Test Definition: NSAI

Neurosyphilis IgG, Antibody Index, Spinal Fluid (Non-Orderable)

Overview

Useful For

Only orderable as part of a profile. For more information see NSAIP / Neurosyphilis IgG Antibody Index with VDRL, Serum and Spinal Fluid.

Aid in the diagnosis of neuroinvasive syphilis as part of a profile

Method Name

Only orderable as part of a profile. For more information see NSAIP / Neurosyphilis IgG Antibody Index with VDRL, Serum and Spinal Fluid.

Enzyme-Linked Immunosorbent Assay (ELISA)

NY State Available

Yes

Specimen

Specimen Type

CSF

Specimen Required

Only orderable as part of a profile. For more information see NSAIP / Neurosyphilis IgG Antibody Index with VDRL, Serum and Spinal Fluid.

Both spinal fluid (CSF) and serum are required for this test. CSF and serum must be collected within a maximum of 24 hours of each other.

Specimen Type: Spinal fluid
Container/Tube: Sterile vial
Specimen Volume: 2.2 mL
Collection Instructions:
1. The CSF specimen **must be** collected within 24 hours of the serum specimen, preferably at the same time.
2. The CSF aliquot should be from the second, third, or fourth CSF vial collected during the lumbar puncture. **Do not submit CSF from the first vial due to the possibility of blood contamination, which will cause specimen rejection**.
3. Label vial as spinal fluid or CSF.
4. Band CSF specimen together with the serum sample.

Specimen Type: Serum

Supplies: Sarstedt Aliquot Tube, 5 mL (T914)
Collection Container/Tube:
Preferred: Serum gel
Acceptable: Red top
Submission Container/Tube: Plastic vial
Specimen Volume: 2.2 mL Serum
Collection Instructions:
1. Within 24 hours of collecting the spinal fluid specimen, a serum specimen **must also be** collected, preferably at the same time.
2. Centrifuge and aliquot serum into a plastic vial.
3. Label tube as serum.
4. Band serum specimen together with the CSF sample.

Specimen Minimum Volume

Spinal fluid/Serum: 1.5 mL

Reject Due To

Gross hemolysis	Reject
Gross lipemia	Reject
Spinal fluid (CSF) contaminated with blood	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
CSF	Refrigerated (preferred)	10 days	
	Frozen	10 days	

Clinical & Interpretive

Clinical Information

Neurosyphilis (NS) caused by the spirochete *Treponema pallidum* can occur at any stage of syphilis. Currently the Centers for Disease Control and Prevention estimate that approximately 2% of patients with syphilis will develop neuroinvasive syphilis if untreated. Early stages of NS may be asymptomatic or symptomatic, with patients typically exhibiting classic meningitis symptoms. Patients with late-stage NS may present with dementia paralytica or tabes dorsalis. Other manifestations of neuroinvasive syphilis include ocular or otologic syphilis, which can occur at any stage, however, are more common during early NS.

The diagnosis of NS is challenging due to a number of factors, including the lack of consensus on the relevance of

abnormal cerebrospinal fluid (CSF) findings in patients who are seropositive for syphilis but neurologically asymptomatic. With respect to diagnostic testing, numerous treponemal and non-treponemal (lipoidal) assays have been evaluated, alongside CSF protein and pleocytosis findings, however direct comparisons of these assays are limited. The Venereal Diseases Research Laboratory (VDRL) assay is currently the only assay with US Food and Drug Administration (FDA) clearance as an aid in the diagnosis of NS, however the sensitivity and specificity of this non-treponemal (lipoidal) assay is highly variable, ranging from 66.7% to 85.7% and 78.2% to 86.7%, respectively. Although no treponemal assay has FDA clearance as an aid for diagnosis of NS, studies evaluating the fluorescent treponemal antibody absorption (FTA-ABS) assay performed in CSF from patients with definitive NS was associated with a sensitivity of 90.9% to 100%. Specificity of this approach ranged from 55% to 100% however, primarily due to the issue of passive diffusion of serum antibodies across the blood-brain barrier.

The NS antibody index assay corrects for passive diffusion across an inflamed blood-brain barrier by measuring quantitative levels of anti-*T pallidum* antibodies in serum and CSF and normalizing those to total IgG and albumin in both specimen sources. A positive NS antibody index indicates true intrathecal antibody synthesis of antibodies to *T pallidum*, which alongside clinical and exposure history can be used to establish a diagnosis of NS. All NS antibody index positive samples are also reflexed for testing by the VDRL assay to acquire a semi-quantitative titer. The NS antibody index should only be ordered in patients who are seropositive for antibodies to *T pallidum* in blood, who also present with neurologic manifestations suspicious for NS or who are at risk for asymptomatic NS.

Reference Values

Only orderable as part of a profile. For more information see NSAIP / Neurosyphilis IgG Antibody Index with VDRL, Serum and Spinal Fluid.

Antibody Index: 0.6-1.2

Reference values apply to all ages.

Interpretation

Negative:
Results indicate lack of intrathecal antibody synthesis to syphilis (*Treponema pallidum*). This suggests the absence of neurosyphilis. The initial screen reactive result may be due to anti-syphilis antibodies present in the cerebrospinal fluid (CSF) due to increased permeability of the blood-brain barrier or transient introduction during lumbar puncture.

Equivocal:
Possible intrathecal antibody synthesis to syphilis (*T pallidum*) detected. Results should be correlated with exposure history and clinical presentation to establish a diagnosis of neurosyphilis. Sample has been reflexed for VDRL testing to establish a titer. False-positive results may occur in patients with other spirochete infections (eg, *Borrelia*, *Leptospira*).

Positive:
Results indicate the presence of intrathecal antibody synthesis to syphilis (*T pallidum*), suggesting neurosyphilis. Results should be correlated with exposure history and clinical presentation to establish the diagnosis. Sample has been reflexed to VDRL testing to establish a titer. False-positive results may occur in patients with other spirochete infections (eg, *Borrelia*, *Leptospira*).

Invalid:
Result is due to abnormally elevated total IgG levels in CSF. This may be due to passive diffusion through the blood-brain barrier or contamination of the CSF with blood during a traumatic lumbar puncture. Consider repeat testing if clinically indicated.

Cautions

A single negative result should not be used to exclude the diagnosis of neuroinvasive syphilis disease in a patient with appropriate exposure history and symptoms suggestive of infection.

False-negative results may be acquired in patients tested soon after infection, prior to the development of a detectable level of antibodies in the spinal fluid.

False-reactive results may occur in patients with *Borrelia* or *Leptospira* infections. Patient management decisions should not be made on a single reactive result.

Antibody index can remain positive for a prolonged period of time after complete resolution of disease. Therefore, a positive result must be interpreted in light of current, presenting symptoms.

Clinical Reference

1. Alberto C, Deffert C, Lambeng N, et al. Intrathecal synthesis index of specific anti-treponema IgG: A new tool for the diagnosis of neurosyphilis. Microbiol Spectr. 2022;10(1):e0147721
2. Papp JR, Park IU, Fakile Y, Pereira L, Pillay A, Bolan GA. CDC laboratory recommendations for syphilis testing, United States, 2024. MMWR Recomm Rep. 2024;73(1):1-32
3. Klein M, Angstwurm K, Esser S, et al. German guidelines on the diagnosis and treatment of neurosyphilis. Neuro Res Pract. 2020;2:33. Published 2020 Nov 17. doi:10.1186/s42466-020-00081-1
4. Wu S, Ye F, Wang Y, Li D. Neurosyphilis: insights into its pathogenesis, susceptibility, diagnosis, treatment and prevention. Front Neurol. 2024;14:1340321
5. Reiber H, Lange P. Quantification of virus-specific antibodies in cerebrospinal fluid and serum: sensitive and specific detection of antibody synthesis in brain. Clin Chem. 1991;37(7):1153-1160

Performance

Method Description

The test kit contains microtiter strips with break-off reagent wells coated with purified recombinant *Treponema pallidum* antigens. In the first reaction step, diluted patient samples are incubated in the wells. In the case of positive samples, *T pallidum*-specific IgG antibodies will bind to the antigens. To detect the bound antibodies, a second incubation is carried out using an enzyme-labelled antihuman IgG (enzyme conjugate), followed by a third incubation using chromogen/substrate, which catalyzes a color reaction that is then measured for optical density (OD) using spectrophotometry. The obtained OD values of the paired patient serum and cerebrospinal fluid (CSF) samples are compared against a 4-level calibration curve to quantitatively determine the relative anti-*T pallidum* IgG antibody titers.(Unpublished Mayo method)

The quantitative test results obtained on paired serum and CSF specimens using the *T pallidum* IgG enzyme-linked immunosorbent assay are expressed as relative units (U/mL) and must be used along with the total IgG and albumin levels in the patient's paired serum and CSF samples to calculate the anti-*T pallidum* antibody index (AI), which determines the absence or presence of intrathecal anti-*T pallidum* IgG antibody synthesis. Total IgG and albumin testing on serum and CSF are performed using the Siemens BN II nephelometric testing system.(Instruction manual: Siemens Nephelometer II Operations. Siemens V 2.3, 2008; Addendum to the Instruction Manual 2.3, 08/2017)

To detect an infection of the central nervous system, it is necessary to differentiate between intrathecally produced antibodies and antibodies passed from blood into the CSF. The AI is the value of intrathecal pathogen-specific antibody production. This AI value represents the portion of pathogen-specific antibodies in total IgG of CSF and the portion of pathogen-specific antibodies in total IgG of serum. The patient's AI is calculated using the Reiber and Lange method.(Reiber H, Lange P. Quantification of virus-specific antibodies in cerebrospinal fluid and serum: sensitive and specific detection of antibody synthesis in brain. Clin Chem. 1991;37[7]:1153-1160)

PDF Report
No

Day(s) Performed
Monday, Wednesday, Friday

Report Available
2 to 5 days

Specimen Retention Time
2 weeks

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Superior Drive

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
82784 x 2
82040

86780 x 2
82042

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
NSAI	Neurosyphilis IgG, Ab Index	105193-7

Result ID	Test Result Name	Result LOINC® Value
NSY3	Neurosyphilis IgG Ab Index Value	105193-7
NSY4	Neurosyphilis IgG Ab Index Interp	69048-7