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Considerations for Cellular Therapy Products

2 | BORNA DISEASE VIRUS

2.1 | Disease agent

- Mammalian 1 Orthobornavirus; species: Borna disease virus (BoDV-1 and 2)

2.2 | Disease agent characteristics

- Family: *Bornaviridae*; Genus: *Orthobornavirus*.
- Virion morphology and size: Enveloped, helical nucleocapsid, spherical, 90–130 nm.
- Nucleic acid: Linear, non-segmented, negative-sense, single-stranded RNA, 8.9 kb in size.
- Physicochemical properties: Cell-free virion infectivity is inactivated by heating at 56°C for 0.5–3 h, but more stable in tissues or in the presence of serum; under *in vitro* conditions, virions are relatively stable when stored at 37°C, with minimal loss of infectivity after 24 h in the presence of serum; stable after drying and for at least 3 months at 4°C; tolerant of alkaline pH, but inactivated below pH 4; sensitive to treatment with organic solvents and detergents, and infectivity is reduced after exposure to ultraviolet light and irradiation.

2.3 | Disease name

- Borna disease

2.4 | Priority level

- Scientific/Epidemiologic evidence regarding blood safety: Theoretical
- Public perception and/or regulatory concern regarding blood safety: Absent
- Public concern regarding disease agent: Absent

2.5 | Background

- 1766: Borna disease first described in European sheep and horses.
- The name Borna refers to the city of Borna, Germany where an equine epidemic occurred during the late 1800s, crippling the Prussian cavalry.
- BoDV-1 naturally infects ostriches, horses, cattle, sheep, dogs, cats, shrews, and foxes. It is experimentally transmitted to non-human primates.
- 1996: BoDV-1 isolated from patients with mood disorders.
- 2015: Novel bornavirus initially discovered in variegated squirrels (variegated squirrel bornavirus-1; VSBV-1), and was confirmed in four human cases of fatal encephalitis.
- 2018: BoDV-1 was identified as a causative agent of severe and fatal encephalitis in three recipients of solid organ transplants from the same donor from Southern Germany. Recipients of both kidneys died; liver recipient in remission; 99.3%–99.7% nucleotide sequence identity from brain tissue of one kidney recipient to shrews and horses in Bavaria.
- Only infrequently has viral nucleic acid been found in human blood.

2.6 | Common human exposure routes

- Unknown, but contact with infected domestic animals, such as horses, sheep, and cats has been proposed.

2.7 | At-risk populations

- Unknown

2.8 | Likelihood of secondary transmission

- Unknown

2.9 | Vector and reservoir involved

- Sporadic enzootic disease of horses and sheep, although host range is wide; however, mode of transmission is unknown.
- Neonatal rats experimentally infected with BoDV-1 develop viral persistence, so rodents are a theoretical reservoir and vector; antibodies against BoDV have been detected in a few wild rodents, but specificity of BoDV antibodies is controversial.
- In 2006, the bi-colored, white-toothed shrew (*Crocidura leucodon*) was identified as a reservoir host in an area of Switzerland and in Southern Germany where BoDV-1 is prevalent in horses and sheep; the existence of other reservoir species has not been ruled out.

2.10 | Blood phase

- Unknown; but transcripts and proteins have been detected in peripheral blood mononuclear cells (PBMC) from patients with acute or chronic

psychiatric disease and in healthy persons. In these studies, cross-contamination and cross-reactivity have not been ruled out.
- BoDV RNA was not detected in 100 white cell pellets and in pools representing 25,000 plasma donations from Scottish blood donors.

2.11 | Survival/persistence in blood products

- Unknown

2.12 | Transmission by blood transfusion

- Never reported. However, the organ transplant cluster justifies continued attention. The organ transplant cluster emphasizes the zoonotic potential of BoDV-1 transmission that can lead to potentially lethal disease, and thus should be considered in cases of viral encephalitis with potential direct or indirect contact with bornavirus reservoirs.

2.13 | Cases/frequency in population

- World-wide natural infection of domestic animals.
- BoDV-1 has been identified as a causative agent in at least 18 naturally acquired sporadic or transplant-associated fatal human encephalitis cases.
- Seroprevalence previously reported in hospitalized patients with psychiatric, neurologic, and/or immunologic disorders ranged from 6% to 37%, but only 1%–2% in healthy volunteers; these data have not been reproduced, and thus may reflect cross-reactivity or non-specificity of the test assay used, or cross-contamination of controls.
- In a study from Bavaria, Germany, brain tissues from 56 encephalitis cases of putative viral origin (1999–2019) were submitted for virological testing and screened for BoDV-1 RNA. BoDV-1 nucleic acid, confirmed with antibodies, was detected in 8 encephalitis cases. Six of the 8 had no record of immunosuppression before the onset of fatal disease, whereas two were immunocompromised after solid organ transplantation. Viral RNA was not detected in any serum sample tested from 7 of the 8 cases. BoDV-1 sequence information and epidemiological analysis indicated spillover transmissions most likely from the local wild animal reservoir.

2.14 | Incubation period

- Approximately 1–3 months for horses and sheep
- Unknown human incubation period

2.15 | Likelihood of clinical disease

- At least 18 BoDV-1 naturally acquired sporadic or transplant-associated fatal human encephalitis cases have been identified.
- There is no information about transfusion transmission.

2.16 | Primary disease symptoms

- Causes severe, frequently fatal neurological disease in horses and sheep.
- Cause of severe often fatal neurologic disorders (encephalitis) in humans.
- Any role in psychiatric diseases remains to be proven.

2.17 | Severity of clinical disease

- Disease in humans believed to be a severe or lethal infection of the central nervous system. For patients with severe neurological disease of unknown etiology, healthcare providers should consider testing for BoDV-1, especially those who reside in, or traveled to, areas endemic for animal Borna disease.

2.18 | Mortality

- Acute Borna disease in animals and humans results in high mortality.

2.19 | Chronic carriage

- Unknown in humans.
- Bi-colored, white-toothed shrews appear to be a natural viral reservoir, with probable lifelong virus persistence. Shrews stay healthy and show no signs of neural inflammation, despite a broad range of infected tissues.
- Horses: Lifelong persistence with short periods of activation and long periods of inactivity.

2.20 | Treatment available/efficacious

- No consensus

2.21 | Agent-specific screening question(s)

- No specific question is in use.
- Not indicated because transfusion transmission has not been demonstrated.
- No sensitive or specific question is feasible.

2.22 | Laboratory test(s) available

- No FDA-licensed blood donor screening test exists.
- Generally accepted standards for diagnosis of human BoDV infection not established.
- Options for laboratory testing include immunofluorescence, immunoprecipitation, and western blot [specific antibodies in serum and cerebrospinal fluid (CSF)], flow cytometry (Borna disease virus nucleic acid and antigens in PBMC), tissue culture (BoDV in CSF), and RT-PCR (saliva, nasal or conjunctival fluid).

2.23 | Currently recommended donor deferral period

- No FDA Guidance or AABB Standard exists.

2.24 | Impact on availability

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: Not applicable

2.25 | Impact on blood safety

- Agent-specific screening question(s): Not applicable
- Laboratory test(s)available: Not applicable

2.26 | Leukoreduction efficacy

- Unknown. If truly highly cell-associated there would be theoretical interest

2.27 | Pathogen reduction efficacy for plasma derivatives

- Multiple pathogen reduction steps used in the fractionation process have been shown to be robust in the removal of enveloped viruses.

2.28 | Other prevention methods

- None

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