathogen comprised of 8 genotypes within the family *Kolmioviridae*. The HDV genome (circular, single-stranded RNA) of ~1700 nucleotides is too small to code for replicative enzymes or envelope proteins and only codes for a single HDV antigen from a single 0.8-kb mRNA open reading frame. HDV relies on HBV for all functions of its life cycle including its surface antigen (HBsAg), viral packaging, infectivity, transmission, and inhibition of host immunity; thus, HDV infection may only occur in an HBV-infected individual.
- HDV is ubiquitous (estimated number of infected persons worldwide ranges from 12 to 72 million, although epidemiologic data are heterogeneous).
  - Chronic HDV infection leads to the most severe and progressive form of viral hepatitis in humans without effective treatment methods.
  - Universal HBV vaccination initiated in the 1990s in high-income countries has resulted in control of HBV infection and thus of HDV infection; consequently, the age-related prevalence of HDV infection is shifting to unvaccinated older persons. In developed countries, chronic HDV infections are now only observed in patients who have cirrhosis or advanced fibrosis.
  - A donor who is an HBsAg chronic carrier co-infected with HDV will have anti-HBc and likely detectable HBV DNA so would be detected even if HBsAg donation testing was not performed. It is rare to extremely unlikely to have an HBsAg chronic carrier who has active infection in which neither anti-HBc nor HBV DNA would be detected, thus any HBV-HDV co-infected individual's blood would not be eligible for transfusion.
- Transfusion transmission of HDV from someone with active HBV infection into either an HBV-naive recipient or one who is HBV infected has not been reported.

### SUGGESTED READING

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