

## Vasculitis - ANCA

### Diagnosis

#### Indications for Testing

- Multisystem disease presentation (including upper airway disease, renal disease, pulmonary disease, palpable purpura, urticaria or mononeuritis multiplex)

#### Laboratory Testing

- Typical test plan includes ruling out other diseases with similar presentation and assessing organ involvement
- CBC – may have anemia, leukocytosis, thrombocytopenia
- Erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP) – usually elevated; nonspecific; lack of elevation does not rule out vasculitis
- Urinalysis – evaluate for presence of hematuria, proteinuria or red-cell casts (suggests glomerulonephritis)
- Renal function tests (BUN/creatinine) – assess for renal involvement
- Liver function tests – provide clues for hepatic involvement (most common in polyarteritis nodosa)
- ANCA
  - Indirect immunofluorescence assay (IFA) – sensitive marker for ANCA-associated vasculitis
  - To confirm, PR3 or MPO specific assays (ELISA, Western blot or multianalyte fluorescence detection [MAFD]) required (European League Against Rheumatism [EULAR] 2009 grade A recommendation)
  - Pattern of ANCA is frequently helpful (pANCA vs. cANCA)
  - May be useful in combination with clinical picture in emergency setting where physician cannot wait for biopsy results
  - Absence of a positive test result does not rule out diagnosis
- Other possible secondary testing – antinuclear antibody, rheumatoid arthritis, hepatitis B and C viruses

#### Histology

- Determines size of artery involved (EULAR 2009 grade C recommendation)
- In conjunction with clinical presentation, ANCA, urinalysis and biopsy can usually diagnose specific vasculitis (see the Vasculitis in Adults Testing Algorithm and Vasculitis in Children Testing Algorithm)

#### Imaging Studies

- Chest x-ray – nonspecific pulmonary nodules, cavitation, consolidation or pleural effusion suggest pulmonary involvement
- Angiogram of affected area – demonstrates aneurysms and vascular occlusion
  - Magnetic resonance angiography or computed tomography angiography may be preferred
- Echocardiography
  - 40% detection rate for Kawasaki
  - Also used in Takayasu
- Ultrasound – for temporal artery diagnosis and monitoring
- CT sinus – useful in Wegener granulomatosis

#### Other Testing

- Nerve conduction testing if neurologic manifestations present

#### Differential Diagnosis

- Large vessel
  - Mycotic aneurysms

- Atherosclerosis
- Congenital
  - Aortic coarctation
- Hereditary disorders
  - Marfan syndrome
  - Ehlers-Danlos syndrome (type IV)
  - Loeys-Dietz syndrome
- Fibromuscular dysplasia
- Postradiation syndrome
- Chronic aortic aneurysm
- Chronic infection
  - *M. tuberculosis*
  - *T. pallidum*
- Medium vessel/small vessel
  - Other vasculitis
    - Cogan syndrome
    - Behcet syndrome
  - Autoimmune disease
    - Systemic lupus erythematosus, rheumatoid arthritis, scleroderma
  - Neoplasm
    - Lymphoma, leukemia (ALL, AML), plasma cell dyscrasias, paraneoplastic syndrome
  - Infection
    - HIV, hepatitis C virus, hepatitis B virus, herpes simplex virus, endocarditis
  - Glomerulonephritis
  - Sickle cell disease
  - Hypercoagulable states
    - Antiphospholipid syndrome
    - Thrombotic thrombocytopenic purpura (TTP)
  - Mycotic aneurysms
  - Hereditary disorders
    - Ehlers Danlos syndrome
    - Neurofibromatosis
    - Grange syndrome
  - Fibromuscular dysplasia
  - Drugs
    - Cocaine
    - Amphetamines
    - Hypersensitivity reactions
- Central nervous system vasculitis
  - Sarcoidosis
  - Infection
    - Bacterial
    - Fungal (yeasts and molds)
    - Viral (progressive multifocal leukoencephalopathy)
    - Parasitic
  - Malignancy

- Glioma
- Angiocentric lymphoma
- Hypercoagulable states
  - TTP
  - Antiphospholipid syndrome
- Stroke-like syndromes
  - Sickle cell disease
  - Migraine headaches
  - Fabry disease
- Cerebral hemorrhage
- Embolic disease
  - Myxoma
  - Endocarditis

## Monitoring

- ANCA
  - Titers may decrease after induction of remission and rise secondary to relapse
    - Rising titers do not reliably predict relapse
    - Cannot use titers to guide treatment
  - Urinalysis should be performed every visit to monitor for renal involvement (EULAR 2009)
  - Inflammatory markers, renal function testing, CBC and [liver function](#) testing should be performed every 1-3 months (EULAR 2009 grade C recommendation)

## Clinical Background

The systemic vasculitides are a group of uncommon conditions characterized by inflammation and necrosis of blood vessel walls. Some of these syndromes are also characterized by the presence of antineutrophil cytoplasmic antibodies (ANCA).

### Epidemiology

- Incidence – 100/1,000,000
- Age – peak onset is 65-74 years; unusual in children
- Sex – M>F (minimal)

### Classification

- Based on affected blood vessel size (small, medium or large)
  - Small – [Wegener granulomatosis](#), [microscopic polyangiitis](#), renal vasculitis, [Henoch Schönlein purpura](#)
  - Medium – [polyarteritis nodosa](#), [Churg-Strauss syndrome](#), [Kawasaki disease](#)
  - Large – [Cogan syndrome](#), [Takayasu arteritis](#), [giant cell \(temporal\) arteritis](#)

Chapel Hill Consensus Conference Nomenclature of Systemic Vasculitis

#### Nomenclature and Definitions of Vasculitis Proposed by the Consensus Conference on the Nomenclature of Systemic Vasculitis (Chapel Hill Consensus)

- Large vessel vasculitis\*
  - [Giant cell arteritis](#)
    - Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery
    - Often involves the temporal artery
    - Usually occurs in patients >50 years and is often associated with polymyalgia rheumatica

- **Takayasu arteritis**
  - Granulomatous inflammation of the aorta and its major branches
  - Usually occurs in patients <50 years
- **Medium-sized vessel vasculitis\***
  - **Polyarteritis nodosa**
    - Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries or venules
  - **Kawasaki disease**
    - Arteritis involving large, medium-sized and small arteries and associated with mucocutaneous lymph node syndrome
    - Coronary arteries are often involved; aorta and veins may be involved
    - Usually occurs in children
- **Small vessel vasculitis\***
  - **Wegener granulomatosis**
    - Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels, eg, capillaries, venules, arterioles, and arteries
    - Necrotizing glomerulonephritis is common
  - **Churg-Strauss syndrome**
    - Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels and associated with asthma and blood eosinophilia
  - **Microscopic polyangiitis**
    - Necrotizing vasculitis with few or no immune deposits affecting small vessels, eg, capillaries, venules or arterioles
    - Necrotizing arteritis involving small and medium-sized arteries may be present
    - Necrotizing glomerulonephritis is very common
    - Pulmonary capillaritis often occurs
  - **Henoch-Schönlein purpura**
    - Vasculitis with IgA-dominant immune deposits affecting small vessels, eg, capillaries, venules or arterioles
    - Typically involves skin, gut and glomeruli and is associated with arthralgias or arthritis
  - **Cryoglobulinemic vasculitis**
    - Vasculitis with cryoglobulin immune deposits affecting small vessels, eg, capillaries, venules or arterioles, and associated with cryoglobulins in serum
    - Skin and glomeruli are often involved
  - **Cutaneous leukocytoclastic angiitis**
    - Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis

\*Large artery refers to the aorta and major branches directed toward body regions (eg, to the extremities and the head); medium-sized artery refers to main visceral arteries (eg, renal, hepatic, coronary and mesenteric arteries); small artery refers to distal arterial radicals that connect with arterioles (small vessels include small arteries, arterioles, venules and capillaries)

### Pathophysiology

- ANCA are directed against certain proteins in the cytoplasmic granules of neutrophils and monocytes
  - Neutrophil cytoplasmic antibodies are found in serum of >90% of patients with certain necrotizing systemic vasculitides and usually in <5% of patients with **connective tissue disease** or arthritis
- ANCA are specific for enzymes in the lysosome-proteinase 3-specific (PR-3) and myeloperoxidase-specific (MPO) antibodies; ANCA have been subdivided into pANCA (perinuclear) and cANCA (cytoplasmic)
  - pANCA pattern mimics anti-nuclear antibodies (ANA)
    - ~90% of patients with pANCA pattern by IFA have antibodies specific for MPO
    - ~85% of patients with cANCA pattern by IFA have antibodies specific for serine proteinase 3 (PR-3)
- Binding of ANCA may induce activation of neutrophils resulting in endothelial cell damage

**Clinical Presentation**

- Nonspecific signs and symptoms early in the disease – fever, arthralgias, fatigue, weight loss, myalgias
- Multisystem involvement later in the disease – dermatologic, ophthalmologic, renal, pulmonary, hepatic, gastrointestinal tract, vascular, central nervous system
- Patients present with diverse organ involvement in most cases

**Lab Tests**

**Indications for Laboratory Testing**

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

Test Name and Number	Recommended Use	Limitations	Follow Up
Anti-Neutrophil Cytoplasmic Antibody with Reflex to Titer and MPO/PR-3 Antibodies <b>2002068</b>  Method: Semi-Quantitative Indirect Fluorescent Antibody/ Semi-Quantitative Multiplex Bead Assay	Differentially diagnose systemic vasculitic syndromes, such as <ul style="list-style-type: none"> <li>• Wegener granulomatosis</li> <li>• Microscopic polyangiitis</li> <li>• Churg-Strauss syndrome</li> <li>• Necrotizing and crescentic glomerulonephritis</li> <li>• Autoimmune hepatitis</li> <li>• Primary sclerosing cholangitis</li> </ul> Monitor treatment of Wegener granulomatosis  If screen is positive, titer and MPO/PR-3 antibodies testing will be added to aid in antibody determination	Cross-reaction may occur with cationic protein 57 (CAP 57), cathepsin G, elastase, lactoferrin and other lysosomal proteins	Test for specific disease identification including serum testing and biopsy of involved site
Urinalysis, Complete <b>0020350</b>  Method: Reflectance Spectrophotometry/ Microscopy	Determine symptoms involved in vasculitic-like infections		
Sedimentation Rate, Westergren (ESR) <b>0040325</b>  Method: Visual Identification	Determine symptoms involved in vasculitic-like infections		
C-Reactive Protein <b>0050180</b>  Method: Quantitative Immunoturbidimetry	Nonspecific test to check for inflammation		

CBC with Platelet Count and Automated Differential <b>0040003</b> Method: Automated Cell Count/Differential	Monitor treatment of vasculitis		
Hepatic Function Panel <b>0020416</b> Method: Quantitative Enzymatic/Quantitative Spectrophotometry	Monitor treatment of vasculitis Panel includes bilirubin direct; bilirubin total (serum or plasma), alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, protein total (serum or plasma), albumin (serum or plasma)		
Renal Function Panel <b>0020144</b> Method: Quantitative Chemiluminescent Immunoassay/Quantitative Enzyme-Linked Immunosorbent Assay	Monitor treatment of vasculitis		

**Additional Tests Available**

Test Name and Number	Comments
MPO/PR-3 (ANCA) Antibodies <b>0050707</b> Method: Semi-Quantitative Multiplex Bead Assay	
Myeloperoxidase Antibody <b>0050526</b> Method: Semi-Quantitative Multiplex Bead Assay	
Serine Protease 3 Antibody <b>0050527</b> Method: Semi-Quantitative Multiplex Bead Assay	
Anti-Neutrophil Cytoplasmic Antibody, IgG <b>0050811</b> Method: Semi-Quantitative Indirect Fluorescent Antibody	Differentially diagnose systemic vasculitic syndromes such as <ul style="list-style-type: none"> <li>• Wegener granulomatosis</li> <li>• Microscopic polyangiitis</li> <li>• Churg-Strauss syndrome</li> <li>• Necrotizing and crescentic glomerulonephritis</li> <li>• Autoimmune hepatitis</li> <li>• Primary sclerosing cholangitis</li> </ul>

<p>Cryoglobulin, Qualitative with Reflex to IFE Typing and Quantitative IgA, IgG, and IgM  <b>2002403</b>                      Method:                      Qualitative Cold Precipitation/Qualitative Immunofixation Electrophoresis/Quantitative Nephelometry</p>	<p>If qualitative is positive, Immunofixation Electrophoresis Typing and Quantitative IgA, IgG and IgM will be added</p>
<p>Glomerular Basement Membrane Antibody Panel  <b>0051001</b>                      Method:                      Semi-Quantitative Multiplex Bead Assay/Qualitative Indirect Fluorescent Antibody</p>	
<p>Cryoglobulin, Qualitative  <b>0050185</b>                      Method:                      Qualitative Cold Precipitation</p>	

**Guidelines**

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### Diagnostic Algorithm(s)

PDF algorithm(s) available at [www.arupconsult.com](http://www.arupconsult.com).

Vasculitis in Adults Testing Algorithm

Vasculitis in Children Testing Algorithm

### Related Content

Allergic Disease

Central Nervous System Tumors - Brain Tumors

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Cryoglobulinemia

Giant Cell Arteritis - Temporal Arteritis

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Henoch Schönlein Purpura - IgA-Associated Vasculitis

Microscopic Polyangiitis

Polyarteritis Nodosa - PAN

Sarcoidosis

Sjögren Syndrome

Systemic Lupus Erythematosus - SLE

Takayasu Arteritis

Wegener Granulomatosis

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