The Diagnosis of Autoimmune Encephalopathies, Dementias, and Epilepsies

Introduction

Many disorders of the central nervous system (CNS) previously considered neurodegenerative and untreatable are now recognized as having an autoimmune cause.\(^1,2\) Autoimmune disorders of the CNS may be paraneoplastic (occurring in the setting of an occult systemic cancer) or idiopathic. Improved recognition of these disorders has been facilitated by an expanding profile of neural-specific autoantibodies discovered and validated for clinical use in academic neuroimmunology laboratories. When detected in serum or cerebrospinal fluid (CSF), these immunoglobulin G (IgG) biomarkers reliably predict an autoimmune cause for...
neurological dysfunction in patients presenting with rapidly progressive brain disorders. New testing profiles relevant to the evaluation of 3 neurological disease states (autoimmune encephalopathy, dementia, and epilepsy) are now available from the Neuroimmunology Laboratory at Mayo Clinic, Rochester, Minnesota. Testing profiles, available for both serum and CSF, include neural antibodies that have been clinically validated as biomarkers of these 3 disorders. (Table 1) Negative results for these antibodies do not exclude an autoimmune basis for encephalopathy, dementia, or epilepsy, so in seronegative cases, a diagnostic trial of immunotherapy should be considered.

**Epidemiology**

Precise frequency data for autoimmune encephalopathies, dementias, and epilepsies are not available. These disorders are clearly underrecognized. A recent review of over 1000 brain autopsy cases referred as Creutzfeldt-Jakob disease to the United States National Prion Disease Pathology Surveillance Center demonstrated a treatable cause for dementia in 7% of cases. Most common among these treatable dementia cases were autoimmune disorders. Among Mayo Clinic patients diagnosed with and treated for autoimmune encephalopathy or dementia, 35% were initially misdiagnosed with a neurodegenerative disorder.

**Symptoms and Other Clues from the Clinical History**

Symptoms are almost always of subacute onset (evolving over days to weeks). Encephalopathies, typically characterized by confusion, seizures, memory loss, and behavioral change, traditionally have been well recognized by neurologists as having an autoimmune cause. In contrast, patients with recent-onset idiopathic epilepsy or rapidly progressive dementia without delirium have usually been classified as having an underlying genetic or neurodegenerative cause. Clinical features suspicious for an autoimmune cause of encephalopathy, dementia, or epilepsy are outlined in Table 2.

Limbic encephalitis is the classically recognized autoimmune encephalopathy syndrome. It is characterized by a confusional state with loss of orientation (delirium), and usually occurs with 1 or more signs of cognitive decline (generally memory problems), seizures, altered mood and personality, and sleep disorders. Magnetic resonance imaging (MRI) of the head often reveals T2 signal abnormality in one or both hippocampal regions. Electroencephalogram (EEG) may reveal unilateral or bilateral temporal slowing or epileptiform discharges. The main excludable differential diagnosis is viral encephalitis caused by herpes simplex virus. Encephalitis may also have an extratemporal localization, affecting 1 or more of the frontal, parietal, and occipital regions.

<table>
<thead>
<tr>
<th>Autoimmune Encephalopathy or Dementia</th>
<th>Autoimmune Epilepsy</th>
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<tbody>
<tr>
<td>Subacute onset</td>
<td>Acute to subacute onset</td>
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<tr>
<td>Fluctuating course</td>
<td>Multiple seizure types or faciobrachial dystonic seizures</td>
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<td>Tremor</td>
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<td>Headache</td>
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<td>Hypometabolism on functional imaging (PET)</td>
<td>Hypermetabolism on functional imaging (PET)</td>
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**Features Common to All**

- Personal or family history (first-degree relative) of autoimmunity
- History of recent or past neoplasia
- Evidence of central nervous system (CNS) inflammation from cerebral spinal fluid (CSF) (elevated protein, pleocytosis, oligoclonal bands, positive CSF index)
- Evidence of CNS inflammation from MRI (mesial temporal or other regional T2 hyperintensity)
- Detection of neural autoantibody

*Table 2.* Clinical and laboratory features suspicious for an autoimmune encephalopathy, dementia, or epilepsy.
Autoimmune dementia phenotypes may resemble Creutzfeldt-Jakob disease, which classically is a rapidly progressive neurodegenerative disorder accompanied by ataxia and myoclonus. Rapidly progressive forms of Alzheimer disease and diffuse Lewy body disease also are difficult to distinguish clinically from an autoimmune dementia. Tremulousness and headache at presentation, marked fluctuations in the clinical course, and spontaneous remission suggest an autoimmune cause.1

Patients with autoimmune epilepsy may present with seizures alone or with a seizure-predominant disorder.2 All patients reported to date have had seizures of focal or multifocal brain origin rather than generalized seizures. The seizures are usually resistant to 2 or more standard antiepileptic medications. A mesial temporal (limbic) onset focus is most common, but extratemporal and multifocal seizure localizations have been described. Additional less prominent manifestations may include memory and cognitive difficulties, personality changes, and depression or anxiety.

In addition to the time course, clues to an autoimmune diagnosis include a personal history of cancer or autoimmunity (eg, autoimmune thyroid disease, insulin-dependent diabetes, systemic lupus erythematosus, rheumatoid arthritis, or vitiligo). Smoking history, review of systemic symptoms, and a family history of autoimmunity or cancer might also be informative.

**Examination Findings**

Impairments in 1 or more categories of attention, memory, reasoning, calculation, and executive function can be documented using brief bedside evaluations such as the mini mental state examination (MMSE), or the Kokmen short test of mental status. A seizure may be witnessed by the examiner. Autoimmune neurological disorders are often multifocal, thus it is important to note any subtle neurologic symptoms and signs accompanying cognitive impairment or seizures. These signs may include ataxia, brainstem abnormalities, parkinsonism, myoclonus, tremor, myelopathy, or a peripheral nervous system disorder.

**Figure 1.** Immunofluorescence patterns of ANNA1 and NMDA receptor antibody reactivities on substrate of mouse tissues. ANNA1 binds to nuclei (and less intensely to perikarya) of all neurons, including cerebellar Purkinje, granular layer and molecular layer (A, right), midbrain (A, left) and myenteric plexus (B). NMDA receptor antibody binds to neural synapses, most prominently in hippocampus (C) and cerebellar granular layer (D).
Testing for Markers of an Autoimmune Diagnosis in Serum and Cerebral Spinal Fluid

Neural-Specific Autoantibody Profiles
Detection of 1 or more neural autoantibodies in serum or CSF is consistent with a diagnosis of an autoimmune encephalopathy, epilepsy, or dementia, and helps direct a search for cancer. Screening tests for these autoantibodies include immunofluorescence (Figure 1, tissue-based or cell-based) and immunoprecipitation assays. In some instances, reflex testing may be indicated to confirm antigen specificity (by Western blot) or to quantitate an endpoint value or titer. The testing algorithms for the 3 disease states are similar. Serum and CSF algorithms for autoimmune encephalopathy are demonstrated in Figures 2A, 2B, 3A, 3B, 4A, and 4B. Oncological accompaniments of the individual autoantibodies are detailed in Table 3. Some autoantibodies are more readily detected in serum (eg, voltage-gated potassium channel [VGKC]-complex IgG and others in CSF (N-methyl D-aspartate [NMDA] receptor antibody). Therefore, the diagnostic yield is maximized by testing both serum and CSF, simultaneously or sequentially.5

Diagnostic Clues from Conventional Serum and CSF Testing
Seroopositivity for nonneural antibodies warrants detailed investigation for an autoimmune pathogenesis for

<table>
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<tr>
<th>Neuronal Nuclear And Cytoplasmic Antibodies</th>
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<tr>
<td>Antibody</td>
<td>Oncological association</td>
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<tr>
<td>ANNA-1</td>
<td>Small-cell lung carcinoma, neuroblastoma</td>
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<td>ANNA-2</td>
<td>Small-cell lung carcinoma, breast adenocarcinoma</td>
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<tr>
<td>ANNA-3</td>
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<tr>
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<td>Small-cell lung carcinoma</td>
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<tr>
<td>PCA-1</td>
<td>Mullerian (ovary, fallopian tube, uterus) adenocarcinoma, breast adenocarcinoma</td>
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<tr>
<td>PCA-2</td>
<td>Small-cell lung carcinoma</td>
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<tr>
<td>PCA-Tr</td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>CRMP5 IgG</td>
<td>Small-cell lung carcinoma, thymoma, thyroid, or renal carcinoma</td>
</tr>
<tr>
<td>Amphiphysin IgG</td>
<td>Small-cell lung carcinoma, breast adenocarcinoma</td>
</tr>
<tr>
<td>GAD65</td>
<td>Thymoma; renal cell, breast or colon adenocarcinoma</td>
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</tbody>
</table>

Table 3. Oncological accompaniments of neural autoantibodies
Abbreviations: ANNA, antineuronal nuclear antibody; PCA, Purkinje cell cytoplasmic antibody; CRMP5, collapsin response mediator protein-5; GAD65, glutamic acid decarboxylase; VGKC, voltage-gated potassium channel; Lgi1, leucine-rich, glioma inactivated 1; NMDA, N-methyl D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA, gamma-aminobutyric acid; AChR, acetylcholine receptor; NMO (AQP4), neuromyelitis optica (NMO)/aquaporin-4.
encephalopathy, dementia, or epilepsy. Informative non-neural autoantibody specificities may be organ specific (such as thyroid autoantibodies) or nonorgan specific (such as antinuclear, anti-smooth muscle, or antimitochondrial antibodies). However, these markers per se lack specificity for neurological autoimmunity. In addition, the detection in CSF of elevated protein, white blood cell count, CSF-exclusive oligoclonal bands, IgG index or IgG synthesis rate also supports an autoimmune etiology. However, these parameters also lack specificity for an autoimmune cause, and may be detected in other inflammatory CNS disorders for which there are no specific biomarkers (eg, multiple sclerosis, sarcoidosis).

**Oncological Significance**

In many instances, an autoimmune encephalopathy, dementia, or epilepsy may be a byproduct of an immune response directed against a systemic cancer. A paraneoplastic autoantibody profile reliably predicts the cancer type. In contrast, serological and oncological associations are not readily predicted by the neurological phenotype. Thus, algorithmic testing for autoantibody profiles is a more sensitive diagnostic strategy than nominal physician-selected single antibody testing. For example, seropositivity for amphiphysin IgG predicts either small-cell lung carcinoma or breast adenocarcinoma, but the presence or absence of coexisting antibodies narrows that differential diagnosis. Among 63 Mayo Clinic patients with amphiphysin antibody and a known history of cancer, 33 had small-cell lung carcinoma. Of those patients, 27 had 1 or more coexisting neural-specific autoantibodies that also predicted small-cell lung carcinoma. In contrast, no coexisting autoantibody was detected among 30 amphiphysin-IgG-positive patients in whom breast adenocarcinoma or other cancer type was found. The frequency of cancer detection in antibody-positive patients (pulmonary or extra-pulmonary small-cell lung carcinoma in almost all cases) varies from 20% for VGKC-complex IgG to 80% for antineuronal nuclear antibody type 1 (ANNA-1). Suspicion for a paraneoplastic cause may be raised by risk factors obtained from the clinical history. This suspicion may be honed to a search for a specific cancer based on the profile of autoantibodies detected. A thorough physical examination and computerized tomography (CT) of chest, abdomen, and pelvis are commonly undertaken as primary screening tests. Other tests may be required depending on age, sex, and other risk factors. Pelvic ultrasound (including transvaginal imaging) or MRI and gynecological examination are required to evaluate for ovarian carcinoma or teratoma.

Mammography and breast examination are required to evaluate for breast carcinoma. Testicular ultrasound, prostate-specific antigen testing, and prostate examination by digital rectal examination are required to evaluate for testicular and prostate carcinomas, respectively. When neuroblastoma is suspected, and CT body imaging is negative, a radiolabeled metaiodobenzylguanidine (MIBG) body scan should be considered. Endoscopic examination of the upper and lower gastrointestinal tracts and bronchial tree should also be considered where appropriate. Positron emission tomography (PET) coregistered with CT (PETCT) imaging increases the diagnostic yield by 20% for patients in whom standard evaluations have not revealed cancer.

**Implications for Treatment**

The profile of antibodies detected may guide immunotherapy and be informative for neurological prognosis. (Table 3) Studies suggest that autoimmune neurological disorders for which the antigens of marker IgG antibodies are intracellular are caused by neural peptide-specific CD8-positive cytotoxic T cells. An example includes encephalitis occurring in patients seropositive for ANNA-1. This autoantibody predicts with 80% certainty the presence of small-cell lung carcinoma. The target antigen is nuclear and, therefore, inaccessible in intact cells to circulating antibody. The neurological deficit rarely improves with antibody-depleting or tumoricidal therapies. On the other hand, IgG antibodies targeting neural cell surface receptors and channels do have a pathogenic role in effecting autoimmune CNS disorders that may be improved by antibody-depleting immunotherapy. For example, patients with antibodies targeting the GluN1 subunit of the NMDA ionotropic glutamate receptor present clinically with encephalopathy that improves (sometimes completely) with early teratoma removal and antibody-depleting and immunosuppressant therapy.

Serial trial of corticosteroids, intravenous immune globulin, and plasma exchange are considered first-line treatments to establish immunotherapy responsiveness. Some patients, such as those with autoimmune NMDA receptor encephalitis, may require many months of treatment. Immunosuppressants such as rituximab or cyclophosphamide may be required to maximize recovery.

**Treatment Monitoring**

Antibody values tend to decrease with immunotherapy regardless of outcome, and have a limited role in the adjudication of a treatment trial. However, a rise in antibody titer from a posttreatment baseline, accompanied by
neurological deterioration, may indicate relapse of the autoimmune neurological disorder or a persistent systemic cancer.

Objective clinical, behavioral, neuroradiological, or electrophysiological measures undertaken pretreatment may be compared to posttreatment findings. Testing recommended for this purpose includes clinical examination, brain imaging (structural [MRI] or functional [PET]), detailed (4 hour) neuropsychological testing, and EEG. Resolution of neuropsychological, EEG, MRI, or functional imaging abnormalities after immunotherapy supports improvements and supports treatment continuation.

Summary

It is critically important to recognize treatable and potentially reversible autoimmune encephalopathies, dementias, and epilepsies in neurological practice. Rapid diagnosis is facilitated by testing for neural-specific autoantibody profiles in serum and CSF. When detected, 1 or more positive antibody result may direct the cancer search and prompt the timely initiation of immunotherapy.

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References

Glossary of Terms

**Aerodigestive carcinoma:** cancer of the combined organs and tissues of the respiratory tract and the upper part of the digestive tract (including the lips, mouth, tongue, nose, throat, vocal cords, and part of the esophagus and windpipe)

**Ataxia:** a lack of muscle coordination during voluntary movements, such as walking or picking up objects

**Dementia:** a mental illness that causes someone to be unable to think clearly or to understand what is real and what is not real

**Encephalitis:** inflammation of the brain

**Encephalopathy:** a disease of the brain; especially one involving alterations of brain structure

**Epilepsy:** a disorder of the nervous system that can cause people to suddenly become unconscious and to have violent, uncontrolled movements of the body known as seizures

**Epileptiform discharges:** distinctive electroencephalogram (EEG) waves or complexes, distinguished from background activity, observed in those with seizure disorders

**Extratemporal and multifocal seizure localizations:** rare brain locations for seizures to arise outside of the temporal lobes.

**Hippocampus:** a major component of the brain that plays an important role in the consolidation of information from short-term memory to long-term memory and spatial navigation.

**Hyperintensities:** small regions of abnormalities on MRI

**Hypermetabolism on functional imaging:** increased rate of metabolic activity in the brain

**Hypometabolism on functional imaging:** lower energy levels, or metabolism, of neurons in certain areas of the brain

**Idiopathic:** of unknown cause

**Immunotherapy:** the treatment of disease by inducing, enhancing, or suppressing the body’s own immune response

**Limbic encephalitis:** an inflammation of 1 or both temporal brain lobes caused by auto-immunity: an abnormal state where the body produces antibodies against itself. Some cases are associated with cancer and some are not

**Limbic system:** a complex set of brain structures that lies on both sides of the thalamus, directly under the cerebrum. The limbic system supports a variety of functions, including emotion, behavior, motivation, long-term memory, and olfaction. It appears to be primarily responsible for emotional life, and it has a great deal to do with the formation of memories.

**Mesial temporal:** the part of the temporal lobe closest to the midline. Contains most of the limbic system

**Myelopathy:** any disorder of the spinal cord

**Myoclonus:** a quick, involuntary muscle jerk

**Neoplasia:** an abnormal mass of tissue as a result of abnormal growth or division of cells

**Neural-specific autoantibodies:** an antibody active against a tissue constituent of the individual producing it, relating to, or involving a nerve or the nervous system

**Neuroblastoma:** a cancer that develops from immature nerve cells found in several areas of the body

**Neurodegenerative disorder:** A disease state relating to or characterized by degeneration of nervous tissue

**Neuroendocrine neoplasm:** a tumor that begins in the hormone-producing cells of the body’s neuroendocrine system, which is made up of cells that are a cross between traditional endocrine cells (or hormone-producing cells) and nerve cells

**Nonneural antibodies:** an antibody not relating to the nervous system, such as thyroid antibodies

**Oligoclonal bands:** bands of immunoglobulins that are seen when a patient’s serum, plasma, or cerebrospinal fluid (CSF) is analyzed

**Paraneoplastic:** occurring in the setting of an occult systemic cancer

**Parkinsonism:** any of a group of nervous disorders similar to Parkinson’s disease, marked by muscular rigidity, tremor, and impaired motor control and often having a specific cause

**Pleocytosis:** an abnormal increase in the number of white cells (as lymphocytes) in the cerebrospinal fluid

**CSF index:** CSF IgG to CSF albumin ratio compared to the serum IgG to serum albumin ratio. The CSF index is, therefore, an indicator of the relative amount of CSF IgG compared to serum. Any increase in the index is a reflection of IgG production in the CNS

**Radiolabeled metaiodobenzylguanidine (MIBG) body scan:** a scan used to image tumors of neuroendocrine origin

**Seronegative:** a negative serum reaction especially in a test for the presence of an antibody

**Teratoma:** an encapsulated tumor with tissue or organ components resembling normal derivatives of more than 1 germ layer

**Thymoma:** a thymic epithelial tumor in which the epithelial component exhibits no overt atypia and retains histologic features specific to the normal thymus

**Tremor:** An involuntary trembling or quivering

**Tremulousness:** Marked by trembling, quivering, or shaking

**Tumoricidal:** destroying tumor cells

**Unilateral or bilateral temporal slowing:** an EEG finding suggesting brain dysfunction

**Vitiligo:** a skin disorder, of unknown cause, characterized by patches of unpigmented skin
Figure 2A  Dementia Autoimmune Evaluation Algorithm, Serum

DEMEC / Dementia, Autimmune Evaluation, Serum
The following tests are always performed

Radioimmunoprecipitation Assay (RIA)
- P/Q-Type Calcium Channel Antibody, Serum
- N-Type Calcium Channel Antibody, Serum
- Acetylcholine Receptor (AChR) Binding Antibody, Serum
- Ganglioside A2 (GQ1B) Antibody, Serum
- Neuronal Voltage-Gated Potassium Channel Complex (VGKC) Autoantibody, Serum
- Glutamic Acid Decarboxylase (GAD65) Antibody Assay, Serum

Immunofluorescence Assay (issue IFA)
- Antineuronal Nuclear Antibody-Type 1 (ANNA-1), Serum
- Antineuronal Nuclear Antibody-Type 2 (ANNA-2), Serum
- Anti-Glial / Neuronal Nuclear Antibody-Type 1 (AGNA-1), Serum
- Collapsin Response-Mediator Protein-5 Neuronal (CRMP-5-IgG) Western Blot, Serum
- Amphiphysin Antibody Assay, Serum
- Collapsin Response-Mediator Protein-5 Neuronal (CRMP-5-IgG), Serum
- Anti-Glial / Neuronal Nuclear Antibody-Type 1 (AGNA-1), Serum

Immunofluorescence Assay (cell binding; CBA)
- NMDA-Receptor Antibody by CBA, Serum
- AMPA-Receptor Antibody by CBA, Serum
- GABA-B-Receptor Antibody by CBA, Serum

Figure 2B  Dementia Autoimmune Evaluation Algorithm, Spinal Fluid

DEMES / Dementia, Autimmune Evaluation, Serum
The following tests are always performed

Radioimmunoprecipitation Assay (RIA)
- P/Q-Type Calcium Channel Antibody, Serum
- N-Type Calcium Channel Antibody, Serum
- Acetylcholine Receptor (AChR) Binding Antibody, Serum
- Ganglioside A2 (GQ1B) Antibody, Serum
- Neuronal Voltage-Gated Potassium Channel Complex (VGKC) Autoantibody, Spinal Fluid
- Glutamic Acid Decarboxylase (GAD65) Antibody Assay, Spinal Fluid

Immunofluorescence Assay (issue IFA)
- Antineuronal Nuclear Antibody-Type 1 (ANNA-1), Spinal Fluid
- Antineuronal Nuclear Antibody-Type 2 (ANNA-2), Spinal Fluid
- Antineuronal Nuclear Antibody-Type 3 (ANNA-3), Spinal Fluid
- Purkinje Cell Cytoplasmic Antibody, Type 2 (PCA-2), Serum
- Purkinje Cell Cytoplasmic Antibody, Type 3 (PCA-3), Serum
- Amphiphysin Antibody Assay, Serum
- Collapsin Response-Mediator Protein-5 Neuronal (CRMP-5-IgG), Serum
- Anti-Glial / Neuronal Nuclear Antibody-Type 1 (AGNA-1), Serum

Immunofluorescence Assay (cell binding; CBA)
- NMDA-Receptor Antibody by CBA, Serum
- AMPA-Receptor Antibody by CBA, Serum
- GABA-B-Receptor Antibody by CBA, Serum

If pattern suggests ANNA-1, ANNA-2, PCA-1, CRMP-5-IgG, or Amphiphysin Antibody and if IFA pattern is indeterminate

If pattern suggests AMPA-Receptor Antibody and AMPA-Receptor Antibody, CBA is positive

If pattern suggests NMDA-Receptor Antibody and NMDA-Receptor Antibody, CBA is positive

If pattern suggests GABA-B-Receptor Antibody and GABA-B-Receptor Antibody, CBA is positive

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**Figure 3A**  Encephalopathy Autoimmune Evaluation Algorithm, Serum

The following tests are always performed:

- Radioimmunoprecipitation Assay (RIA)
  - PQ-Type Calcium Channel Antibody, Serum
  - N-Type Calcium Channel Antibody, Serum
  - Acellulohydroxyte Receptor (Muscle AChR) Binding Antibody, Serum
  - Glutamic Acid Decarboxylase (GAD65) Antibody Assay, Serum
- Immunofluorescence Assay (tissue IFA)
  - Antineuronal Nuclear Antibody-Type 1 (ANNA-1), Serum
  - Antineuronal Nuclear Antibody-Type 2 (ANNA-2), Serum
  - Antineuronal Nuclear Antibody-Type 3 (ANNA-3), Serum
  - Purkinje Cell Cytoplasmic Antibody, Type 1 (PCA-1), Serum
  - Purkinje Cell Cytoplasmic Antibody, Type 2 (PCA-2), Serum
  - Purkinje Cell Cytoplasmic Antibody, Type 3 (PCA-3), Serum
  - Collapsin Response-Mediator Protein-5 (CRMP-5-IgG) Antibody Assay, Serum
  - Collapsin Response-Mediator Protein-5 Neuronal (CRMP-5-IgG) Antibody Assay, Serum
  - Purkinje Cell Cytoplasmic Antibody, Type 4 (PCA-4), Serum
  - Purkinje Cell Cytoplasmic Antibody, Type 5 (PCA-5), Serum
  - GABA-B Receptor Antibody by CBA, Serum
- Immunofluorescence Assay (cell binding, CBA)
  - AMPA-Receptor Antibody by CBA, Serum
  - NMDA-Receptor Antibody by CBA, Serum
  - GABA-B Receptor Antibody by CBA, Serum

In addition:

- Paraneoplastic Autoantibody Western Blot Confirmation, Serum
- Collapsin Response-Mediator Protein-5 IgG (CRMP-5-IgG) Western Blot, Serum
- Ampiphsyn Antibody Western Blot, Serum
- Neurofilament Optica (NMO)/Aquaporin-4-IgG Cell-Binding Assay, Serum
- AMPA-Receptor Antibody IFT assay
- NMDA-Receptor Antibody IFT assay
- GABA-B Receptor Antibody IFT assay

**Figure 3B**  Encephalopathy Autoimmune Evaluation Algorithm, Spinal Fluid

The following tests are always performed:

- Radioimmunoprecipitation Assay (RIA)
  - Glutamic Acid Decarboxylase (GAD65) Antibody Assay, Spinal Fluid
  - Neuronal Voltage-Gated Potassium Channel Complex (VGKC) Autoantibody, Spinal Fluid
- Immunofluorescence Assay (tissue IFA)
  - Antineuronal Nuclear Antibody-Type 1 (ANNA-1), Spinal Fluid
  - Antineuronal Nuclear Antibody-Type 2 (ANNA-2), Spinal Fluid
  - Antineuronal Nuclear Antibody-Type 3 (ANNA-3), Spinal Fluid
  - Purkinje Cell Cytoplasmic Antibody, Type 1 (PCA-1), Spinal Fluid
  - Purkinje Cell Cytoplasmic Antibody, Type 2 (PCA-2), Spinal Fluid
  - Purkinje Cell Cytoplasmic Antibody, Type 3 (PCA-3), Spinal Fluid
  - Collapsin Response-Mediator Protein-5 Neuronal (CRMP-5-IgG) Antibody Assay, Spinal Fluid
  - Collapsin Response-Mediator Protein-5 Neuronal (CRMP-5-IgG) Antibody Assay, Spinal Fluid
  - Purkinje Cell Cytoplasmic Antibody, Type 4 (PCA-4), Spinal Fluid
  - Purkinje Cell Cytoplasmic Antibody, Type 5 (PCA-5), Spinal Fluid
- Immunofluorescence Assay (cell binding, CBA)
  - AMPA-Receptor Antibody by CBA, Spinal Fluid
  - NMDA-Receptor Antibody by CBA, Spinal Fluid
  - GABA-B Receptor Antibody by CBA, Spinal Fluid

In addition:

- Paraneoplastic Autoantibody Western Blot Confirmation, Spinal Fluid
- Collapsin Response-Mediator Protein-5 IgG (CRMP-5-IgG) Western Blot, Spinal Fluid
- Ampiphsyn Antibody Western Blot, Spinal Fluid
- Neurofilament Optica (NMO)/Aquaporin-4-IgG Cell-Binding Assay, CSF
- AMPA-Receptor Antibody IFT assay
- NMDA-Receptor Antibody IFT assay
- GABA-B Receptor Antibody IFT assay

**ANTECEDENTS / Encephalopathy, Autoimmune Evaluation, Serum**

**ANTECEDENTS / Encephalopathy, Autoimmune Evaluation, Spinal Fluid**
Figure 4A  Epilepsy Autoimmune Evaluation Algorithm, Serum

**EPEES / Epilepsy, Autoimmune Evaluation, Serum**

The following tests are always performed:

- Radioimmunoprecipitation Assay (RIA)
  - Glutamic Acid Decarboxylase (GAD65) Antibody Assay, Serum
  - Neuronal Voltage-Gated Potassium Channel Complex (VGKC) Antibody, Serum
- Immunofluorescence Assay (tissue IFA)
  - Anti-Glial / Neuronal Nuclear Antibody-Type 1 (AGNA-1), Serum
  - Collapsin Response-Mediator Protein-5 Neuronal (CRMP-5-IgG), Serum
- AMPA-Receptor Antibody Assay, Serum
- Purkinje Cell Cytoplasmic Antibody, Type 1 (PCA-1), Serum
- Purkinje Cell Cytoplasmic Antibody, Type 2 (PCA-2), Serum
- Antineuronal Nuclear Antibody-Type 1 (ANNA-1), Serum
- Antineuronal Nuclear Antibody-Type 2 (ANNA-2), Serum
- GABA-B-Receptor Antibody and GABA-B-Receptor Antibody, CBA is positive
- GABA-B-Receptor Antibody IF titer assay
- Epitope-Associated Protein-2 (EAP-2) Antibody Assay, Spinal Fluid
- N-Methyl-D-Aspartate-Receptor Antibody Assay, Serum

IFA pattern suggests:

- ANNA-1, ANNA-2, PCA-2, CRMP-5-IgG, or Amphiphysin Antibody, CBA is positive
- CRMP-5 IgG
- NMDA-Receptor Antibody, CBA is positive
- GABA-B-Receptor Antibody IF titer assay
- CRMP-5-IgG Western Blot, Serum

Figure 4B  Epilepsy Autoimmune Evaluation Algorithm, Spinal Fluid

**EPEC / Epilepsy, Autoimmune Evaluation, Spinal Fluid**

The following tests are always performed:

- Radioimmunoprecipitation Assay (RIA)
  - Glutamic Acid Decarboxylase (GAD65) Antibody Assay, Spinal Fluid
  - Neuronal Voltage-Gated Potassium Channel Complex (VGKC) Antibody, Spinal Fluid
- Immunofluorescence Assay (tissue IFA)
  - Anti-Glial / Neuronal Nuclear Antibody-Type 1 (AGNA-1), Spinal Fluid
  - Collapsin Response-Mediator Protein-5 Neuronal (CRMP-5-IgG), Spinal Fluid
- AMPA-Receptor Antibody Assay, Spinal Fluid
- Purkinje Cell Cytoplasmic Antibody, Type 1 (PCA-1), Spinal Fluid
- Purkinje Cell Cytoplasmic Antibody, Type 2 (PCA-2), Spinal Fluid
- Antineuronal Nuclear Antibody-Type 1 (ANNA-1), Spinal Fluid
- Antineuronal Nuclear Antibody-Type 2 (ANNA-2), Spinal Fluid
- NMDA-Receptor Antibody and GABA-B-Receptor Antibody, CBA is positive
- GABA-B-Receptor Antibody IF titer assay
- Epitope-Associated Protein-2 (EAP-2) Antibody Assay, Spinal Fluid
- N-Methyl-D-Aspartate-Receptor Antibody Assay, Serum

IFA pattern suggests:

- ANNA-1, ANNA-2, PCA-2, CRMP-5-IgG, or Amphiphysin Antibody, or if IFA pattern is indeterminate
- CRMP-5-IgG Western Blot, Serum

Collapsin Response-Mediator Protein-5 Neuronal (CRMP-5-IgG) Western Blot, Serum
- GABA-B-Receptor Antibody IF titer assay
- CRMP-5-IgG Western Blot, Spinal Fluid
- Antineuronal Nuclear Antibody-Type 1 (ANNA-2), Spinal Fluid

Neuronal NMDA Receptor, Western Blot (NMDA-R)
- CRMP-5-IgG Western Blot, Spinal Fluid
- Antineuronal Nuclear Antibody-Type 1 (ANNA-1), Spinal Fluid

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An estimated 3.2 million persons in the United States have chronic hepatitis C virus (HCV) infection. HCV is the primary cause of cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease requiring liver transplantation. Current management of chronic hepatitis C is aimed at halting disease progression, preventing cirrhosis decompensation, reducing the risk of HCC, and treating extrahepatic complications of the infection.

Because of the slow evolution of chronic hepatitis C over several decades, it is difficult to demonstrate that therapy prevents complications of liver disease. Accordingly, treatment responses are defined by a surrogate virological parameter rather than a clinical endpoint. The latest recommendations from the American Association for the Study of Liver Disease (AASLD), the Infectious Diseases Society of America, as well as the product inserts for the FDA-approved anti-HCV therapy with these agents (telaprevir, boceprevir, simeprevir, and sofosbuvir) now indicate that patients receiving these agents should be tested with a HCV RNA assay that can quantify down to 15 IU/mL in serum or plasma.

Mayo Medical Laboratories offers an assay that meets these new requirements: HCVQU / Hepatitis C Virus (HCV) RNA Detection and Quantification by Real-Time Reverse Transcription-PCR (RT-PCR), Serum. This test is FDA approved with the lower and upper limits of quantification at 15 and 100,000,000 IU/mL, respectively, and Mayo Medical Laboratories recommends this assay as the molecular diagnostic test to detect and quantify HCV RNA. The analytical sensitivity of this assay is as good as, if not better than, some of the current commercially available qualitative HCV RNA detection assays. This assay has been validated by Mayo Medical Laboratories for use to confirm the presence of chronic HCV infection, to determine pretreatment (baseline) HCV RNA levels in serum, and to monitor a patient’s response to antiviral therapy.

There are 4 possible results from this assay (HCVQU):

1. Undetected: HCV RNA is absent.

2. Detected, but <15 IU/mL: HCV RNA is detected, but the level present is <15 IU/mL, and cannot be accurately quantified below this level.

3. Quantitative Value: The quantitative result indicates the degree of active HCV viral replication in the patient (eg, 15,000 IU/mL). Monitoring HCV RNA levels over time is important to assess disease progression and/or a patient’s response to anti-HCV therapy.

4. Detected, but >100,000,000 IU/mL: HCV RNA level detected is >100,000,000 IU/mL and indicates the presence of active HCV viral replication. The HCV RNA level present cannot be quantified accurately above this upper limit of quantification of this assay.

References


Education Calendar

Clinical and Laboratory Updates in Thrombosis, Anticoagulation, and Vascular Medicine: A Board Review Primer
September 10–12, 2014
Rochester, Minnesota

Utilization Management 2014: Demonstrating and Delivering Value
September 22–23, 2014
Rochester, Minnesota

2014 Leveraging the Laboratory Outreach Conference: Outreach Acceleration
September 24–25, 2014
Rochester, Minnesota

Data-Driven Algorithms for Optimizing Laboratory Test Utilization for Hematologic Malignancies
December 5, 2014
San Francisco, California

COMMUNIQUÉ

The Communiqué is published by Mayo Medical Laboratories to provide laboratorians with information on new diagnostic tests, changes in procedures or normal values, and continuing medical education programs and workshops.

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Complete information on the following new tests is available, real-time and on-demand, at MayoMedicalLaboratories.com. This site provides the most current and accurate information available about Mayo’s test offerings.

**LBAB**

*Babesia* species Molecular Detection, PCR, Blood

**Useful For**
- An initial screening method for suspected babesiosis during the acute febrile stage of infection in patients from endemic areas, especially when Giemsa-stained peripheral blood smear do not reveal any organisms or the organism morphology is inconclusive.

**CALR**

*CALR* Mutation Analysis, Myeloproliferative Neoplasm (MPN)

**Useful For**
- Rapid and sensitive detection of insertion and deletion-type mutations in exon 9 of *CALR*
- An aid in distinction between reactive thrombocytosis and/or leukocytosis versus a myeloproliferative neoplasm (MPN), especially essential thrombocytopenia (ET) and primary myelofibrosis (PMF), and is highly informative in cases in which *JAK2* and *MPL* testing are negative
- Especially helpful to the pathologist in those bone marrow cases with ambiguous etiology of thrombocytosis, equivocal bone marrow morphologic findings of MPN, and/or unexplained reticulin fibrosis
- An aid in prognostication of PMF and thrombosis risk assessment in ET.

**COXIS**

*Coccidioides* Antibody with Reflex, Serum

**Useful For**
- Screening for detection of antibodies to *Coccidioides immitis/posadasii*

**COXIC**

*Coccidioides* Antibody with Reflex, Spinal Fluid

**Useful For**
- An aid for the diagnosis of meningeal infection with *Coccidioides immitis/posadasii*

**SLFA**

*Cryptococcus* Antigen Screen with Titer, Serum

**Useful For**
- An aid in the diagnosis of cryptococcosis

**CLFA**

*Cryptococcus* Antigen Screen with Titer, Spinal Fluid

**Useful For**
- An aid in the diagnosis of cryptococcosis
<table>
<thead>
<tr>
<th>Test Code</th>
<th>Test Name</th>
<th>Usefulness</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLFAT</td>
<td><em>Cryptococcus</em> Antigen Titer, LFA, Serum</td>
<td>• Monitoring <em>Cryptococcus</em> antigen titers in serum and/or cerebrospinal fluid</td>
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<tr>
<td>CLFAT</td>
<td><em>Cryptococcus</em> Antigen Titer, LFA, Spinal Fluid</td>
<td>• Aiding in the diagnosis of cryptococcosis</td>
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<tr>
<td>LFACX</td>
<td><em>Cryptococcus</em> Antigen with Reflex, LFA, Spinal Fluid</td>
<td>• An aid in the diagnosis of cryptococcosis</td>
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<td></td>
<td></td>
<td>• Monitoring <em>Cryptococcus</em> antigen titers in cerebrospinal fluid</td>
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<td></td>
<td></td>
<td>• Diagnosing fungal infections in cerebrospinal fluid</td>
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<tr>
<td>DEMES</td>
<td>Dementia, Autoimmune Evaluation, Serum</td>
<td>• Investigating new onset dementia and cognitive impairment plus 1 or more of the following:</td>
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<tr>
<td>DEMEC</td>
<td>Dementia, Autoimmune Evaluation, Spinal Fluid</td>
<td>- Rapid onset and progression</td>
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<td></td>
<td></td>
<td>- Fluctuating course</td>
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<td></td>
<td></td>
<td>- Psychiatric accompaniments (psychosis, hallucinations)</td>
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<td>- Movement disorder (myoclonus, tremor, dyskinesias)</td>
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<td>- Headache</td>
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<td>- Autoimmune stigmata (personal history or family history or signs of diabetes mellitus,</td>
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<td>thyroid disorder, vitiligo, poliosis [premature graying], myasthenia gravis, rheumatoid</td>
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<td>arthritis, systemic lupus erythematosus)</td>
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<td>- Smoking history (20+ pack years) or other cancer risk factors</td>
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<td>- History of cancer</td>
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<td></td>
<td></td>
<td>- Inflammatory cerebral spinal fluid</td>
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<td></td>
<td></td>
<td>- Neuroimaging findings atypical for degenerative etiology</td>
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<td></td>
<td>- Suspected cancer recurrence: a rising autoantibody titer in a previously</td>
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<td>positive patient suggests cancer recurrence</td>
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<td>ENCES</td>
<td>Encephalopathy, Autoimmune Evaluation, Serum</td>
<td>• Evaluating new onset encephalopathy (comprising confusional states, psychosis, delirium,</td>
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<tr>
<td>ENCEC</td>
<td>Encephalopathy, Autoimmune Evaluation, Spinal Fluid</td>
<td>memory loss, hallucinations, movement disorders, sensory or motor complaints, seizures,</td>
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<td>dyssomnias, ataxias, nausea, vomiting, inappropriate antidiuresis, coma, dysautonomias,</td>
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<td>or hypoventilation) plus 1 or more of the following accompaniments:</td>
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<td>- Autoimmune stigmata (personal or family history or signs of diabetes mellitus, thyroid</td>
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<td>disorder, vitiligo, poliosis [premature graying], myasthenia gravis, rheumatoid arthritis,</td>
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<td>systemic lupus erythematosus)</td>
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<td>- History of cancer</td>
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<td></td>
<td>- Smoking history (20+ pack years) or other cancer risk factors</td>
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<td></td>
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<td>- Inflammatory cerebral spinal fluid (or isolated protein elevation)</td>
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<td>- Neuroimaging signs suggesting inflammation</td>
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<td>- Suspected cancer recurrence: a rising autoantibody titer in a previously</td>
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<td>positive patient suggests cancer recurrence</td>
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<tr>
<td></td>
<td></td>
<td>• Evaluating limbic encephalitis (noninfectious)</td>
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<td>• Directing a focused search for cancer</td>
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</tbody>
</table>
• Investigating encephalopathy appearing in the course or wake of cancer therapy and not explainable by metastasis or drug effect

**EPIES**  
Epilepsy, Autoimmune Evaluation, Serum

**EPIEC**  
Epilepsy, Autoimmune Evaluation, Spinal Fluid

**Useful For**

• Investigating new onset cryptogenic epilepsy with incomplete seizure control and duration of <2 years

• Investigating new onset cryptogenic epilepsy plus 1 or more of the following accompaniments:
  - Psychiatric accompaniments (psychosis, hallucinations)
  - Movement disorder (myoclonus, tremor, dyskinesias)
  - Headache
  - Cognitive impairment/encephalopathy
  - Autoimmune stigmata (personal history or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, premature graying of hair, myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, idiopathic adrenocortical insufficiency), or multiple sclerosis
  - History of cancer
  - Smoking history (20+ pack years) or other cancer risk factors
  - Seizures occurring within the context of a subacute multifocal neurological disorder without obvious cause, especially in a patient with past or family history of cancer
  - Suspected cancer recurrence: a rising autoantibody titer in a previously positive patient suggests cancer recurrence

**HCCPR**  
Hepatocellular Carcinoma Risk Panel

**Useful For**

• Risk assessment of patients with chronic liver disease for development of hepatocellular carcinoma

**HIBLS**  
Histoplasma/Blastomyces Antibody Panel, Serum

**Useful For**

• Evaluating persons with symptoms of respiratory disease, as an aid in the presumptive laboratory diagnosis of Histoplasma infection

• Detection of antibodies in patients having blastomycosis

**HIBLC**  
Histoplasma/Blastomyces Antibody Panel, Spinal Fluid

**Useful For**

• Aiding in the diagnosis of Histoplasma meningitis

• Detection of antibodies in patients having blastomycosis

**HIVDI**  
HIV-1 and HIV-2 Antibody Differentiation, Serum

**Useful For**

• Detection and differentiation of HIV-1 and HIV-2 antibodies

• Supplemental testing of specimens that are reactive by FDA-approved HIV-1/-2 antigen and antibody combination tests

**HIVCO**  
HIV-1 and HIV-2 Antigen and Antibody Evaluation, Serum

**Useful For**

• Screening for HIV-1 and/or HIV-2 infection in asymptomatic patients

• Diagnosis of HIV-1 and/or HIV-2 infection in symptomatic patients
HLCA  Immunoglobulin Heavy and Light Chain (HLC) Pairs, IgA Kappa and IgA Lambda

Useful For
• Distinguishing between broadly migrating monoclonal proteins and restricted polyclonal immunoglobulin responses
• Quantitating monoclonal IgA proteins that are difficult to quantitate on serum protein electrophoresis
• Providing a more specific quantitation of the monoclonal protein than quantitating total IgA

HLCG  Immunoglobulin Heavy and Light Chain (HLC) Pairs, IgG Kappa and IgG Lambda

Useful For
• Distinguishing between broadly migrating monoclonal proteins and restricted polyclonal immunoglobulin responses
• Quantitating monoclonal IgG proteins that are difficult to quantitate on serum protein electrophoresis
• Providing a more specific quantitation of the monoclonal protein than quantitating total IgG

HLCM  Immunoglobulin Heavy and Light Chain (HLC) Pairs, IgM Kappa and IgM Lambda

Useful For
• Distinguishing between broadly migrating monoclonal proteins and restricted polyclonal immunoglobulin responses
• Quantitating monoclonal IgM proteins that are difficult to quantitate on serum protein electrophoresis
• Providing a more specific quantitation of the monoclonal protein than quantitating total IgM

62512  Small Lymphocytic Lymphoma, FISH, Tissue

Useful For
• Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with small lymphocytic lymphoma (SLL) and other low-grade B-cell lymphomas.
• Distinguishing patients with 11;14 translocations who have mantle cell lymphoma from patients who have SLL.

TICKP  Tick-Borne Panel, Molecular Detection, PCR, Blood

Useful For
• Evaluation of the most common tick-borne diseases found in the United States, including human monocytic and granulocytic ehrlichiosis, and babesiosis
• Evaluation of patients with a history of, or suspected, tick exposure who are presenting with fever, myalgia, headache, nausea, and other nonspecific symptoms