

Tick-Borne Encephalitis Virus Complex

Disease Agents:

- Tick-borne encephalitis virus (TBEV)
- Powassan virus (POWV) / deer tick virus (DTV)
- Other potentially relevant members of the TBEV complex include Kyasanur Forest disease virus (KFDV) and its related variant Alkhurma virus (ALKV), and Omsk hemorrhagic fever virus (OHFV)

Disease Agent Characteristics:

- Family: *Flaviviridae*; Genus: *Flavivirus*; Species: TBEV (subtypes: European, Far Eastern, and Siberian); POWV/DTV
- Virion morphology and size: Enveloped, polyhedral nucleocapsid symmetry, spherical particles, 40-60 nm in diameter
- Nucleic acid: Linear, positive-sense, single-stranded RNA, ~11.0 kb in length
- Physicochemical properties: Nonionic detergents solubilize the entire envelope; infectivity sensitive to acid pH and high temperatures (total inactivation at 56°C for 30 min); virus stable at low temperatures, especially at -60°C or below; aerosol hazard noted; virus inactivated by UV light, gamma-irradiation and disinfectants (relatively more resistant than mosquito-borne flaviviruses)

Disease Name:

- Tick-borne encephalitis (TBE)

Priority Level:

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

Background:

- TBEV clinically described in 1931 and virus isolated in 1937
- Natural distribution of TBEV throughout north central Eurasia and China.
- POWV is the only member of the TBEV complex found in North America, primarily in the northeastern and north central states in the US and in the southern regions of Canada. POWV was named in 1958 for the town in Northern Ontario where the first case of encephalitis caused by POWV was recognized in a 5-year old boy.
- Recently, a virus closely related to POWV has been designated as deer tick virus (DTV) that shows 84% and 94% of nucleotide and amino acid identity to POWV. POWV/DTV are considered the same virus species; the two viruses likely will be divided into two lineages.

Common Human Exposure Routes:

- Bite of infected ticks, usually from April to October
- Consumption of unpasteurized goat, sheep, or cow milk or cheese from virus-infected livestock

- Aerosol hazard in laboratory

Likelihood of Secondary Transmission:

- Unlikely

At-Risk Populations:

- Forestry workers, farmers, military, outdoor enthusiasts

Vector and Reservoir Involved:

- *Ixodes ricinus* (Western Europe); *I. persulcatus* (eastern Eurasia); *I. ovatus* (China and Japan); *I. cookei* (North America)
- *Dermacentor* species and *Haemaphysalis* species also implicated vectors in Ixodes-free areas
- Maintained in nature in small wild vertebrate hosts (rodents and insectivores); large mammals, such as goats, sheep, and cattle are a less important source of infection
- POWV is maintained primarily in a woodchuck-mustelid-*I. cookei* cycle; humans infrequently come into contact with infectious ticks that are found only rarely outside of the burrows of their host animal; generations of ticks are associated with a single animal. This tick behavior is referred to as nidicolous.
- *I. scapularis* is presumably a vector for DTV, but the frequency of finding POWV associated with *I. scapularis* is unknown.

Blood Phase:

- Viremia can occur prior to the onset of symptoms (based on a single example of transfusion-transmitted TBEV) and likely persists for some days after onset of symptoms. Duration of viremia is not well documented.
- Transient viremia is probable in subclinical infections.
- Fever associated with TBE may be biphasic, especially with the European subtype of TBEV, and commonly follows invasion of the CNS. The possibility of a second phase of viremia at that time has not been established.

Survival/Persistence in Blood Products:

- Unknown

Transmission by Blood Transfusion:

- Two recipients in Finland developed symptoms after receiving components from a donor who became symptomatic (febrile) hours after donating blood. A serological diagnosis of TBE was made in the donor and both recipients, and no other risk factors were identified in the recipients.

Cases/Frequency in the Population:

- ~3000 cases of TBEV annually in Europe; ~11,000 cases annually in Russia and former Soviet Union
- Five cases of imported TBEV were identified in US travelers returning from Europe and China between 2001-2009. For travelers to areas where TBEV is endemic, the estimated risk is one case per 10,000 person-months.

- TBEV seroprevalence studies, primarily in Europe (endemic areas), show rates ranging from 3% to 23%.
- Cases of POWV in North America limited to 27 cases reported between 1958-1998 with an additional 11 cases from 1999-2009 documented; higher numbers in recent years have anecdotally been reported. The majority of cases in the US have been in the NE (New York, Maine, Pennsylvania, Massachusetts and Vermont); Wisconsin and Michigan reported their first cases in 2002-2003. Ontario and Quebec are the provinces in Canada that have reported clinical cases. Increased recognition of Powassan-associated encephalitis is likely due to increased testing for WNV-related neuroinvasive disease.
- POWV seroprevalence rates based on neutralizing antibodies have ranged from 0% to 5.8% in Ontario with a rate of 0.7% in New York State over a 3-year period in the 1970s where human infections occur infrequently.
- The epidemic potential of POWV may be unrecognized since many cases are likely missed.

Incubation Period:

- 2-34 days to onset of symptoms, but usually between 7 and 14 days

Likelihood of Clinical Disease:

- Clinical symptoms may develop in ~1 out of 60 persons infected but may approach 25% in some endemic areas

Primary Disease Symptoms:

- The European TBEV subtype typically shows a biphasic course. The first phase is flu-like including fever, headache, and myalgia; the second phase involves the CNS including aseptic meningitis, meningoencephalitis, meningoencephalomyelitis, and meningoencephaloradiculitis.
- Onset of illness with the Siberian and Far Eastern subtypes of TBEV is more insidious and severe and usually presents as a monophasic illness with a febrile prodrome that includes headache, anorexia, nausea, vomiting, and photophobia followed by stiff neck, sensorial changes, visual disturbances, and neurologic manifestations that include paresis, paralysis, sensory loss, and convulsions.
- Powassan encephalitis is severe with focal features and profound muscle wasting and weakness. It often results in neurologic sequelae with cognitive impairment. Fever is the universal finding with temperatures reported as high as 41°C.

Severity of Disease:

- Infections with the Far Eastern and Siberian subtypes of TBEV are generally more severe than with the European subtype, especially in children, with neurologic sequelae in up to 80% of survivors. A bimodal distribution of POWV cases is observed in children less than 10 years old and adults over 60 years old after outdoor exposure to ticks that carry the virus. Although most patients with POWV infections recover

from acute disease, approximately one-third can experience long-term neurological sequelae.

Mortality:

- Case-fatality rate for the European subtype of TBEV is 1-2%.
- Case-fatality rate for the Far Eastern and Siberian subtypes is ~20%, but this is possibly biased by not including mild cases in the calculation.
- Powassan case-fatality rates are intermediate to these extremes.

Chronic Carriage:

Persistent infection of neural tissue, but not viremia, has been observed.

Treatment Available/Efficacious:

- Supportive primarily; IVIG and steroid therapy have been administered for acute disseminated encephalitis, but data are inadequate to assess the impact.

Agent-Specific Screening Question(s):

- No specific question is in use.
- Not indicated because transfusion transmission is limited to a single report.
- No sensitive or specific question is feasible. A history of tick bites is given in <50% of the cases of TBEV and POWV infections. Thus, this question probably lacks sensitivity and specificity for this agent.

Laboratory Test(s) Available:

- No FDA-licensed blood donor screening test exists.
- Diagnosis is made serologically by detection of IgM antibodies (EIA, IFA) and/or virus isolation from blood in cell culture or experimental animals, but sensitivity of the latter is ~10%. Heterologous cross-reactions within the TBEV complex are problematic and require virus-specific neutralizing antibody testing for resolution. In areas where other flaviviruses co-circulate, similar cross-reacting antibodies may be present. Some cases of POWV have been identified when evaluating encephalitis cases for WNV infection; POWV antibodies may cross react with other flaviviruses including WNV and SLEV that require neutralizing antibody assays to distinguish one from another. However, since POWV is genetically distinct from WNV/SLEV, acute-phase sera would be only weakly reactive in WNV antibody tests versus highly reactive when assays containing POWV envelope antigens are employed. POWV and DTV cannot be distinguished serologically; sequencing is generally required.
- Protocols are available for NAT.

Currently Recommended Donor Deferral Period:

- No FDA Guidance or AABB Standard exists.
- At a minimum, donors should be recovered and free of signs and symptoms, but there are insufficient data (i.e., unknown

duration of viremia) to make recommendations regarding a deferral period.

Impact on Blood Availability:

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

Impact on Blood Safety:

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

Leukoreduction Efficacy:

- Unlikely to have an impact

Pathogen Reduction Efficacy for Plasma Derivatives:

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

Other Prevention Measures:

- No TBEV vaccines are licensed and available in the US, but two effective inactivated vaccines are available in Canada and Eurasia.
- TBE immunoglobulin (TBE IG) was at one time used as post-exposure prophylaxis after a tick bite in TBE endemic countries. However, there are concerns that it may have a negative effect on the course of the disease. TBE IG is therefore no longer recommended in England or other European countries for postexposure prophylaxis for travelers in the event of a tick bite in a TBE-endemic country.
- Avoidance of tick bites in tick-infected forested areas during early spring and summer by using insect repellants (e.g., DEET) and using protective clothing in addition to inspecting body and clothing for ticks; avoiding unpasteurized dairy products; avoid contact with rodent nests
- Education

Suggested Reading:

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