42 | TICK-BORNE ENCEPHALITIS VIRUS COMPLEX (THERE IS A SEPARATE FACT SHEET ON POWV)

42.1 | Disease agents

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

42.2 | Disease agent characteristics

- Family: *Flaviviridae*; Genus: *Flavivirus*; Species: TBEV (subtypes: European, Far Eastern, and Siberian)
- 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)

42.3 | Disease name

- Tick-borne encephalitis (TBE)

42.4 | 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 to low

42.5 | 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 United States 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.

42.6 | 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

42.7 | Likelihood of secondary transmission

- Unlikely

42.8 | At-risk populations

- Forestry workers, farmers, military, outdoor enthusiasts

42.9 | 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 reservoir of infection.

42.10 | 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 TBEV infections 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.

42.11 | Survival/persistence in blood products

- Unknown

42.12 | 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.
- Transmissibility through solid organ transplantation has been shown in a cluster of cases linked to a single donor in Poland. Susceptibility of these recipients may have been enhanced by pharmacological immunosuppression.

42.13 | Cases/frequency in the population

- ~3000 cases of TBEV annually in Europe; ~11,000 cases annually in Russia and former Soviet Union
- Eleven cases of imported TBEV were identified in US travelers returning from Europe, Russia and China between 2000 and 2020. 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%.

42.14 | Incubation period

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

42.15 | Likelihood of clinical disease

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

42.16 | 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 a stiff neck, sensorial changes, visual disturbances, and neurologic manifestations that include paresis, paralysis, sensory loss, and convulsions.

42.17 | 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.

42.18 | Mortality

- Case-fatality rate for the European subtype of TBEV is 1%–2%.
- Case-fatality rate for the Far Eastern and Siberian subtypes is between 5% and 20%, but this is possibly biased by not including mild cases in the calculation.

42.19 | Chronic carriage

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

42.20 | Treatment available/efficacious

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

42.21 | 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 infection. Asking donors about tick bites has been shown to lack sensitivity and specificity.

42.22 | Laboratory test(s) available

- No FDA-licensed blood donor screening tests exist.
- Clinical diagnosis is challenging due to the nonspecific signs and symptoms of early disease: leukopenia, thrombocytopenia, and elevated liver enzymes.
- Diagnosis is made serologically during the second phase of disease 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 serocomplex 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. Protocols are available for NAT.

42.23 | 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.

42.24 | Impact on blood availability

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

42.25 | Impact on blood safety

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

42.26 | Leukoreduction efficacy

- Unlikely to have an impact.

42.27 | 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.

42.28 | Other prevention measures

- A TBEV vaccine is licensed and available in the United States, but several effective inactivated vaccines are currently available in Europe, Russia, and China. Since vaccination requires several months to complete the required 3 doses for maximal efficacy, other preventive measures are recommended for travelers or visitors to endemic areas.
  - The US-licensed vaccine is TicoVac™ manufactured by Pfizer (Tick-borne encephalitis vaccine); and induces protective antibodies against the three most prevalent subtypes of the TBEV circulating globally. It is an inactivated vaccine derived from TBEV propagated in chick embryo fibroblast cells and has been available outside of the US for >20 years. The vaccine is recommended for persons who are traveling or moving to a TBE-endemic area who are planning extensive tick exposure.
- TBE immunoglobulin (TBE IG) was at one time used as postexposure 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, pets, and clothing for ticks, avoiding unpasteurized dairy products, avoiding contact with rodent nests
- Education

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