Japanese Encephalitis Virus Complex

Disease Agent:

- Japanese encephalitis virus (JEV) and Usutu virus (USUV)

Disease Agent Characteristics:

- Family: *Flaviviridae*; Genus: *Flavivirus*
- Virion morphology and size: Enveloped, icosahedral nucleocapsid symmetry, spherical particles, 40 to 60 nm in diameter
- Nucleic acid: Linear, positive-sense, single-stranded RNA genome, ~11.0 kb in length
- Physicochemical properties: Infectivity inactivated and destroyed by heating for 10 minutes at >56°C; half life of 7 hours at 37°C; sensitive to treatment with lipid solvents, detergents, ether, trypsin, chloroform, formaldehyde, heat and β-propiolactone; infectivity reduced after exposure to irradiation and inactivated at pH 1-3

Disease Name:

- Japanese encephalitis

Priority Level:

- Scientific/Epidemiologic evidence regarding blood safety: Theoretical; because of the similarity to West Nile virus (WNV), transfusion risk during JEV outbreaks may occur.
- Public perception and/or regulatory concern regarding blood safety: Absent
- Public concern regarding disease agent: Absent

Background:

- Recognized in horses and humans in 1871; severe epidemic occurred in Japan in 1924; isolated from human brain in 1935
- Increasing in India, Nepal, and South East Asia while declining in Japan, S. Korea, Taiwan, and China since 1970 because of widespread vaccination programs and other preventive measures. Most recently detected in Australia.
- 35,000-50,000 cases and 10,000 deaths occur annually in Asia, but the disease is greatly underreported.
- A closely related member of the JEV complex, USUV, was implicated in the development of neuroinvasive disease in two immunosuppressed patients in northern Italy; one who was viremic immediately prior to orthotopic liver transplantation and the other who became infected following chemotherapy. Virus-specific RNA was detected by RT-PCR in the plasma of both patients and virus was isolated from the blood in one patient and CSF in the other patient; in both cases, sequencing revealed 98% identity with known USUV isolates. Transmission in both cases occurred while USUV was circulating in the area; prior to these two cases, USUV had not been associated with neurological disease in humans. In one of the cases, the patient was identified due to low-level reactivity in a WNV transcription-mediated amplification assay (Procleix, Novartis). The same patient was negative when tested with the Cobas Taqscreen (Roche) WNV PCR assay.

Common Human Exposure Routes:

- Vector-borne (*Culex* mosquitoes)

Likelihood of Secondary Transmission:

- For JEV, absent except for rare intrauterine transmission recorded
- Undocumented for USUV

At-Risk Populations:

- Widely distributed in Asia
- Affects all ages, but especially children and the elderly

Vector and Reservoir Involved:

- Main epidemic JEV vectors are mosquitoes of the *Culex* species, especially *C. tritaeniorhynchus*, which is an evening- and nighttime-biting mosquito that feeds preferentially on pigs and birds and infrequently on humans. Culicine mosquitos are also the vectors for USUV.
- In temperate regions, pigs and birds (principally ardeid species, such as egrets and black-crowned night herons, and possibly ducks) are effective amplifying hosts for JEV. USUV circulates in birds.

Blood Phase:

- Virus can be isolated from the blood infrequently after the appearance of symptoms. It is unknown whether a biologically relevant viremic phase occurs during asymptomatic infections.

Survival/Persistence in Blood Products:

- Unknown

Transmission by Blood Transfusion:

- No cases documented; however, because of similarity to WNV (i.e., mosquito-borne flavivirus that results in community epidemics), transfusion transmission is plausible during JEV and USUV outbreaks.

Cases/Frequency in Population:

- JEV is widely distributed in Asia; infection rates may exceed 1% during periods of peak transmission, which usually occurs from June to November
- Where vaccination programs are not in place, nearly all persons in endemic areas have been infected (antibody-positive) by young adulthood.
- JEV is not endemic in the US but imported by travelers returning from endemic areas with an estimated risk of one case per million travelers; risk increases with a prolonged stay in a rural area where active JEV transmission is occurring. From 1973-2008, 55 cases of travel-associated JE were reported from 17 countries (15 from the US). Thailand,

Indonesia and China were where the disease was most commonly acquired.
- USUV is found in sub-Saharan Africa, central and southern Europe.

Incubation Period:

- 6-16 days from exposure to onset of symptoms

Likelihood of Clinical Disease:

- Inapparent-to-apparent infection rate ranges from 200-300 to 1

Primary Disease Symptoms:

- **JEV**
  - Febrile headache syndrome
  - Aseptic meningitis
  - Encephalitis characterized by rapid onset with a 2- to 4-day prodrome of headache, fever, chills, nausea, vomiting, dizziness, and drowsiness followed by nuchal rigidity, photophobia, altered states of consciousness, seizures, hyperexcitability, and focal neurologic signs of CNS involvement.
  - Acute flaccid paralysis similar to poliomyelitis can occur
- **USUV**
  - Clinical illness is unusual and described only in case reports. In immunocompromised hosts, it appears capable of causing neuroinvasive disease broadly similar to JEV.

Severity of Clinical Disease:

- Severe manifestations of the disease can occur with accompanying mortality.
- Neuropsychiatric sequelae are frequent (45%-70% of JEV survivors) often with thalamic or other lesions on MRI. These include a Parkinsonian syndrome, convulsive disorders, paralysis, mental retardation, and psychiatric disorders.

Mortality:

- Children and the elderly are at the highest risk for JEV mortality, which ranges from 5%-40% (2%-11% reported in US military personnel) with the highest frequency usually associated with poor medical care.

Chronic Carriage:

- Evidence for persistent/latent infection in humans is based on recovery of JEV from PBMC of asymptomatic children 9 months after acute JEV as well as in children developing recurrent disease. JEV was also recovered from CSF 4 months after onset of symptoms. The relevance of these data remains to be elucidated.

Treatment Available/Efficacious:

- Supportive treatment

Agent-specific Screening Question(s):

- No specific question is in use.
- No sensitive or specific question is feasible.

Laboratory Test(s) Available:

- No FDA-licensed blood donor screening tests exist.
- Virus can occasionally be isolated in cell culture from the blood of symptomatic cases. Isolation possibilities are better from the CSF (up to one-third of cases).
- Serology on paired serum samples showing fourfold rise in titer by neutralization, CF or HI is diagnostic.
- An IgM-capture EIA test is helpful in diagnosing JEV by detection of serum and intrathecal antibody.
- PCR and viral sequencing are used for both JEV and USUV

Currently Recommended Donor Deferral Period:

- No FDA Guidance or AABB Standard exists.
- Prudent practice would be to defer for 1 year after resolution of symptoms based on limited data regarding persistence in PBMC.

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:

- Unknown, but PBMC isolation study mentioned previously suggests that leukoreduction might lower a theoretical risk from JEV

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:

- Formalin-inactivated vaccines for humans have an efficacy of 91%; a live attenuated vaccine is in use in China yielding seroconversion in 95% after one dose. Genetically engineered vaccines are in development.
- Mosquito control

Suggested Reading:

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