

Screening for renal involvement in ANCA-associated vasculitis: room for improvement?

E. Houben¹, J.W. van der Heijden², B. van Dam¹, W.A. Bax¹, A.E. Voskuyl³, E.L. Penne^{1*}

¹Department of Internal Medicine, Northwest Clinics, Alkmaar, the Netherlands, ²Department of Nephrology, VU University Medical Centre, Amsterdam, the Netherlands, ³Department of Rheumatology, Amsterdam Rheumatology and Immunology Centre, VU University Medical Centre, Amsterdam, the Netherlands, *corresponding author: tel.: +31 (0)72-5484444, fax: +31 (0)72-5482165, email: e.l.penne@nwz.nl

ABSTRACT

Background: Renal involvement in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) requires prompt and aggressive immunosuppressive therapy. The aim of this study was to evaluate screening practice for renal involvement in AAV and its potential effect on renal outcomes.

Methods: Between 2005 and 2015, ANCA-positive AAV patients in a teaching hospital in the Netherlands were retrospectively included. Complete screening for renal involvement was defined as: assessment of erythrocyturia, proteinuria and serum creatinine within two weeks of the diagnosis of AAV. Characteristics at presentation and at 12 months were compared between patients with and without complete screening.

Results: A total of 109 AAV patients (63% male) were identified with a mean age of 62 ± 14 years. Complete screening for renal involvement was performed in 90 of the 109 patients (83%). Patients with incomplete screening had a lower serum creatinine (86 ± 53 vs. 190 ± 185 $\mu\text{mol/l}$, $p < 0.001$) and were more often diagnosed outside the renal department (100% vs. 78%, $p = 0.02$). Three patients with incomplete screening had a rise in serum creatinine of $\geq 30\%$ at 12 months. Incomplete screening was not associated with the development of end-stage renal disease. Urine analysis of patients with renal biopsy-proven AAV ($n = 31$) showed erythrocyturia in 58% after one sample and in 94% after three samples.

Conclusion: Screening for renal involvement in AAV was suboptimal, primarily in patients who presented outside the renal department. A higher sensitivity for erythrocyturia is achieved if urine analysis is repeated. Incomplete screening may lead to renal impairment if renal involvement is not treated appropriately.

KEYWORDS

ANCA-associated vasculitis, end-stage renal disease, renal screening practice

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a life-threatening disease that affects multiple organ systems.^{1,2} By the time it is diagnosed, renal involvement is present in 60-80% of patients.^{3,4} Renal involvement in AAV progresses rapidly and may lead to the need for renal replacement therapy within days.⁵ In AAV patients with kidney damage it is generally recommended to immediately start aggressive immunosuppressive therapy (cyclophosphamide or rituximab in combination with glucocorticoids with or without plasma exchange) in order to prevent progression to end-stage renal disease (ESRD).⁶⁻⁸

Deterioration of renal function in AAV is often preceded by urinary abnormalities, such as erythrocyturia and/or proteinuria.⁹⁻¹² A recent study in AAV patients with crescentic glomerulonephritis showed that renal outcomes were similar between patients with and without renal impairment at diagnosis.¹¹ This indicates that baseline renal function alone is a poor marker for renal outcomes in AAV. The benefit of aggressive immunosuppressive therapy in patients with crescentic glomerulonephritis and a preserved renal function has not been addressed in randomised controlled trials so far. Nevertheless, observational data showed better renal outcomes if these patients are treated with cyclophosphamide.¹¹ It is therefore suggested to treat patients with renal AAV and a preserved renal function with aggressive immunosuppressive

therapy, similar to patients with renal impairment at presentation.^{11,13}

Early and complete screening for renal involvement is required in order to immediately start adequate treatment. Recent guidelines recommend screening for renal involvement early in the diagnostic process.¹⁴ So far, the implementation of renal screening and its effects on renal outcome in AAV have not been studied. The aim of the present study is to evaluate whether screening for renal involvement is timely and complete in clinical practice in a teaching hospital in the Netherlands and to determine whether the failure of adequate screening had an impact on renal function after 12 months and the development of ESRD. Furthermore we investigated the diagnostic properties of urine analysis that preceded renal biopsy-proven AAV.

MATERIALS AND METHODS

We performed a retrospective cohort study in the Northwest Clinics, a teaching hospital group in Alkmaar and Den Helder in the Netherlands. The local medical ethics committee approved the study and waived the requirement for informed consent. Patients who were positive for ANCA proteinase-3 (PR3) or myeloperoxidase (MPO) between February 2005 and February 2015 were screened for the clinical diagnosis of AAV, in accordance with Watts algorithm entry criteria for epidemiological studies.¹⁵ All AAV patients who were diagnosed within the Northwest Clinics were included in the study. ANCA serology was assessed by indirect immunofluorescence on neutrophil substrate (NOVA Lite® ANCA, INOVA Diagnostics Inc, San Diego, USA) and, if positive, followed by immunoassays for the detection of antibodies to PR3 and myeloperoxidase MPO (Autostat™ II Anti-PR-3 and Anti-MPO ELISAs, Hycor Biomedical Ltd, UK, from February 2005 until August 2012, and EliA™ PR3^S and EliA™ MPO^S run on a Phadia 250 analyser, Thermo Fisher Scientific, Immunodiagnosics, Sweden from August 2012 until the end of the study period).

Medical records of all enrolled AAV patients were reviewed for patient demographic data, the department diagnosing AAV and the date of diagnosis. Furthermore data on renal outcome, including serum creatinine, estimated glomerular filtration rate (eGFR), using the abbreviated Modification of Diet in Renal Disease (MDRD) equation¹⁶ and the development of ESRD at 12 months after diagnosis were recorded. The Birmingham Vasculitis Activity Score for Wegener's granulomatosis (BVAS/WG)⁹ was calculated in all patients based on symptoms at presentation. Renal involvement was defined as either kidney biopsy-proven AAV or renal involvement in accordance with the BVAS/WG. The patient's medical records were reviewed for

complete screening for renal involvement within two weeks before or after the diagnosis of AAV. Complete screening for renal involvement was defined in accordance with the Dutch guideline 'Diagnostics of small-vessel vasculitis'¹⁴: assessment of serum creatinine and assessment of erythrocyturia and assessment of proteinuria. Proteinuria was defined as ≥ 500 mg/24 hours in accordance with proteinuria in the Vasculitis Damage Index.¹⁷ Erythrocyturia was defined as ≥ 10 red blood cells/high power field, in accordance with the BVAS/WG.⁹ Renal impairment was defined as serum creatinine ≥ 125 $\mu\text{mol/l}$, in accordance with BVAS version 3.¹⁸ All samples of serum creatinine and urine analysis three months prior to the biopsy were recorded in patients with renal biopsy-proven AAV.

Statistical analysis

The characteristics of patients who received complete screening for renal involvement within two weeks were compared with characteristics of patients without complete screening. A Wilcoxon signed-rank test was used to analyse the difference between serum creatinine at diagnosis and at 12 months in each group. In addition, renal outcomes defined as the development of ESRD and/or a rise in serum creatinine of $> 30\%$ at 12 months were compared between the two groups. The analysis was repeated with complete screening for renal involvement within four weeks instead of two weeks before or after the diagnosis of AAV. Chi-square tests, unpaired Student t-tests and Mann-Whitney's U tests were used where appropriate. A p value < 0.05 was considered statistically significant. For data management and statistical analysis, Statistical Package for Social Sciences (SPSS®) version 20.0 was used.

RESULTS

Between 1 February 2005 and 1 February 2015 a total of 239 patients tested positive for MPO or PR3 ANCA, of which 119 patients (50%) were diagnosed with AAV. The remaining 120 patients were diagnosed with inflammatory bowel disease (n = 24), other rheumatic diseases (n = 23), infection (n = 11), other (n = 29) or unknown (n = 2) diagnosis, or had unclassified symptoms (n = 31). After the exclusion of AAV patients who were diagnosed in a different hospital (n = 10), 109 patients were enrolled in this study. Patient characteristics are summarised in *table 1*. In short, the mean age was 62 ± 14 years and 63% were male. The median time between the first hospital visit with an AAV-related symptom and the diagnosis AAV was six weeks (interquartile range (IQR) 2-44).

Screening practice

In 90 of the 109 patients (83%) screening for renal involvement was completed within two weeks before

Table 1. Baseline characteristics of 109 AAV patients

Age (years, mean \pm SD)	62 \pm 14
Male sex (no, %)	69 (63)
Serum creatinine $\mu\text{mol/l}$ (median, IQR)	102 (70-207)
Serum creatinine < 125 $\mu\text{mol/l}$ (no, %)*	66 (61)
Renal involvement (no, %)**	66 (61)
Lung involvement (no, %)**	50 (46)
Ear nose throat involvement (no, %)**	49 (45)
Skin and soft tissue involvement (no, %)**	21 (19)
Arthritis/arthralgia's (no, %)**	42 (38)
BVAS/WG (median, percentiles)	5 (4-7)
MPO ANCA (no, %)	45 (41)
PR ₃ ANCA (no, %)	64 (59)
Patients with biopsy proven AAV (no, %)***	50 (46)
Weeks between first hospital visit and diagnosis AAV (median, IQR)	6 (2-44)
*Serum creatinine as far as tested at presentation. **Organ involvement defined in accordance with items on the BVAS/WG. ***Biopsy sites were: kidney (n = 31), lung (n = 3), skin (n = 11) and nasal mucosa (n = 5). SD = standard deviation, IQR = interquartile range, BVAS/WG = Birmingham Vasculitis Activity Score for Wegener's granulomatosis, MPO = myeloperoxidase, ANCA = antineutrophil cytoplasmic antibody, PR ₃ = proteinase-3.	

or after the diagnosis. Of the 19 patients (17%) without complete renal screening: assessment of proteinuria was missing in all patients, urine sedimentation for erythrocyturia in 12 patients and serum creatinine in one patient. Screening in these patients was completed within four weeks in four patients, within two months in seven patients and within four years in three patients. In five patients, screening for renal involvement was not completed during a median follow-up of 2.2 years.

In comparison with patients with complete renal screening, patients with incomplete renal screening had a lower serum creatinine (median 70 (56-89) vs. 109 (74-248) $\mu\text{mol/l}$, $p = 0.001$) and a lower BVAS/WG (median 4 (3-7) vs. 5 (4-7), $p = 0.03$) (table 2). Notably, median BVAS/WG did not differ significantly after excluding erythrocyturia from the BVAS/WG.

All patients (100%) diagnosed with AAV in the renal department had complete renal screening, as compared with 78% of patients who were diagnosed in other departments ($p = 0.02$, table 2 and table 3). Of the 88 patients who were diagnosed with AAV in other hospital departments than the renal department, 54 patients (61%) developed renal involvement at any time during follow-up. Repeating the analysis using a cut-off for renal screening of four weeks instead of two weeks before or after the diagnosis yielded similar results.

Most patients with complete renal screening, ($n = 72$, 80%) were treated with a cyclophosphamide-based regimen

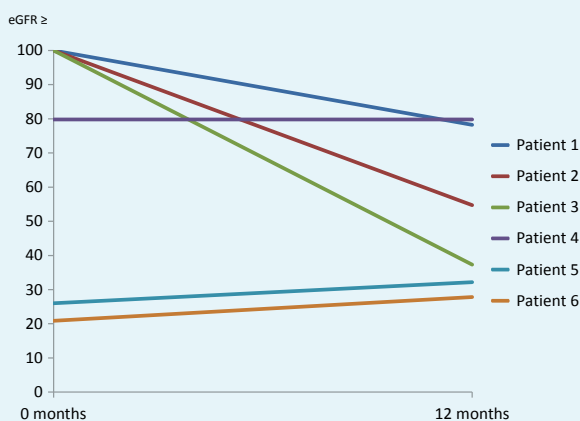
Table 2. Characteristics of patients who were completely screened for renal involvement and patients who were not completely screened. Complete screening included: assessment of serum creatinine and urinalysis for erythrocyturia and proteinuria within two weeks of the diagnosis of AAV. Other induction regimens than cyclophosphamide in the group with complete screening were: glucocorticoids with/without azathioprine ($n = 14$), rituximab ($n = 1$), methotrexate ($n = 1$), mycophenolate mofetil ($n = 1$), unknown due to referral to another hospital for induction treatment ($n = 1$). Other induction regimens in the group without complete screening were: glucocorticoids with/without azathioprine ($n = 11$) or methotrexate ($n = 1$)

	Complete n = 90	Incomplete n = 19	p-value
Age (mean, SD)	62 \pm 13	63 \pm 19	0.59
Male sex (no, %)	58 (64)	11 (58)	0.82
Anti-PR ₃ positivity (no, %)	55 (61)	9 (47)	
Anti-MPO positivity (no, %)	35 (39)	10 (53)	0.27
Serum creatinine $\mu\text{mol/l}$ (median, IQR)	109 (74-248)	70 (56-89)	0.001
Serum creatinine < 125 $\mu\text{mol/l}$ (no, %)	49 (54)	17 (89)	0.01
BVAS/WG (median, IQR)	5 (4-7)	4 (3-7)	0.03
Cyclophosphamide based induction regimen (no, %)	72 (80)	7 (37)	< 0.001
Need for renal replacement therapy at 12 months (no, %)	7 (8)	0 (0)	0.21
Rise in serum creatinine of $\geq 30\%$ at 12 months (no, %)	11 (12)	3 (16)	0.77
SD = standard deviation, IQR = interquartile range, MPO = myeloperoxidase, ANCA = antineutrophil cytoplasmic antibody, PR ₃ = proteinase-3, BVAS/WG = Birmingham Vasculitis Activity Score for Wegener's granulomatosis.			

Table 3. Complete screening performed within two weeks at different departments

Department	AAV patients diagnosed (no)	Complete renal screening (no, %)	Renal involvement during follow-up (no, %)
Internal medicine	33	29 (88)	27 (82)
Nephrology	21	21 (100)	20 (95)
Pulmonology	21	14 (67)	9 (43)
Otolaryngology	13	8 (62)	4 (31)
Rheumatology	13	12 (92)	9 (69)
Neurology	3	2 (67)	1 (33)
Cardiology	1	1 (100)	1 (100)
Dermatology	1	0 (0)	0 (0)
Geriatrics	1	1 (100)	1 (100)
Family medicine	1	1 (100)	1 (100)
Gastroenterology	1	1 (100)	1 (100)
Total	109	90 (83)	74 (68)

Figure 1. Kidney function at diagnosis and after 12 months in 6 patients with incomplete renal screening that developed renal involvement during follow-up. Three patients showed a decline in eGFR. In patient 1: a urinary sediment 9 days after diagnosis and after the initiation of treatment did not show erythrocyturia. However, a urinary sediment 6 weeks prior to the diagnosis did show erythrocyturia. In patient 2: the first urinary sediment was performed one month after diagnosis and showed erythrocyturia and proteinuria. The delay in treatment was 2 months. In patient 3: a urinary sediment 3 days prior to diagnosis showed erythrocyturia. Proteinuria was not assessed. Cyclophosphamide was directly started at diagnosis based on severe pulmonary involvement



for induction of remission. In patients without complete screening, seven patients (37%) were treated with a cyclophosphamide-based regimen (table 2). A total of 79 patients (73%) were treated with azathioprine and glucocorticoids for remission maintenance.

Renal prognosis

The median serum creatinine declined from 109 (74-248) to 103 (82-163) $\mu\text{mol/l}$ in patients with complete screening ($p = 0.20$) and rose from 70 (56-89) to 81 (69-92) $\mu\text{mol/l}$ in patients without complete screening ($p = 0.65$). None of the patients with incomplete renal screening developed ESRD. Of the 19 patients with incomplete screening, renal impairment or urinary abnormalities were documented in six patients at any point during a median follow-up of 5.2 years (2.1-9.7). Three of these patients had a decline in kidney function over the 12 months after diagnosis (figure 1). In all three patients the deterioration of kidney function coincided with erythrocyturia. In one patient the deterioration of kidney function coincided with proteinuria. Proteinuria was not assessed in the other two patients. In one patient there was a delay in treatment of two months. In the other two patients treatment was initiated at diagnosis. Of these three patients, one was treated with cyclophosphamide and two were treated with prednisolone induction therapy.

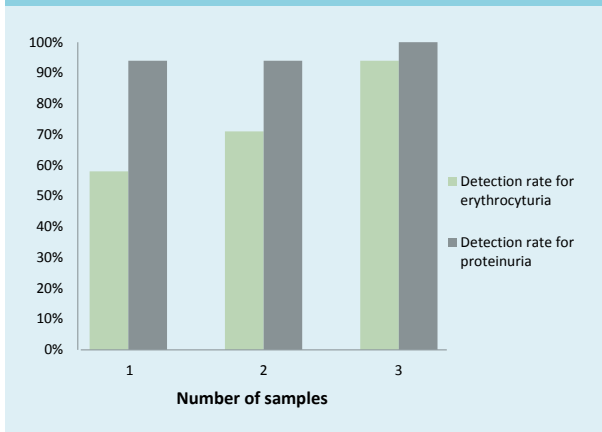
Laboratory findings in patients with kidney biopsy proven AAV

In 35 patients a kidney biopsy was performed, of which 31 were typical for AAV and four were inconclusive. The kidney biopsies were performed as part of the initial diagnostic process. The indication for a biopsy was established based on clinical decision, not on a standardised protocol. Of the 31 patients with kidney biopsy proven AAV, five (16%) did not have renal impairment. A median of three (2-4) urinary sediments were collected and examined for erythrocyturia in the three months preceding the biopsy. Results from these urine analyses were variable within these patients. In 18 of the 31 patients (58%), all urine samples showed erythrocyturia. Three samples were required to detect erythrocyturia in 94% of patients (figure 2). In 29 of 31 patients proteinuria was detected in all samples (figure 2). The number of required samples for the detection of erythrocyturia or proteinuria was not related to kidney function.

DISCUSSION

In this cohort of AAV patients from a teaching hospital in the Netherlands, screening for renal involvement was performed in 83% of AAV patients within two weeks before or after the diagnosis. Patients with normal kidney function and patients who presented outside the renal

Figure 2. Detection rate for erythrocyturia and proteinuria in 31 patients with biopsy-proven renal involvement in AAV



department were at risk of incomplete screening for renal involvement, which may ultimately lead to kidney function loss. In three patients with incomplete screening for renal involvement, kidney function decreased in the year after diagnosis; two of these patients were not treated with appropriate immunosuppressive induction therapy covering renal involvement. Unawareness of renal involvement may have played a role in the choice for the type of immunosuppressive agents in these patients and therefore may have contributed to the kidney function loss. The question arises whether all AAV patients require full renal screening. Although the clinical course of patients with AAV is variable, in most patients the acute phase of systemic vasculitis is preceded by a phase with more mild symptoms.^{11,19} During this phase of the disease, many patients suffer from upper respiratory complaints and arthralgia. Patients then usually progress to a more acute phase of the disease, in which rapidly progressive renal failure is a common feature.^{5,19} Unfortunately, if renal involvement is diagnosed too late, some patients will have already developed severe kidney damage, occasionally with the need for renal replacement therapy.^{5,10} In our cohort 61% of AAV patients who were diagnosed outside the renal department developed renal involvement at any time during follow-up. This indicates the high occurrence of renal involvement in AAV patients who present with other than renal symptoms and emphasises the necessity of complete and repeated renal screening in all patients. Early screening for renal involvement may have considerable clinical implications. So far randomised controlled studies have not assessed the benefit of aggressive immunosuppressive therapy specifically in patients with early renal disease without loss of renal function. However, observational studies suggest that patients with urinary abnormalities but preserved renal function benefit from aggressive treatment. As

already briefly mentioned in the introduction, Hanaoka and colleagues studied 27 patients with biopsy-proven renal involvement, of which 12 patients had preserved eGFR. These patients were divided into two groups according to intravenous cyclophosphamide exposure. At three-year follow-up, patients without cyclophosphamide treatment had significantly lower eGFR than those with cyclophosphamide treatment (42.1 vs. 62.1 ml/min/1.73 m², $p = 0.01$).¹¹ It is therefore suggested that when patients with renal AAV and urinary abnormalities but a preserved eGFR are treated with aggressive immunosuppressive therapy, irreversible damage due to glomerulonephritis can be prevented.^{2,11,13} Apart from the direct therapeutic implications of renal screening, renal baseline parameters also serve the interpretation of future laboratory variables. Current guidelines recommend urine analysis at each patient visit in order to screen for a possible renal relapse or therapy toxicity.^{6,20} Knowledge on the course of erythrocyturia (new onset/decreasing) enhances comprehension of disease activity and can guide clinical decision-making.

Based on our findings, we agree with the Dutch guideline 'Diagnostics of small-vessel vasculitis'¹⁴ that screening for renal involvement should include serum creatinine and urine analysis for both erythrocyturia and proteinuria, early in the diagnostic process. In addition, we found that a higher sensitivity for erythrocyturia is achieved if urine sediments are repeated up to three times. Urinary abnormalities in AAV with a preserved renal function require a renal biopsy in order to determine renal involvement. If a renal biopsy confirms renal involvement of AAV, aggressive immunosuppressive agents are indicated. Screening for renal involvement in the diagnostic process of AAV may serve two purposes. First, if erythrocyturia, proteinuria or a rise in serum creatinine are present, this may support the diagnosis of AAV. Second, if AAV is diagnosed based on other findings, screening for renal involvement establishes the extensiveness of the disease and may guide the choice of therapy.^{2,8,11} If AAV is suspected in patients outside the internal medicine/nephrology/rheumatology department, early consultation of a physician with expertise in the field of nephrology is suggested.

To our knowledge, this is the first study evaluating the adequacy and reproducibility of screening for renal involvement in AAV patients in clinical practice. Hence, it is unknown to what extent these results would apply to other centres. However, the presence of renal involvement in our population seems consistent with previous reports.^{3,4} Furthermore, the number of patients with biopsy proven renal vasculitis ($n = 31$) in our study was relatively low. However, previous studies found comparable laboratory findings preceding renal biopsy-proven AAV.^{21,22} In this study the median BVAS/WG was 5.0 (4-7) (mean 5.8 ± 2.8).

These results were slightly lower than in the Rituximab in ANCA-Associated Vasculitis (RAVE) trial (mean 8.5 ± 3.2) and in the Wegener's Granulomatosis Etanercept Trial (WGET) (mean 6.9 ± 3.4).^{23,24} These higher scores could be explained by study selection criteria in the RAVE trial: an indication for cyclophosphamide and BVAS/WG ≥ 3 . Furthermore, the slightly higher BVAS/WG in these trials may be due to the prospective collection of data. Although the historical patient files were of high quality, the retrospective design of our study may account for an information bias on documented symptoms and in some cases the exact date of the diagnosis.

In conclusion, in this cohort screening for renal involvement was performed within two weeks of the diagnosis in the majority of AAV patients. However, especially in patients with normal eGFR and a first presentation to other departments than the renal department, there may be room for improvement. These results suggest that a multi-disciplinary collaboration is warranted for an optimal diagnostic process. More awareness for the clinical features of renal involvement in AAV is a key element in the prevention of irreversible kidney damage.

DISCLOSURES

All authors declare no conflicts of interest.

REFERENCES

- Walton EW. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). *Br Med J*. 1958;2:265-70.
- Exley AR, Carruthers DM, Luqmani RA, et al. Damage occurs early in systemic vasculitis and is an index of outcome. *QJM*. 1997;90:391-9.
- De Jooode AA, Sanders JS, Stegeman CA. Renal survival in proteinase 3 and myeloperoxidase ANCA-associated systemic vasculitis. *Clin J Am Soc Nephrol*. 2013;8:1709-17.
- Bligny D, Mahr A, Toumelin PL, Mouthon L, Guillevin L. Predicting mortality in systemic Wegener's granulomatosis: a survival analysis based on 93 patients. *Arthritis Rheum*. 2001;51:83-91.
- Falk RJ, Jennette JC. ANCA small-vessel vasculitis. *J Am Soc Nephrol*. 1997;8:314-22.
- Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis*. 2009;68:310-7.
- Ntatsaki E, Carruthers D, Chakravarty K, et al. BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. *Rheumatology (Oxford)*. 2014;53:2306-9.
- Jayne DR, Gaskin G, Rasmussen N, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol*. 2007;18:2180-8.
- Stone JH, Hoffman GS, Merkel PA, et al. A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. International Network for the Study of the Systemic Vasculitides (INSSYS). *Arthritis Rheum*. 2001;44:912-20.
- Hruskova Z, Casian AL, Konopasek P, et al. Long-term outcome of severe alveolar haemorrhage in ANCA-associated vasculitis: a retrospective cohort study. *Scand J Rheumatol*. 2013;42:211-4.
- Hanaoka H, Ota Y, Takeuchi T, Kuwana M. Poor renal outcomes in patients with anti-neutrophil cytoplasmic antibody-associated crescentic glomerulonephritis and normal renal function at diagnosis. *Clin Rheumatol*. 2016;35:495-500.
- Gaffo AL. Diagnostic approach to ANCA-associated vasculitides. *Rheum Dis Clin North Am*. 2010;36:491-506.
- McAdoo SP, Tanna A, Randone O, et al. Necrotizing and crescentic glomerulonephritis presenting with preserved renal function in patients with underlying multisystem autoimmune disease: a retrospective case series. *Rheumatology (Oxford)*. 2015;54:1025-32.
- Thio HB, Balak DM, Meilof JF, Stegeman CA, Voskuyl AE. Guideline 'Diagnostics of small-vessel vasculitis'. *Ned Tijdschr Geneesk*. 2012;156:A4317.
- Watts R, Lane S, Hanslik T, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. *Ann Rheum Dis*. 2007;66:222-7.
- Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006;145:247-54.
- Exley AR, Bacon PA, Luqmani RA, et al. Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides. *Arthritis Rheum*. 1997;40:371-80.
- Mukhtyar C, Lee R, Brown D, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). *Ann Rheum Dis*. 2009;68:1827-32.
- Reinhold-Keller E, Beuge N, Latza U, et al. An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. *Arthritis Rheum*. 2000;43:1021-32.
- McGeoch L, Twilt M, Fomorca L, et al. CanVasc Recommendations for the Management of Antineutrophil Cytoplasm Antibody-associated Vasculitides. *J Rheumatol*. 2016;43:97-120.
- Cordova-Sanchez BM, Mejia-Vilet JM, Morales-Buenrostro LE, Loyola-Rodriguez G, Uribe-Urbe NO, Correa-Rotter R. Clinical presentation and outcome prediction of clinical, serological, and histopathological classification schemes in ANCA-associated vasculitis with renal involvement. *Clin Rheumatol*. 2016;35:1805-16.
- Van Paasen P, van Breda Vriesman PJ, van Rie H, Tervaert JW. Signs and symptoms of thin basement membrane nephropathy: a prospective regional study on primary glomerular disease-The Limburg Renal Registry. *Kidney Int*. 2004;66:909-13.
- Stone JH. Limited versus severe Wegener's granulomatosis: baseline data on patients in the Wegener's granulomatosis etanercept trial. *Arthritis Rheum*. 2003;48:2299-309.
- Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med*. 2010;363:221-32.