





**Churg-Strauss Syndrome:
Dispelling the Myths**

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**Facts or Fiction?
Controversies in Churg-Strauss Syndrome**

1. Perinuclear (p) ANCA has limited utility in the diagnosis of CSS
2. pANCA levels do not correlate with disease activity
3. CSS carries a grave prognosis
4. Leukotriene receptor antagonists exacerbate CSS, playing a role in pathogenesis

Clinical Criteria for CSS

- Lanham's criteria (all of the following)
 - Asthma
 - Peak eosinophilia $>1.5 \times 10^9$ cells/L
 - Systemic vasculitis, two or $>$ extrapulmonary sites
- American College of Rheumatology (4 of the following in the setting of vasculitis)
 - Asthma
 - Peak eosinophilia $>10\%$ total WBC
 - Peripheral neuropathy attributed to vasculitis
 - Transient pulmonary infiltrates
 - Paranasal sinus disease
 - Biopsy showing blood vessels with extravascular eosinophils

**Clinical Criteria for CSS
(continued)**

- Chapel Hill Consensus Conference
 - Asthma
 - Peripheral Eosinophilia
 - Eosinophil-rich granulomatous inflammation involving the respiratory tract
 - Necrotizing vasculitis affecting small to medium vessels

These clinical criteria are consistent in the diagnosis of CSS. Mayo series shows 92% of subjects with CSS fulfill at least one of these classification schemes and 86% fulfill two or more (Keogh & Specks, American Journal of Medicine, 2003)

Utility of the pANCA in patients who fulfill clinical criteria for CSS

- Variable reported prevalence of positive pANCA in CSS
 - 38% Sinco, Arthritis & Rheum, 2005
 - 38% Sable-Fourtassou, Ann Intern Med, 2005
 - 73%, Keogh, Am J Med, 2003
 - 73-75% diagnosis and during flare
 - 16-36% during remission or at Dx/after treatment
- Are the results of the ACNA be utilized correctly?

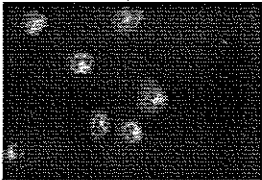

Utility of the pANCA in patients who fulfill clinical criteria for CSS

- CSS clinical entities based on MPO ANCA results.
 - MPO-ANCA positive subjects are more likely to display
 - Mononeuritis multiplex
 - Purpura
 - Renal vasculitis
 - ANCA negative patients
 - Tissue infiltrates with eosinophils
 - More frequent cardiac and pulmonary disease
- CSS represents two distinct disease entities with distinct pathogenesis and genetics

Sinico, 2005, Sable-Fourtassou, 2005, Sinicio 2009 (review)

ANCA recognition patterns

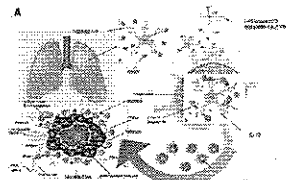
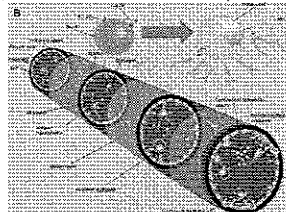
- Cytoplasmic (c)ANCA
- Recognition of Proteinase 3 (PR3)
- Wegener's Granulomatosis
- Perinuclear (p) ANCA
- Recognition of Myeloperoxidase (MPO)
- Churg-Strauss Angitis

Kallenberg, Nature Clinical Practice Rheumatology, 2006

ANCA: more than just a biomarker

- TNF primed PMNs express PRO and MPO on their surface.
- When incubated with IgG fractions from sera containing MPO ANCA and PR3-ANCA, primed PMN produce O₂ free radicals and lytic enzymes.
- IgG from healthy subjects did not induce PMN activation.
- Activation only occurs when PMN adhere to a surface (blood vessel) not when in solution (circulating).
- Blockade of FcγRII prevents ANCA-mediated activation.

Gomez-Puerta, AJP, 2009

Factors associated with poor prognosis in CSS

- Factor 5 score- (French Vasculitis Study Group)
 - Elevated Serum Creatinine (> 1.58mg/dl)
 - Proteinuria
 - Severe GI tract involvement
 - Cardiomyopathy
 - Central Nervous System involvement

No factors present = five year mortality 12%
 1 factor = five year mortality of 25%
 > 2 factors = five year mortality of 46%

Guillevin, Medicine, 1996

Can the ANCA's role in pathogenesis be used as a marker of disease activity?

- Keogh, Am J Med, 2005- Positive ANCA
 - 73% at diagnosis
 - 75% during flare
 - 16% during remission
 - 36% at diagnosis but after treatment
- ANCA positive more like to have small vessel vasculitis
 - Renal disease, mononeuritis multiplex, alveolar hemorrhage, and purpura
 - Relapse more likely
 - Higher proportion treated with Cytoxin
 - HLA DRB4 association

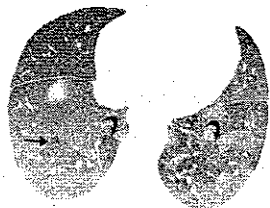
ANCA Negative CSS

- Clinical patterns:
 - Pericarditis
 - Livedo
 - Symmetrical polyneuropathy
 - pleuritis
- Eosinophil rich tissue infiltrates
- IL-10 genetic polymorphisms

What criteria is needed for diagnosis of CSS? (Sinico 2009)

- Clinical criteria based on Lanham, ACR, or Chapel Hill
 - Asthma
 - Eosinophilia
 - Multi-system disease- renal, CNS, paranasal sinuses, pulmonary infiltrates
- At least one of the following:
 - Histologic proof of vasculitis
 - Positive ANCA

Surrogate markers of Vasculitis



Sinopulmonary Disease

- Lower Airways
 - Fixed infiltrates
 - Nodules
 - Cavitations
 - Stenosis
- Upper Airways
 - Chronic sinusitis
 - Sub-glottic stenosis
 - Saddle nose deformity

Key Considerations

- Histologic evidence is needed in the diagnosis and as prognostic guides for CSS
- Surrogate markers of vasculitis can be applied in the proper clinical setting
- While only positive in 40%, the ANCA has prognostic value in CSS
- Without poor prognosis factors, treatment need not be aggressive

Suggested treatment Algorithms

- Without Factor Five Score- >90% successfully treated with corticosteroids alone
 - 35% relapse
 - Add azathioprine or cyclophosphamide pulse
- Factor Five Score ≥ 1
 - Corticosteroids plus pulse cyclophosphamide
 - Treatment duration 6 to 12 months

What about Leukotriene Receptor Antagonists (LTRA)?

- Leukotriene receptors found in the endothelium and up-regulate p-selectin
- LTRA decrease leukotriene production and may increase receptor expression, promoting CSS
- Keogh/Specks-2005
 - 25% of subjects treated with LTRA
 - 80% treated prior to diagnosis
 - 30% relapse rate
 - No difference in relapse or vasculitis compared to subjects not treated with LTRA
 - LTRA unlikely to play a role in pathogenesis of CSS

Key Points

- MPO ANCA used valuable in the diagnosis and management of patients with CSS
- Clinical classification requires histologic assessment for vasculitis
- Use of evidenced-based prognostic criteria can be used prospectively to guide treatment and management
- Leukotriene Receptor Antagonists do not exacerbate the clinical course of CSS

References

1. Kallenberg, Heerings, & Stegeman, Mechanisms of Disease: pathogenesis and treatment of ANCA-associated vasculitides, *Nature Clinical Practice Rheumatology*, 2006, 2: 661.
2. Gomez-Puerta & Bosch, Anti-Neutrophil Cytoplasmic Antibody Pathogenesis in Small Vessel Vasculitis, *American Journal of Pathology*, 2009, 175: 1790
3. Winter, Systemic Lung Disease, *Medicine*, 2008, 36: 253
4. Mukhopadhyay & Gal, Granulomatous Lung Disease, *Archives of Pathology and Laboratory Medicine*, 2010, 134: 667.
5. Sinico & Bottero, Churg-Strauss Angitis, *Best Practices & Research Clinical Rheumatology*, 2009, 23: 355.
6. Sable-Fourtassou, Cohen, et al, ANCA and Churg Strauss Syndrome, *Annals of Internal Medicine*, 2005, 143: 632
7. Sinicio, Toma et al, Prevalence and Clinical Significance of ANCA in Churg Strauss Syndrome, *Arthritis and Rheumatism*, 2005, 52: 2926
8. Keogh & Specks, Churg Strauss Syndrome: Clinical Presentation, ANCA, and Leukotriene Receptor Antagonists, *American Journal of Medicine*, 2003, 115:284
9. Gullemin, Ihote, et al, Prognostic Factors in polyarteritis nodosa and Churg Strauss Syndrome: a prospective study of 342 patients, *Medicine*, 1996, 75:17