**Research Article**

# ANCA Vasculitis in Algeria

**Sabiha Gadiri[1]\*, Meriche H[1], Alliouch-Kerboua A[1] and Atik A[2]**

[1]*Department of Immunology, Clinique St Therese UHC, Annaba, Algeria*
[2]*Department of Nephrology, Hospital IbnSina UHC, Annaba, Algeria*

## Article Info

**\*Corresponding author:**
**Sabiha Gadiri**
Professor
Department of Immunology
Clinique St Therese UHC,
Annaba, Algeria
E-mail: sabigadiri@gmail.com

## Abstract

**Background:** Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis comprises microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic GPA (EGPA). Major target antigens of ANCA associated with vasculitis are myeloperoxidase (MPO) and proteinase 3 (PR3). MPO-ANCA is related to MPA and EGPA, and PR3-ANCA is the marker antibody in GPA.

**Objective:** We aim to report the clinical-immunological characteristics of 92 patients with positive ANCA vasculitis

**Patients and Methods:** 92 patients (64 Female et 28 male), with ANCA vasculitis according to the Chapel Hill classification. ANCA was performed by indirect immunofluorescence, supplemented by immune dot to determine their specificity MPO/PR3.

**Results:** The mean age of patients was 51 years, the diagnosis was: 14 cases of GPA, 21 cases of microscopic polyangiitis (MPA), 04 cases of EGPA, 53 subjects had signs of overlap between the GPA and MPA. The clinical picture was dominated by renal disease followed by lung disease and rheumatologic signs. Some patients had cardiac involvement. 71 patients had p-ANCA (77, 2%), of which 43 was anti-MPO specificity (46.7%), 21 patients had c-ANCA (22.8%), including 9 with a specific anti-PR3 (98%), 40 patients showed no 2 searched specificities (43.4%).

**Conclusion:** ANCA vasculitis is rare, clinical and immunological spectrum is very heterogeneous. The demonstration of ANCA directed vis-a-vis PR3 and MPO specific as an aid in the diagnosis of systemic vasculitis

**Keywords:** Vasculitis; Antineutrophil Cytoplasmic Antibodies (ANCA); Myeloperoxidase (MPO); Proteinase 3 (PR3).

## Introduction

Vasculitis are Vessel's wall inflammation. Vasculitis is classified from the Conference Chapel Hill by size of affected vessels (Figure 1) [1]. ANCA-Associated Vasculitis are affecting vessels of small caliber, they are a collection of relatively rare autoimmune diseases of unknown cause, characterized by inflammatory cell infiltration causing necrosis of blood vessels [2].

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis comprises microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic (EGPA). Definitions for the AAV were described at the Chapel Hill Consensus Conference (CHCC) in 1994 and were revised in 2012 (Table 1) [1].
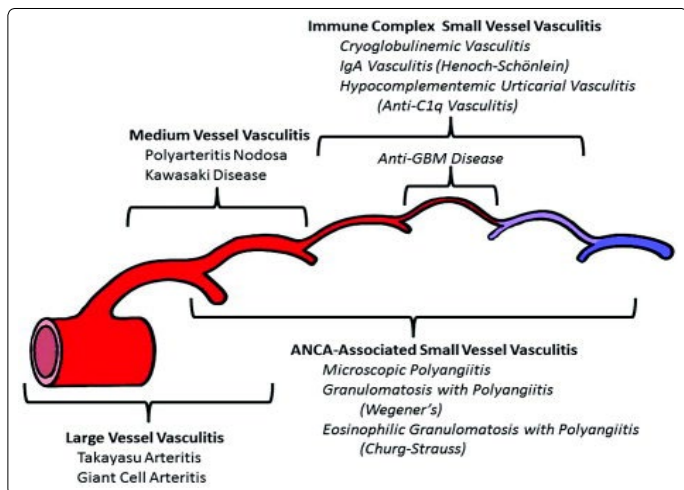
**Figure 1.** Distribution of vessel's involvement by large vessel vasculitis, medium vessel vasculitis, and small vessel vasculitis [1].

**Table 1.** 2012 Chapel Hill Consensus Conference definitions for ANCA-associated vasculitis.

| | |
|---|---|
| ANCA-associated vasculitis | Necrotisingvasculitis, with few or no immune deposits, predominantly affecting small vessels (iecapillaries, venules, arterioles and small arteries), associated with MPO-ANCA or PR3-ANCA. Not all patients have ANCA. Add a prefix indicating ANCA reactivity, eg PR3-ANCA, MPO-ANCA, ANCA-negative. |
| Granulomatosis with polyangiitis (Wegener's) | Necrotising granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotisingvasculitis affecting predominantly small to medium vessels (eg capillaries, venules, arterioles, arteries and veins). Necrotising glomerulonephritis is common. |
| Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) | Eosinophil-rich and necrotising granulomatous inflammation often involving the respiratory tract, and necrotisingvasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present. |
| Microscopic polyangiitis | Necrotisingvasculitis, with few or no immune deposits, predominantly affecting small vessels (iecapillaries, venules or arterioles). Necrotising arteritis involving small and medium arteries may be present. Necrotising glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent. |
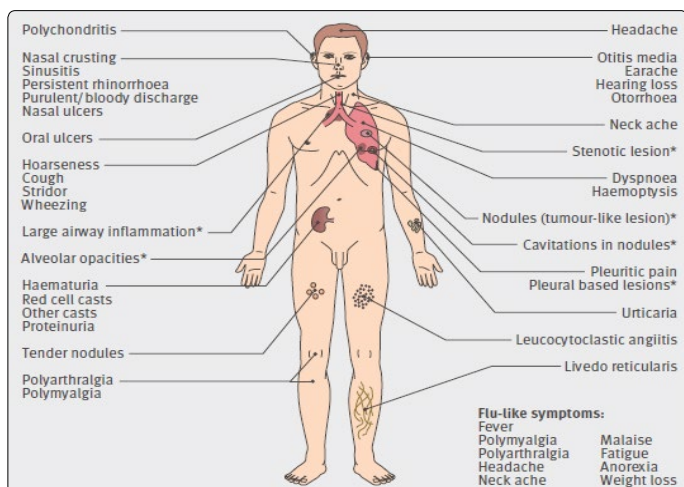


**Figure 2.** Clinical features of ANCA associated vasculitis [3].

Major target antigens of ANCA associated with vasculitis are myeloperoxidase (MPO) and proteinase 3 (PR3). MPO-ANCA is related to MPA and EGPA, and PR3-ANCA is the marker antibody in GPA.

In c-ANCA reactivity, PR3 is responsible for more than 90% of such reactions. Other antigens may occasionally contribute bactericidal permeability-inducing protein (BPI), rarely MPO.

In p-ANCA reactivity, MPO is responsible for ~10% of such reactivity. Other antigens include lastase, azurocidin, cathepsin Glysozyme, lactoferrin, antinuclear antibodies (ANA) can also have p-anca patterns.
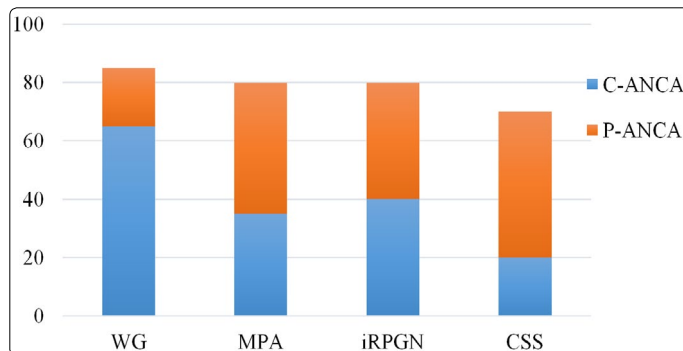


**Figure 3.** ANCA frequencies Invasculitis [4].

# Objective

The objective of this review is to study the clinical and immunological characteristics of 92 patients with positive ANCA vasculitis from the nephrology department.

# Patients and Methods

The study was a retrospective study interesting vasculitis patients with patient consent statement, hospitalized in the unit from 2014 October to February 2017. The study includes 92 patients with ANCA vasculitis (64 women and 28 men) according to the Chapel Hill classification. All patients ANCA Positive were included.

ANCA serology was examined by indirect immunofluorescence (IIF) on neutrophil substrate (NOVA Lite ANCA, INOVA Diagnostics Inc, San Diego), regarded as positive, the serums giving a fluorescence >1+. The Titration of the serums (+) takes place on smear of PN fixed at ethanol and, if positive, followed by immunoassays for the detection of antibodies to PR3 and myeloperoxidase MPO (NOVA Lite ANCA, INOVA Diagnostics Inc, San Diego). They are tests ELISA Indirect, which uses micropuits sensitized by PR3 and purified MPO. Upper limits of the normal range were provided by the manufacturer of the assays: MPO 9 IU/ml and PR3 3.5 IU/ml. Medical records of all patients with one or more positive MPO and/or PR3 ANCA test were reviewed for a clinical diagnosis of AAV (i.e., GPA, MPA, or EGPA). Demographic and clinical parameters were collected: age at presentation, sex, symptoms at presentation, number of affected organ systems, date and level of the first positive ANCA titre, laboratory parameters.

### Statistical analysis

Patients of this study were compared with patients with a clinical diagnosis AAV from other parts of the globe. Chi-square tests were used for categorical data.

# Results

## Characteristics of patients

During the study period, a total of 92 patients were hospitalized in the service. The mean age of vasculitis patients was 51 ± 17 years. Concerning gender, women represented 69.6% of patients and men represented 30.4% of patients. Twenty eight were male and sixty four were females (M:F 1:2). 92 cases satisfied diagnosis of AVV. Of them 14 (15.2%) had GPA, 21 (22.9%) had MPA, 04 (4.3%) had EGPA and 53 (57.6%) subjects had signs of overlap between the GPA and MPA.

## Clinical features compared in AAV diseases

The patients present various clinical signs. The majority has a renal (83.3%) and/or respiratory attack (61.1%), but there are also arthralgias (27.7%), purpura (16.6%), fever (15%) and pericarditis (5.55%) (Figure 4). The renal attack is the most common clinical sign in patients mainly in the form of an IRA (44%) with prevalent proteinuria (72%) and/or fever (15%). This triad of renal clinical signs is almost constant, HBP (38%) is less present (Figure 5).

Pulmonary attack is present at a high frequency in patients, represented by dyspnea (44%), cough and/or hemoptysia had at 16%. An ORL attack, in particular sinusian were to find (22%) (Figure 6).
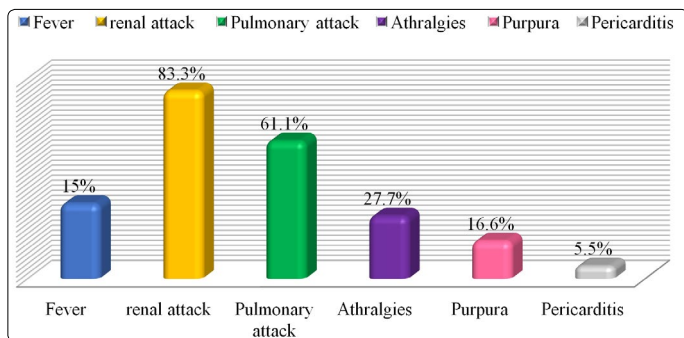


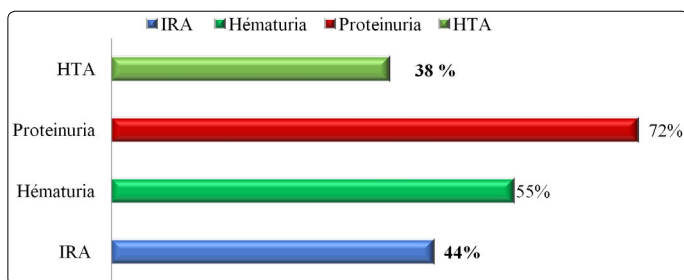**Figure 4.** Clinical signs of 92 ANCA Positive vasculitis.
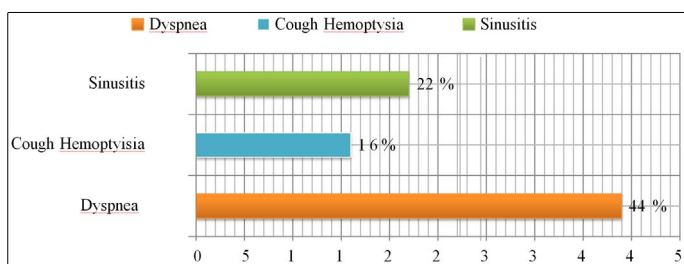


**Figure 5.** Symptoms of renal disease.



**Figure 6.** Symptoms of pulmonary disease.

## Immunological features of AAV

c- ANCA were detected in 21 (22.8%) and p-ANCA in 71 ANCA positive AAV patients (77.2 %) and specificity of ANCA was PR3 directed in 9 (9.8%) and MPO directed in 43 (46.7%) of the 71 p-ANCA positive patients tested for PR3 / MPO specificity. 40 patients (43.4%) showed no 2 searched specificities (Table 2).

C-ANC As were found in 66.6% of GPAs and 33.4% of overloap (SO) syndromes, whereas P-ANCAs were detected only in 5.6% of EGPAs and 64.8% of S0. Anti-PR3 antibodies were found for 9 cases of GPA, the distribution of anti-MPO antibodies is more heterogeneous, in 5 patients with GPA (11.6%), 21 subjects with an MPA (48.8%) and 13 subjects with a OS (30.2%) and finally 4 patients with EGPA (9.3%) (Table 3).

**Table 2.** Overall immunological results in ANCA associated vasculitis patients.

| Parameters | C-ANCA(+) | P-ANCA(+) | MPO (+) | PR3(+) | PR3/MPO (-) |
|---|---|---|---|---|---|
| Nb (N=92) | 21 | 71 | 43 | 9 | 40 |
| % | 22.8% | 77.2% | 46.7% | 9.8% | 43.3% |

**Table 3.** Immunological parameters in ANCA associated vasculitis patients.

| Parameter | GPA n=14 N (%) | MPA n=21 N (%) | EGPA n=4 N (%) | OS n=53 N (%) |
|---|---|---|---|---|
| c-ANCA positive n=21 | 14 66.6% | 00 0% | 00 0% | 7 33.4% |
| p- ANCA positive n=71 | 00 0% | 21 29.6 | 04 5.6% | 46 64.8% |
| PR3 positive n=9 | 9 100% | 00 0% | 00 0% | 00 0% |
| MPO positive n=43 | 5 11.6% | 21 48.8% | 04 9.3% | 13 30.2% |
| PR3/MPO negative n=40 | 00 0% | 00 0% | 00 0% | 40 100% |

OS: overloap syndromes

# Discussion

## Characteristics of patients

In our study we report our experience with AAV in Algeria. Many studies have reported geographic variations in the prevalence of different AAVs. In our series, GPAs and EGPAs were less frequent than MPAs. The different frequencies of vasculitis found were significantly lower than European studies (p<0.05) [2,5]. On the other hand, for Japanese studies, the frequencies found for GPA and EGPA were less frequent without significant differences (p<0.1) whereas for the MPAs in our study the frequencies were lower than those reported by Sada et al. [6] (p<0.05). As for the frequency of overlap syndromes (unclassifiable syndromes), it was more common in our study compared to Japanese studies Sada et al. [6].

In the literature, AAVs report that men were more frequently affected than women [7,8]. For our study, females were more prominent. The average age of patients in our series was close to those reported in the literature [9,10].

## Clinical features compared in AAV diseases

At the time of diagnosis, the general signs (fever) were reported respectively in 15% of patients and rheumatologic manifestations in 27.7% of patients. Pulmonary involvement was observed in 61% with cough and haemoptysis and dyspnoea. Cutaneous manifestations of the type of vascular purpura were noted in 16.6% of patients. ENT manifestations were present in 22% of patients in the form of sinusitis. Renal involvement was present in 83.3% of patients, revealed by renal insufficiency in 83.3% of cases, proteinuria in 72% of subjects and hematuria in 55 % of cases. These clinical signs have been reported by many authors [11-13].

## Immunological features of AAV

ANCA are auto antibodies directed against constituents of primary granules of neutrophils polynuclear. They are associated with small vessels vasculitis which includes granulomatosis with polyangiitis, microscopic polyangiits, Churg-Strauss syndrome and localised variants of these diseases (eg. pauci-immune necrotising). As recommended, ANCA were screened by IFI. When they were positive, their specificity was determined by ELISA [14,15].

The prevalence of ANCA detected by IFI and the prevalence of MPO and PR3 specificity detected by ELISA were lower than that reported by the Saudi study of A.S. Al Arfaj (p<0.05) [16]. According to Wiik in the generalized and active form of GPA, c-ANCAs are only detected in 73% of cases and ANCA-PR3 between 70%-80% of cases and ANCA-MPO in only 10% of cases [17]. For the GPAs of our series, the frequencies of c-ANCA, and ANCA -PR3 and MPO observed correlate with those reported by Wiik [17-19] and by the Arabic study of AL arfadj [16]. Numerous studies have confirmed the presence of p-ANCA in MPA [20-22]. Micropolyangéitis has generally been associated with ANCAs, more frequently of anti-MPO p-ANCA appearance, rather than anti-PR3 (proteinase 3) [23,24]. The prevalence of anti-MPO p-ANCA ranges from 54% for Ronco et al. [25] to 82% for Gross et al. [26] and Jenette et al. [27]. The frequency of p-ANCAs found in the MPAs of our study was lower than that reported by Tsiveriotis [20] and Savige [15,28] (p<0.05), whereas the frequency of p-ANCA MPO was close to that of Ronco [25]. EGPAs usually associated with ANCAs of p-ANCA appearance with specificity antigenic MPO, are found with a frequency ranging from 40% to 60% [29-31]. Anti-PR3 antibodies of cANCA appearance are present in 10% of cases [32].

The EGPAs of our series had a frequency in p-ANCA MPO lower than those reported by the Arabic and Japanese studies of Al Arfadj and Sada (p<0.05), but the frequency of this antibody was close to the Tunisian study.

In addition, the discovery of high-titre anti-PR3 c-ANCA is predictive of vasculitis more readily affecting the ENT and pulmonary spheres with relapse propensity, whereas observation of high-titre anti-MPO pANCA is more suggestive. vasculitis with renal tropism and reduced relapse potential [33]. For SO, the frequency of ANCA-MPO was lower than that reported by Sada (p<0.05) [6].

# Conclusion

ANCA vasculitis is rare, clinical and immunological spectrum is very heterogeneous. The demonstration of ANCA directed vis-a-vis PR3 and MPO specific as an aid in the diagnosis of systemic vasculitis.

# References

1. Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum*. 2013; 65(1): 1-11. doi: 10.1002/art.37715

2. Yates M, Watts R. ANCA-associated vasculitis. *Clin Med*. 2017; 17(1): 60-64. doi: 10.7861/clinmedicine.17-1-60

3. Berden A, Göçeroglu A, Jayne D, et al. Diagnosis and management of ANCA associated vasculitis. *BMJ*. 2012; 344(21): e26. doi: 10.1136/bmj.e26

4. Hagen EC, Daha MR, Hermans J, et al. Diagnostic value of standardized assays for anti-neutrophil cytoplasmic antibodies in idiopathic systemic vasculitis. EC/BCR Project for ANCA Assay Standardization. *Kidney Int*. 1998; 53(3): 743-753. doi: 10.1046/j.1523-1755.1998.00807.x

5. Watts RA, Mahr A, Mohammad AJ, Gatenby P, Basu N, Flores-Suárez LF. Classification, epidemiology and clinical sub grouping of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. *Nephrol Dial Transplant*. 2015; 30: i14-i22. doi: 10.1093/ndt/gfv022

6. Sada KE, Yamamura M, Harigai M, et al. Classification and characteristics of Japanese patients with antineutrophil cytoplasmic antibody-associated vasculitis in a nationwide, prospective, inception cohort study. *Arthritis Res Ther*. 2014; 16(2): R101. doi: 10.1186/ar4550

7. Chen M, Kallenberg CG. The environment, geoepidemiology and ANCA-associated vasculitides. *Autoimmun Rev*. 2010; 9(5): A293-A298. doi: 10.1016/j.autrev.2009.10.008

8. Mansi IA, Opran A, Rosner F. ANCA-associated small-vessel vasculitis. *Am Fam Physician*. 2002; 65(8): 1615-1620.

9. Mahr AD, Neogi T, Merkel PA. Epidemiology of Wegener's granulomatosis: lessons from descriptive studies and analyses of genetic and environmental risk determinants. *Clin Exp Rheumatol*. 2006; 24: S82-S91.

10. Terrier B, Dechartres A, Deligny C, et al. Granulomatosis with polyangiitis according to geographic origin and ethnicity: clinical-biological presentation and outcome in a French population. *Rheumatology (Oxford)*. 2017; 56(3): 445-450. doi: 10.1093/rheumatology/kew423

11. Ben Ghorbel I, Belfeki N, Baouendi N, Ben Salem T, Houman MH. Granulomatosis with polyangiitis in Tunisia. *Reumatismo*. 2017; 69(1): 23-29. doi: 10.4081/reumatismo.2017.935

12. Houben E, Bax WA, Van Dam B, et al. Diagnosing ANCA-associated vasculitis in ANCA positive patients. A retrospective analysis on the role of clinical symptoms and the ANCA titre. *Medicine (Baltimore)*. 2016; 95(40): e5096. doi: 10.1097/MD.0000000000005096

13. Gaffo AL. Diagnostic approach to ANCA-associated vasculitides. *Rheum Dis Clin North Am*. 2010; 36: 491-506. doi: 10.1016/j.rdc.2010.05.009

14. Vassilopoulos D, Niles JL, Villa-Forte A, et al. Prevalence of antineutrophil cytoplasmic antibodies in patients with various pulmonary diseases or multiorgan dysfunction. *Arthritis Rheum*. 2003; 49: 151-5. doi: 10.1002/art.10997

15. Savige J, Dimech W, Fritzler M, et al. Addendum to the international Consensus Statement on testing and reporting of antineutrophil cytoplasmic antibodies. Quality control, guidelines, comments, and recommendations of for testing in other autoimmune diseases. *Am J Clin Pathol*. 2003; 120: 312-318. doi: 10.1309/WAEP-ADW0-K4LP-UHFN

16. Al Arfaj AS, Khalil N. ANCA associated vasculitis in patients from Saudi Arabia. *Pak J Med Sci*. 2018; 34(1): 88-93. doi: 10.12669/pjms.341.13881

17. Wiik AS. Rational use of ANCA in the diagnosis of vasculitis. *Rheumatology*. 2002; 41: 481-483. doi: 10.1093/rheumatology/41.5.481

18. Wiik AS. Clinical use of serological tests for antineutrophil cytoplasmic antibodies. What do the studies say? *Rheum Dis Clin North Am*. 2001; 27(4): 799-813.

19. Specks U, Wheatley CL, McDonald TJ, Rohrbach MS, DeRemee RA. Anticytoplasmic autoantibodies in the diagnosis and follow-up of Wegener's granulomatosis. *Mayo Clin Proc*. 1989; 64: 28-36.

20. Tsiveriotis K, Tsirogianni A, Pipi E, Soufleros K, Papasteriades C. Antineutrophil Cytoplasmic Antibodies Testing in a Large Cohort of Unselected Greek Patients. *Autoimmune Dis*. 2011; 2011: 626495. doi: 10.4061/2011/626495

21. Savige JA, Gallicchio M, Georgiou T, Davies DJ. Diverse target antigens recognized by circulatingantibodies in anti-neutrophil cytoplasm antibody associated renal vasculitides. *Clin Exp Immunol*. 1990; 82: 238-43.

22. Venning MC, Quinn A, Broomhead V, Bird AG. Antibodies directed against neutrophils (C-ANCA and P-ANCA) are of distinct diagnostic value in systemic vasculitis. *Q J Med*. 1990; 77: 1287-1296.

23. Radice A, Sinico RA. Antineutrophil cytoplasmic antibodies (ANCA). *Autoimmunity*. 2005; 38(1): 93-103. doi: 10.1080/08916930400022673

24. Radice A, Sinico RA. Antineutrophil cytoplasmic antibodies (ANCA) testing: detection methods and clinical application. *Clin Exp Rheumatol*. 2014; 32: S112-S117.

25. Bindi P, Mougenot B, Mentre F, et al. Glomérulonéphrite extra capillairenécrosante sans dépôtsd' immunoglobuline. Localisation rénale d'une vascularite systémique avec anticorps anti-cytoplasme des polynucléaires. *Presse Med*. 1991; 20: 1939-43.

26. Schmitt WH, Csernok E, Gross WL. ANCA and infection. *Lancet*. 1991; 337: 1416-1417.

27. Jennette JC, Nachman PH. ANCA Glomerulonephritis and Vasculitis. *Clin J Am Soc Nephrol*. 2017; 12: 1680-1691. doi: 10.2215/CJN.02500317

28. Savige J, Trevisin M, Pollock W. Testing and reporting antineutrophil cytoplasmic antibodies (ANCA) in treated vasculitis and non-vasculitic disease. *J Immunol Methods*. 2018; 458: 1-7. doi: 10.1016/j.jim.2018.02.016

29. Gioffredi A, Maritati F, Oliva E, Buzio C. Eosinophilic granulomatosis with polyangitis: an overview. *Front Immunol*. 2014; 5: 549. doi: 10.3389/fimmu.2014.00549

30. Sinico RA, Di Toma L, Maggiore U, et al. Renal involvement in Churg-Strauss syndrome. *Am J Kidney Dis*. 2006; 47(5): 770-779. doi: 10.1053/j.ajkd.2006.01.026

31. Sinico RA, Di Toma L, Maggiore U, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. *Arthritis Rheum*. 2005; 52(9): 2926-2935. doi: 10.1002/art.21250

32. Mahr A, Guillevin L, Poissonnet M, Aymé S. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg- Strauss syndrome in a French urban multiethnic population in 2000: a capture-recapture estimate. *Arthritis Rheum*. 2004; 51: 92-99. doi: 10.1002/art.20077

33. Savige J, Trevisin M, Hayman M, Pollock W. Most proteinase3- and myeloperoxidase-antineutrophil cytoplasmic antibodies enzyme-linked immunosorbent assays perform less well in treated small-vessel vasculitis than in active disease. *APMIS Suppl*. 2009; (127): 60-62. doi: 10.1111/j.1600-0463.2009.02479.x