Insights into ANCA-Associated Vasculitis
Introduction to vasculitis
  – Characteristics of vasculitis
  – Classification of systemic vasculitides
Description of ANCA*-associated vasculitis (AAV)
Risk factors and proposed pathogenesis for AAV
Diagnosis of AAV
  – Clinical manifestations of AAV
Disease activity scores and subgroups
  – BVAS and BVAS/WG
  – EUVAS
Treatment
Summary

*ANCA, anti-neutrophil cytoplasmic antibody
Introduction to Vasculitis
What is vasculitis?

- Vasculitis is inflammation of blood vessel walls.¹
- It is defined by injury of vessel walls by leukocytes.¹
- Pathology results from loss of vascular integrity.²
- Vasculitides are classified by the size of the involved blood vessels—whether predominantly small, medium, or large vessels.³

Large- to medium-sized artery

Small-sized artery

Arteriole

Capillary

Venule

Vein

Aorta

Giant cell arteritis
Takayasu arteritis

Polyarteritis nodosa
Kawasaki disease

Henoch-Schönlein purpura
Cryoglobulinemic vasculitis

Anti-GBM
Leucocytoclastic vasculitis

Microscopic polyangiitis

Wegener's granulomatosis
Churg-Strauss syndrome

GBM, glomerular basement membrane

ANCA-Associated Vasculitis
ANCA-associated vasculitis comprises three systemic vasculitides that primarily affect small-sized vessels:\(^1\):

- Wegener’s granulomatosis (WG)
- Microscopic polyangiitis (MPA)
- Churg-Strauss syndrome (CSS)

Vasculitis complications include necrosis that can obstruct vessels.\(^2\)

Organ pathology results from vascular injury leading to\(^2\):

- Ischemia
- Hemorrhage
- Loss of function

Immunofluorescence typically shows few to no immune complex deposits (pauci-immune).\(^3\)

- Immune complex deposition can sometimes be detected by electron microscopy\(^4\)

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Patients with ANCA-associated vasculitis often have antibodies to specific neutrophil cytoplasmic proteins\textsuperscript{1,2}:

- ANCAs directed to proteinase 3 (PR3) are predominantly associated with WG
- ANCAs directed to myeloperoxidase (MPO) are more frequently associated with MPA and CSS

ANCA titers may fluctuate over the course of the disease.\textsuperscript{1}

• Not all patients have ANCAs.¹
• PR3- and MPO-ANCAs have been observed in WG, MPA, and CSS²
  - WG: 75%–90% anti-PR3
  - MPA: 50%–80% anti-MPO
  - CSS: 2%–50% anti-MPO
• Approximately 25% of patients with anti-GBM* antibodies are also ANCA-positive, most frequently MPO-ANCA³
  - ANCAs have been observed before and after anti-GBM antibodies

*GBM, glomerular basement membrane
ANCA-Associated Vasculitis
Risk Factors and Proposed Pathogenesis
Infection may be a triggering factor:\(^1\):

- *Staphylococcus aureus* is frequently isolated from the upper airways of patients with WG
- Nasal carriage of *S. aureus* has been linked with higher risk of relapse in WG

Environmental risk factors for AAV may include:\(^1\):

- Exposure to particulate silica
- Seasonal differences in disease onset in some series

Genetic risk factors for AAV may include:\(^1\):

- Alpha-1 antitrypsin deficiency
- Genetic polymorphisms in key regulators of the immune response

Some medications have been associated with the development of ANCA-associated vasculitis.\(^2\)

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The pathogenesis of ANCA-associated vasculitis is incompletely understood, but it is believed to involve adherence of ANCAs to primed neutrophils, which then interact with endothelial cells on blood vessel walls.

Activating events, such as infection or exposure to environmental stimuli, cause proinflammatory cytokines to be secreted. These cytokines prime neutrophils, inducing migration of PR3 and MPO to the cell surface.

interaction of ANCA with cell surface antigens and with Fc receptors further primes neutrophils.

What Is the Proposed Pathogenesis of ANCA-Associated Vasculitis?¹

The conformation of neutrophil adhesion molecules changes, …

...causing adherence of neutrophils to endothelial cells.

Reactive oxygen species, proteolytic enzymes, and factors that activate the alternative complement pathway are thought to be released…

What Is the Proposed Pathogenesis of ANCA-Associated Vasculitis?¹

Endothelial cell damage

...causing damage to the endothelium and vascular wall.

Activated neutrophils release proinflammatory cytokines, recruiting more neutrophils and other inflammatory cells and amplifying the vasculitic process.

ANCA-activated neutrophils and other inflammatory cells infiltrate and destroy the vessel wall and may extend into the perivascular tissue causing fibrinoid necrosis.

Diagnosing ANCA-Associated Vasculitis
## What Are the Key Manifestations of ANCA-Associated Vasculitis?¹-³

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>WG</th>
<th>MPA</th>
<th>CSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulomatous inflammation of respiratory tract</td>
<td>No granulomatous inflammation</td>
<td>Eosinophil-rich, granulomatous inflammation</td>
<td></td>
</tr>
<tr>
<td>Renal manifestations</td>
<td>Focal, segmental, necrotizing, crescentic glomerulonephritis</td>
<td>Focal, segmental, necrotizing, crescentic glomerulonephritis</td>
<td>Less common</td>
</tr>
<tr>
<td>Pulmonary manifestations</td>
<td>Infiltrates; nodules; hemorrhage; alveolar capillaritis</td>
<td>Hemorrhage; alveolar capillaritis</td>
<td>Asthma; infiltrates; nodules</td>
</tr>
<tr>
<td>ANCA</td>
<td>Most frequently PR3</td>
<td>Most frequently MPO</td>
<td>Most frequently MPO</td>
</tr>
<tr>
<td>Other manifestations</td>
<td>Perforation of nasal septum; saddle-nose deformity; mononeuritis multiplex</td>
<td>Mononeuritis multiplex; fever</td>
<td>Fever; allergic rhinitis; mononeuritis multiplex</td>
</tr>
</tbody>
</table>

Frequency of Sinopulmonary Manifestations

Smaller bars show range

Frequency of Renal and Other Manifestations

- Glomerulonephritis
- Gastrointestinal problems
- Peripheral nervous system
- Cardiac involvement
- Ocular involvement

Smaller bars show range

Other Manifestations of AAV

<table>
<thead>
<tr>
<th>Organ/organ system</th>
<th>Manifestation</th>
</tr>
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<tr>
<td>Respiratory tract</td>
<td>Nasal crusting, septal perforation, saddle-nose deformity, tracheal stenosis</td>
</tr>
<tr>
<td>Musculoskeletal system</td>
<td>Myalgia, arthralgia, arthritis</td>
</tr>
<tr>
<td>Eyes</td>
<td>Conjunctivitis, corneal ulceration</td>
</tr>
<tr>
<td>Skin</td>
<td>Vesicular, palpable purpuric, ulcerative and hemorrhagic lesions</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Mononeuritis multiplex, CNS vasculitis</td>
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AAV patients, especially those with active disease, have a higher risk of developing venous thromboembolism.²

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Disease Activity Scores and Subgroups
The Birmingham Vasculitis Activity Score (BVAS) was originally developed and validated in 1994.¹

- Constructed by a consensus group of physicians
- Comprises 59 items in 9 organ systems
- Positive findings only recorded if attributable to disease
- Items weighted between 1 and 9 based on relative importance
- Overall range 0 to 63, with higher score representing more active disease

**BVAS version 2**²

- Scored in 2 components—new/worse disease (BVAS1), persistent disease (BVAS2)

**BVAS version 3 (2009)**³

- Reduced items to 56
- Single “persistent” box for the whole form

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The Birmingham Vasculitis Activity Score for Wegener’s granulomatosis (BVAS/WG) is an adaptation of the BVAS\textsuperscript{1}:

- Includes only those items in the BVAS relevant to WG
- Weights 15 major items considered a threat to life or organ function more heavily
- Includes determination of disease status
  - Severe disease/flare
  - Limited disease/flare
  - Persistent disease
  - Remission
- Overall range 0 to 68, with higher score representing more active disease

The EUVAS has created a classification system for ANCA-associated vasculitis with clinical subgroups that are used to harmonize treatment and patient eligibility for clinical trials.

**European Vasculitis Study Group (EUVAS) classification**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Systemic, outside ENT and lung</th>
<th>Threatens vital organ function</th>
<th>Constitutional symptoms</th>
<th>Serum creatinine, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>&lt;1.3</td>
</tr>
<tr>
<td>Early systemic</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>&lt;1.3</td>
</tr>
<tr>
<td>Generalized</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>&lt;5.6</td>
</tr>
<tr>
<td>Severe</td>
<td>Yes</td>
<td>Organ failure</td>
<td>Yes</td>
<td>&gt;5.6</td>
</tr>
<tr>
<td>Refractory</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Any</td>
</tr>
</tbody>
</table>

Current Treatment Approaches for ANCA-Associated Vasculitis
Treatment of ANCA-Associated Vasculitis

Treatment of ANCA-associated vasculitis is often divided into two phases: induction and maintenance.

**Induction therapy**
- Goals
  - Rapidly arrest the inflammatory and destructive processes of the disease
  - Put the disease into remission

**Maintenance therapy**
- Goals
  - Sustain remission
  - Prevent disease relapse
  - Allow the body to repair damage sustained during acute disease
There are three types of ANCA-associated vasculitis:

- Wegener’s granulomatosis (WG)
- Microscopic polyangiitis (MPA)
- Churg-Strauss syndrome (CSS)

ANCA-associated vasculitis primarily affects small- to medium-sized vessels. Many patients test positive for ANCAs, which are believed to be involved in disease pathogenesis. Risk factors for AAV include infectious agents, environmental and genetic factors, and certain medications. ANCA-associated vasculitis can have life-threatening renal and pulmonary manifestations. Treatment is divided into induction and maintenance phases.