West Nile Virus

Clinical Policy ID: CCP.1251

Recent review date: 9/2021

Next review date: 1/2023

Policy contains: Immunoglobulin M antibody testing; plaque-reduction neutralization testing; reverse transcriptase-polymerase chain reaction testing; West Nile virus.

This policy is a Sandhills Center Clinical Coverage Policy adopted from AmeriHealth Caritas of North Carolina. These clinical policies are used to assist with making coverage determinations. Sandhills Center's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Sandhills Center when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Sandhills Center clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Sandhills Center's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Sandhills Center will update its clinical policies as necessary. Sandhills Center clinical policies are not guarantees of payment.

Coverage policy

Care management of persons with West Nile virus exposure or illness is evolving. In instances where AmeriHealth Caritas policies and Centers for Disease Control and Prevention guidelines conflict, Centers for Disease Control and Prevention guidance will govern.

The following over-the-counter services are medically necessary up to plan limit in at-risk areas (Centers for Disease Control and Prevention, 2020):

- Medications to relieve symptoms, such as pain and fever.
- Environmental Protection Agency (2019)-registered insect repellents when used as directed.
- See other Centers for Disease Control and Prevention (2019) recommendations for prevention.

West Nile virus testing is clinically proven and, therefore, medically necessary when performed in accordance with Centers for Disease Control and Prevention guidelines (2004, 2013, and 2018b):

- Indications for West Nile virus testing:
    - Symptomatic individuals as part of the differential diagnosis of febrile or acute neurologic illnesses associated with recent West Nile virus exposure to mosquitoes, blood transfusion, or organ transplantation.
    - Neonates whose mothers were infected with West Nile virus during pregnancy or while breastfeeding.

- Test selection should consider the range of pathogens in the differential diagnosis, the criteria for classifying a West Nile virus case as confirmed or probable, and the capability of the primary and confirming diagnostic laboratories (2018b):
    - Antibody testing:
        - West Nile virus immunoglobulin M (preferred) or immunoglobulin G of serum or cerebrospinal fluid within eight days of illness onset using U.S. Food and Drug Administration-approved commercial test kits or Centers for Disease Control and Prevention-defined immunoglobulin M and immunoglobulin G enzyme-linked immunosorbent assay testing.
        - Convalescent phase serum testing to confirm negative screen or retrospective diagnosis of infection with a specific agent.
        - Plaque reduction neutralization test to confirm positive screen.
    - Virus isolation of cerebrospinal fluid, serum, or tissue.
    - West Nile virus ribonucleic acid testing (e.g., reverse transcriptase-polymerase chain reaction) to confirm diagnosis in acute-phase serum, cerebrospinal fluid, or tissue specimens, and to screen transplant donors in at-risk areas.
- Required documentation includes: 1) symptom onset date (when known); 2) date of sample collection; 3) unusual immunological status of patient (e.g., immunosuppression); 4) state and county of residence; 5) travel history (especially in flavivirus-endemic areas); 6) history of prior vaccination (e.g., yellow fever, Japanese encephalitis, or Tick-borne encephalitis viruses); and 7) brief clinical summary including clinical diagnosis (e.g., encephalitis, aseptic meningitis).

The following services are clinically proven and, therefore, medically necessary when performed in accordance with current guidelines (American College of Radiologists, 2019; Centers for Disease Control and Prevention, 2004, 2018a):

- Prenatal obstetrical ultrasound of the fetus with no upper limit on the number of tests, no sooner than two to four weeks after onset of West Nile virus illness in the mother, unless earlier examination is otherwise indicated.
- For infants born to a mother with known or suspected West Nile virus infection during pregnancy, immunoglobulin M and immunoglobulin G antibody serum testing and neurological and hearing examinations.
- For infants born with suspected or clinical/laboratory evidence of West Nile virus infection, brain imaging, ophthalmological (including retina) evaluation, West Nile virus immunoglobulin M antibody testing of cerebrospinal fluid, hearing screen, immunoglobulin M/immunoglobulin G antibody testing at six months, and further examination of abnormalities as needed.
- Histopathologic evaluation of the placenta and umbilical cord.

Limitations

The following services are not medically necessary (Centers for Disease Control and Prevention, 2013, 2015; Tunkel, 2008):

- Vaccines to prevent West Nile virus infection, as their clinical benefit has not been established.
- Screening asymptomatic individuals for West Nile virus due to the high portion of infected individuals who are asymptomatic with no associated health problems.
- Treatment for West Nile virus illness using antiviral agents, nucleic acid analogues, missense sequences, immunomodulating agents, and angiotensin-receptor blockers, as their clinical benefit has not been established.

For Medicare members only

Intravenous immunoglobulin is medically necessary when used in the treatment of West Nile virus infection, including meningitis and encephalitis (Centers for Medicare & Medicaid Services, 2019, 2021a).

Alternative covered services

- Standard of care for clinical examination and differential diagnosis (e.g., testing for flavivirus infection, brain imaging and ophthalmic and neurological examination).
- Supportive in-hospital care.
- Physical therapy and occupational therapy.

Background

West Nile virus is spread by mosquitoes (Centers for Disease Control and Prevention, 2020). In a very small number of cases, West Nile virus has spread through blood transfusions, organ transplants, and from mother to baby during pregnancy, delivery, or breastfeeding. As an arbovirus, West Nile virus is a nationally notifiable condition.

Most people (70% to 80%) who become infected with West Nile virus remain asymptomatic (Centers for Disease Control and Prevention, 2020). The rest may present with abrupt onset of common nonspecific symptoms such as fever, headache, altered mental status, vomiting, diarrhea, and maculopapillary rash. Less than 1% of people who are infected will develop a serious neurologic illness (e.g., encephalitis, meningitis, poliomyelitis, and other forms of acute flaccid paralysis), and about 10% of those will die of the infection. Severity of neurologic illness at initial presentation does not necessarily correlate with eventual outcome. While most recover completely, recovery from severe disease may take several weeks or months, and in some the neurologic effects may be permanent.

Detection and diagnosis

Diagnosis is based on clinical symptoms, laboratory testing, recent exposure, and vaccination history. Laboratory diagnosis includes detection of viable West Nile virus, West Nile virus ribonucleic acid, and West Nile virus-specific antibodies (Centers for Disease Control and Prevention, 2018b).

Laboratory diagnosis is generally accomplished by testing for West Nile virus-specific immunoglobulin M antibodies in serum or cerebrospinal fluid, plaque reduction neutralization tests, and virus cultures of cerebrospinal fluid. Nucleic acid amplification tests (e.g., reverse transcriptase-polymerase chain reaction) in serum, cerebrospinal fluid, and tissue specimens, which detect the presence of West Nile virus ribonucleic acid, are routinely used to screen units of donated blood for West Nile virus and may be performed on the blood of tissue and organ donors prior to transplantation.

Immunoassays for West Nile virus-specific immunoglobulin M are available commercially and through state public health laboratories. Commercially-available test kits from different manufacturers for detection of West Nile virus immunoglobulin M and immunoglobulin G antibodies and Centers for Disease Control and Prevention-defined immunoglobulin M and immunoglobulin G enzyme-linked immunosorbent assay may be used (Centers for Disease Control and Prevention, 2018b; U.S. Food and Drug Administration, 2021).

Findings

One literature review by Centers for Disease Control and Prevention (2015) and six evidence-based guidelines from Centers for Disease Control and Prevention (2015 updated 2017, 2013, and 2004), the Infectious Disease Society of America (Tunkel, 2008), the American College of Radiologists (2013), and the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology (2008) provide the basis for this policy.

Numerous pathogens can cause encephalitis, aseptic meningitis, and febrile disease with clinical presentations similar to those caused by West Nile virus. West Nile virus disease should be considered in the differential diagnosis of febrile or acute neurologic illnesses associated with recent exposure to mosquitoes, blood transfusion, or organ transplantation, and of illnesses in neonates whose mothers were infected with West Nile virus during pregnancy or while breastfeeding.

Testing should be performed in symptomatic individuals and not for screening asymptomatic individuals, as there is a high proportion of infected individuals who are asymptomatic with no associated health problems (Centers for Disease Control and Prevention, 2013; Tunkel, 2008). Selection of diagnostic test procedures should take into consideration the range of pathogens in the differential diagnosis, the criteria for classifying a West Nile virus case as confirmed or probable, as well as the capability of the primary and confirming diagnostic laboratories.

West Nile virus immunoglobulin M antibody testing in serum or cerebrospinal fluid is preferred as an initial screen for West Nile virus infections (Centers for Disease Control and Prevention, 2004, 2013; Tunkel, 2008). The sensitivity of polymerase chain reaction testing is inferior to immunoglobulin M testing, as peak viremia occurs three to four days before symptom onset. West Nile virus-specific immunoglobulin M antibodies are usually detectable in the acute phase three to eight days after onset of symptoms and persist for 30 to 90 days and possibly longer. The presence of virus-specific immunoglobulin M in cerebrospinal fluid is usually indicative of neuroinvasive disease, because immunoglobulin M antibodies do not readily diffuse across the blood-brain barrier. If serum is collected within eight days of illness onset, the absence of detectable virus-specific immunoglobulin M does not rule out infection, and the test may need to be repeated on a later sample.

In general, immunoglobulin G antibodies are detectable shortly after the appearance of immunoglobulin M antibodies and persist for years following a symptomatic or asymptomatic infection. The presence of immunoglobulin G antibodies alone is only evidence of previous infection. Presence of immunoglobulin M or immunoglobulin G antibodies may reflect cross-reactivity with other flaviviruses or non-specific reactivity. Clinically compatible cases with the presence of immunoglobulin G, but not immunoglobulin M, should be evaluated for other etiologic agents.

Plaque reduction neutralization test should be used to confirm all positive antibody tests to differentiate flavivirus infections (Centers for Disease Control and Prevention, 2004, 2013; Tunkel, 2008). At the time of initial presentation, serum samples should be stored and tested at a later time with convalescent phase serum samples. Such testing is indicated for the retrospective diagnosis of infection with a specific agent rather than for initiating therapy. A fourfold or greater change in West Nile virus-specific neutralizing antibody titer between acute- and convalescent-phase serum samples collected two to three weeks apart confirms acute infection.

Virus culture and reverse transcriptase-polymerase chain reaction testing to detect West Nile virus ribonucleic acid in serum or cerebrospinal fluid of clinically ill, immunocompetent patients have limited utility in diagnosing human West Nile virus neuroinvasive disease due to the low level viremia present in most cases at the time of clinical presentation. However, these tests may prove useful in immunocompromised patients, in whom antibody development is delayed or absent. Negative virus culture and reverse transcriptase-polymerase chain reaction results should not be used to rule out an infection.

Routine clinical laboratory studies are generally nonspecific. In patients with neuroinvasive disease, typical cerebrospinal fluid findings, particularly in West Nile meningitis, include pleocytosis (generally less than 500 cells/mm^3) with elevated protein but normal glucose levels. Features of the pleocytosis that are indicative of West Nile virus infection include a prolonged predominance of polymorphonuclear cells and the presence of abnormal-appearing reactive lymphocytes or monocytes, including plasma cell-like and mollaret-like cells.

Computed tomography and magnetic resonance imaging are most frequently used to evaluate patients with possible central nervous system infection, with magnetic resonance imaging being preferred when available (American College of Radiologists, 2013; Tunkel, 2008). The incidence of acute abnormalities in patients with

West Nile virus neuroinvasive disease has been extremely variable, but magnetic resonance imaging may detect early changes in the basal ganglia, thalamus, and brainstem in approximately 30 percent of patients with encephalitis, and in the anterior spinal cord in patients with poliomyelitis. Diffusion-weighted magnetic resonance imaging is superior to conventional and is the preferred neuroimaging modality. Computed tomography with and without intravenous contrast administration should be used only if magnetic resonance imaging is unavailable, impractical or cannot be performed.

Prevention and treatment

There are no effective vaccines to prevent West Nile virus infection (Centers for Disease Control and Prevention, 2015). Several have completed phase I or phase II human clinical trials with promising results, but lack of predictability of the magnitude and location of outbreaks are problematic for designing phase III trials. Prevention includes avoiding mosquito bites (e.g., mosquito repellant and clothing) and reducing the number of mosquitos (e.g., eliminating standing water).

There is no effective treatment for West Nile virus infection (Centers for Disease Control and Prevention, 2015). Milder cases are generally self-limiting or can be treated with over-the-counter medications to relieve symptoms such as pain and fever. In more severe cases, patients often need to be hospitalized to receive supportive treatment and rehabilitation to address neurological and cognitive consequences of central nervous system infection. There is empiric use without proof of benefit of several therapeutic modalities, including antiviral agents, nucleic acid analogues, missense sequences, immunomodulating agents, and angiotensin-receptor blockers.

Perinatal and reproductive considerations

Pregnant women are not at higher risk for West Nile virus infection. Neither the proportion of West Nile virus infections during pregnancy that result in congenital infection nor the spectrum of clinical abnormalities associated with congenital West Nile virus infection is known. The risk of transmitting West Nile virus through breastfeeding to the newborn appears to be very low. In light of the well-established health benefits of breastfeeding, there are no recommendations for a woman to stop breastfeeding because of West Nile virus illness. Pregnant women and women who are breastfeeding should take preventive measures, including insect repellant, to reduce their risk for West Nile virus infection (Centers for Disease Control and Prevention, 2015d). Centers for Disease Control and Prevention recommend clinical evaluation of infants born to mother with known or suspected West Nile virus infection during pregnancy.

In 2017, we updated one guideline from the Centers for Disease Control and Prevention (2015, updated 2017). No policy changes are warranted.

In 2018, we added one updated guidance related to mother-to-baby virus transmission that is consistent with our current policy (Centers for Disease Control and Prevention, 2017). The policy ID was changed from CP# 17.01.07 to CCP.1251.

In 2019, we updated four guidelines from Centers for Disease Control and Prevention (2018a, 2018b, 2018c, and 2018d) that are consistent with our current policy. We deleted the guideline from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology, (2012, updated 2018), because it addresses a fertility service that is not a covered benefit for Medicaid populations.

In 2020, we updated guidance from the American Society of Neuroradiology (2019, updated of American College of Radiology, 2013) and Centers for Disease Control and Prevention (2020, update of 2018d; 2019, update of 2018c). We added one local coverage article (A56771) and local coverage determination (L33447) to the references. No policy changes are warranted.

In 2021, we updated the references with no policy changes.

References

On May 18, 2021, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “West Nile virus” (MeSH), “West Nile Virus vaccines” (MeSH,), “West Nile fever,” and “West Nile virus.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

American Society of Neuroradiology. ACR–ASNR–SPR practice parameter for the performance and interpretation of magnetic resonance imaging (MRI) of the brain. Res. 17. https://www.asnr.org/wp-content/uploads/2019/06/MR-Brain-1.pdf. Revised 2019.

Centers for Disease Control and Prevention. Interim guidelines for the evaluation of infants born to mothers infected with West Nile virus during pregnancy. *MMWR Morb Mortal Wkly Rep.* 2004;53(7):154-157. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5307a4.htm.

Centers for Disease Control and Prevention. Mother to baby during pregnancy, delivery, or breast feeding. http://www.cdc.gov/westnile/faq/pregnancy.html. Reviewed December 2018.(a)

Centers for Disease Control and Prevention. West Nile virus disease therapeutics. Review of the literature for healthcare providers. http://www.cdc.gov/westnile/resources/pdfs/wnv-therapeutics-summary.pdf. Revised June 15, 2015.

Centers for Disease Control and Prevention. West Nile Virus in the United States: Guidelines for surveillance, prevention, and control. http://www.cdc.gov/westnile/resources/pdfs/wnvguidelines.pdf. Updated June 14, 2013.

Centers for Disease Control and Prevention. West Nile virus. Diagnostic testing. https://www.cdc.gov/westnile/healthcareproviders/healthCareProviders-Diagnostic.html. Reviewed December 2018.(b)

Centers for Disease Control and Prevention. West Nile virus. https://www.cdc.gov/westnile/index.html. Reviewed June 2020.

Centers for Disease Control and Prevention. West Nile virus. Prevention. http://www.cdc.gov/westnile/prevention/index.html. Reviewed December 7, 2020.

Centers for Medicare & Medicaid Services. Local Coverage Article. A52446 Intravenous Immune Globulin (IVIG) - Related to Local Coverage Determination L33394. https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleid=52446&ver=68&keyword=west%20nile&keywordType=all&areaId=all&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=AAAAAAQAAAAA&KeyWordLookUp=Doc&KeyWordSearchType=And. Effective May 1, 2021.(a)

Centers for Medicare & Medicaid Services. Local Coverage Determination. L33394 Drugs and Biologicals, Coverage of, for Label and Off-Label Uses. https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=33394&ver=44&articleid=52446&keyword=west+nile&keywordType=all&areaId=all&docType=NCA%2cCAL%2cNCD%2cMEDCAC%2cTA%2cMCD%2c6%2c3%2c5%2c1%2cF%2cP&contractOption=all&sortBy=relevance&KeyWordLookUp=Doc&KeyWordSearchType=And&bc=AAAAAAQAEAAAAAAA&. Effective November 7, 2019.

Centers for Medicare & Medicaid Services. Local Coverage Determination. L33447 Special electroencephalography. https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?lcdid=33447&ver=42&keyword=L33447&keywordType=all&areaId=all&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=AAAAAAQAAAAA&KeyWordLookUp=Doc&KeyWordSearchType=And. Effective March 11, 2021.(b)

Environmental Protection Agency. Find the repellent that is right for you. https://www.epa.gov/insect-repellents/find-insect-repellent-right-you. Updated June 2019.

Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: Clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis.* 2008;47(3):303-327. Doi: 10.1086/589747.

U.S. Food and Drug Administration. 510(k) Premarket notification database using product code NOP. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. Published 2021.

Policy updates

7/2016: initial review date and clinical policy effective date: 10/2016

9/2017: Policy references updated.

9/2018: Policy references updated. Policy ID changed.

9/2019: Policy references updated.

9/2020: Policy references updated.

9/2021: Policy references updated.