25 | LA CROSSE VIRUS

25.1 | Disease agent

- La Crosse virus (LACV)

25.2 | Disease agent characteristics

- Family: *Peribunyaviridae* Genus: *Orthobunyavirus* and a member of the California encephalitis serogroup.
- Enveloped, helical nucleocapsid symmetry, spherical to pleomorphic particles, 90–110 nm in diameter.
- Three segments of circular, negative-sense, single-stranded RNA, 12.5 kb in length with four structural proteins.
- Orthobunyaviruses are sensitive to inactivation by heat, detergents, formaldehyde, and low pH.

25.3 | Disease name

- La Crosse encephalitis

25.4 | Priority level

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

25.5 | Background

- Early in the 1960s, physicians in southwestern Wisconsin and southeastern Minnesota investigated children with a summer "rural encephalitis." La Crosse virus was isolated at autopsy from the brain of a fatal case.
- Encephalitis due to LACV infection has been initially reported in the upper Midwest, in Minnesota, Wisconsin and Ohio. Moreover, high number of cases have been reported from the Appalachian region, since the 1980s in West Virginia and since the 1990s in Tennessee and North Carolina. In 2018 LACV disease cases were reported from seven states, primarily in the East North Central and South Atlantic regions.
- 30–180 neuroinvasive cases of severe LACV disease are reported annually with an incidence of 0.1–0.6 cases per 100,000 in the most affected areas. LACV is rapidly becoming a leading cause of encephalitis in the United States.
- LACV and WNV account for the overwhelming majority of pediatric arboviral encephalitis cases in the United States.
- More than 130 arboviruses are known to cause human disease; most of public health importance belong to the genera: *Flavivirus*, *Alphavirus* and *Orthobunyavirus*. Many are nationally notifiable via state reporting to the US CDC (ArboNet); for example, dengue viruses, Zika virus, California serogroup viruses, chikungunya virus, eastern equine encephalitis virus, Powassan virus, St. Louis encephalitis virus, West Nile virus, western equine encephalitis virus and yellow fever virus.

25.6 | Common human exposure routes

- Transmitted primarily by the bite of *Aedes triseriatus* mosquitoes from June to October.

25.7 | Likelihood of secondary transmission

- Viruses in the California encephalitis serogroup are not known to be transmitted from person-to-person or through blood transfusion.

25.8 | At-risk populations

- La Crosse encephalitis is predominantly a childhood disease; 75% of cases occur in children under 10 years of age and only 3% in persons 20 years or older.
- Seroprevalence surveys in endemic areas have tended to show higher prevalence rates in rural than in urban sites (30% vs. 15% in one study), many cases occur in suburban residential locations.

25.9 | Vector and reservoir involved

- Transmitted by female *A. triseriatus*, a "tree-hole mosquito," the reservoir and vector for LACV.
- Although their main breeding site is in holes in hardwood trees, the mosquitoes can also breed in artificial containers that hold rainwater, including discarded tires.
- Persistence in endemic areas is a result of vertical transmission of LACV from *A. triseriatus* females to their offspring, venereal transmission among adult mosquitoes, and horizontal transmission to small

mammals (e.g., chipmunks, gray squirrels, woodchucks, and foxes) that serve as amplifying hosts.
- *A. albopictus* and *A. japonicus* invaded the US in the mid-1980s and mid-1990s, respectively and have since spread throughout the Appalachian region. For both species, LACV-positive adult insects have been found at case sites of LACV encephalitis in eastern Tennessee, implicating these species as vectors of human cases in the Appalachian region. Humans do not maintain prolonged viremias and therefore are "dead-end" hosts unable to amplify the virus and reinfect the vector.

25.10 | Blood phase

- No data available for blood phase in asymptomatic persons.
- Virus is introduced by the feeding mosquito, and viral replication is presumed to cause viremia; amplification of the viremia occurs in the reticuloendothelial system followed by invasion of the central nervous system (CNS).
- Entrance to the CNS is probably first gained by infection of vascular endothelial cells followed by infection of neurons and glial cells.
- Neither LACV nor other members of the California serogroup have been isolated from human blood. The length of the incubation period (about 1 week for LACV) provides time for antibody production and "quenching" of the relatively brief putative viremia (estimated duration, 1–3 days).

25.11 | Survival/persistence in blood products

- Unknown

25.12 | Transmission by blood transfusion

- LACV has not been associated with transmission by blood transfusion.

25.13 | Cases/frequency in population

- LACV is the most common cause of neuroinvasive arboviral disease in children in the United States.
- Annually the US CDC report 30–130 cases of neuroinvasive LACV cases in the United States. In 2018, more LACV disease cases were reported than in any year since 2011.
- Accurate data for non-neuroinvasive disease are not available.

25.14 | Incubation period

- 5–15 days

25.15 | Likelihood of clinical disease

- Low, but highest in children and adolescents

25.16 | Primary disease symptoms

- Of children infected with LACV, only a small fraction (~0.3%–4%) have symptoms.
- Fever, headache, nausea, and vomiting are common.
- Symptomatic infection ranges from a mild febrile illness to aseptic meningitis and fatal encephalitis.

25.17 | Severity of clinical disease

- Most infections are asymptomatic, but children presenting to a physician generally have signs of encephalitis, which can be severe.
- Initial symptoms can include fever (usually lasting 2–3 days), headache, nausea, vomiting, fatigue, and lethargy.
- LACV can cause severe disease, such as encephalitis.
  - Symptoms of severe disease include high fever, headache, neck stiffness, stupor, disorientation, coma, tremors, seizures, muscle weakness, vision loss, numbness, and paralysis.
  - Severe disease occurs most frequently in children under the age of 16 years. Recovery time from severe illness varies and some effects to the CNS can persist over time. These can include recurrent seizures and cognitive or behavioral impairments. Up to 15% have a variety of neurological sequelae.

25.18 | Mortality

- The case fatality rate is much less than 1% overall but approaches 2% of hospitalized cases.

25.19 | Chronic carriage

- None recognized

25.20 | Treatment available/efficacious

- No antiviral or vaccines are available to prevent or treat the infection.
- Supportive care is given to patients presenting with LACV encephalitis.

25.21 | Agent-specific screening question(s)

- No specific question is in use.
- Not indicated because transfusion transmission has not been demonstrated.
- A question about mosquito contact in endemic areas would have low positive predictive value.

25.22 | Laboratory(s) test available

- No FDA-licensed blood donor screening test exists.
- Virus isolation from tissue is difficult.
- Serological tests (EIA, IFA, HAI, CF, neutralization) detect IgM and IgG antibodies.
- IgM antibodies have been known to persist for up to 7 years.
- NAT (primarily nucleic acid sequence-based amplification [NASBA] and RT-PCR) has been used to detect RNA in CSF and CNS tissue and appears very specific and more sensitive than virus isolation.

25.23 | Currently recommended donor deferral

- No FDA Guidance or AABB Standard exists.
- The appropriate deferral period for clinical infection is not known but would likely be on the order of several weeks after the resolution of symptoms.

25.24 | Impact on blood availability

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

25.25 | Impact on blood safety

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

25.26 | Leukoreduction efficacy

- Unknown

25.27 | 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.

25.28 | Other preventive measures

- Unknown

SUGGESTED READING

1. Basile AJ, Horiuchi K, Panella AJ, Laven J, Kosoy O, Lanciotti RS, et al. Multiplex Microsphere immunoassays for the detection of IgM and IgG to arboviral diseases. PLoS One. 2013;8:e75670.
2. Bewick S, Agusto F, Calabrese J, Muturi EJ, Fagan WF. Epidemiology of la crosse virus emergence, appalachia region, United States. Emerg Infect Dis. 2016;22:1921–9.
3. Calisher CH. Medically important arboviruses of the United States and Canada. Clin Microbiol Rev. 1994;7:89–116.
4. Centers for disease control and Prevention. LaCrosse encephalitis virus. https://www.cdc.gov/lac/index.html. Accessed 7 Feb 2023
5. Centers for Disease Control and Prevention. Confirmed and Probable California Serogroup Viral (mainly La Crosse) Encephalitis Cases, Human, United States, 1964-2006. [cited 2009 May]. Available from: http://www.cdc.gov/ncidod/dvbid/arbor/pdf/CAL_LAC.pdf
6. Day CA, Odoi A, Fryxell RT. Geographically persistent clusters of La Crosse virus disease in the Appalachian region of the United States from 2003-2021. PLoS Negl Trop Dis. 2023;17:e0011065.
7. Gerhardt RR, Gottfried KL, Apperson CS, Davis BS, Erwin PC, Smith AB, et al. First isolation of La Crosse virus from naturally infected *Aedes albopictus*. Emerg Infect Dis. 2001;7:807–11.
8. Harding S, Greig J, Mascarenhas M, Young I, Waddell LA. La Crosse Virus: a scoping review of the global evidence. Epidemiol Infect. 2019;147:e66. https://doi.org/10.1017/S0950268818003096
9. Hughes HR, Alkhovskiy S, Beer M, Adkins S, Blair C, Calisher CH, et al. ICTV virus taxonomy profile: peribunyaviridae. Kuhn JH, Siddell SG Eds. J Gen Virol. 2020;101:1–2.
10. Lambert AJ, Nasci RS, Cropp BC, Martin DA, Rose BC, Russell BJ, Lanciotti RS. Nucleic acid amplification assays for detection of La Crosse virus RNA. J Clin Micro. 2005;43:1885–9.
11. Matthews E, Chauhan L, Piquet AL, Tyler KL, Pastula DM. An overview of La Crosse virus disease. Neurohospitalist. 2022;12:587–8.

12. McJunkin JE, Khan RR, de los Reyes EC, Parsons DL, Minnich LL, Ashley RG, Tsai TF. Treatment of severe La Crosse encephalitis with intravenous ribavirin following diagnosis by brain biopsy. Pediatrics. 1997;99:261–7.
13. McDonald E, Martin SW, Landry K, Gould CV, Lehman J, Fischer M, Lindsey NP. West Nile virus and other domestic nationally notifiable arboviral diseases-United States, 2018. MMWR. 2019;68:673–8.
14. McJunkin JE, Khan RR, Tsai TF. California-La Crosse encephalitis. Infect Dis Clin North Am. 1998;12:83–93.
15. Miller S, Carchman R, Long R, Denslow SA. La Crosse viral Infection in hospitalized pediatric patients in western North Carolina. Hosp Pediatr. 2012;2:235–42. https://doi.org/10.1542/hpeds.2012-0022
16. Peters CJ. California encephalitis, hantavirus pulmonary syndrome, and *Bunyaviridae* hemorrhagic fevers. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. 6th ed. Philadelphia: Elsevier, Churchill, Livingstone; 2005. p. 2086–90.
17. Slater B, Huang C, Bloch K, Jones T, Woodlief G, McPherson T. Detection of La Crosse virus in cerebrospinal fluid and tissues by reverse transcription polymerase chain reaction. International Conference on Emerging Infectious Diseases. Atlanta, GA. March 24-27, 2002. [cited 2009 May]. Available from: http://www.cdc.gov/iceid/webcast/molecular_d2.htm