ANCA-associated vasculitis (AAV) is a group of diseases encompassing granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and Churg–Strauss disease (eosinophilic GPA). Patients often present with a rapidly progressive GN associated with focal necrotizing and crescentic lesions on renal biopsy and a lack of significant deposition of Igs in glomeruli (pauci-immune). Extrainflammatory, especially sino-pulmonary, and peripheral nervous system involvement may be present. Although AAV can occur in young patients, it is primarily a disease of older adults, with the peak age between 65 and 74 years old (1,2). In the very elderly (age >80 years old), AAV accounts for 19% of kidney biopsies performed and is the most common cause of biopsy-proven AKI in this population (3). The reasons for this older age of presentation remain unclear. One might have considered the senescent immune system to be less likely to promulgate an autoimmune disorder in the same way that acute transplant rejection is less common in older patients.

The clinical presentation in older patients (>65 years old) is similar to that in younger patients (<65 years old) with AAV, although certain features may be more common (1,4). In older patients, studies have noted that the clinical presentation is more consistent with MPA rather than GPA and that anti-myeloperoxidase (MPO-ANCA) is more common (1,4–6). Renal disease may be more prominent, with fewer systemic features (in particular, less upper respiratory tract involvement), although lung involvement is not uncommon. Older patients often have nonspecific symptoms, and diagnosis is often delayed, by which time there may be very significant and irreversible renal injury. The presence of myalgias and headaches may be misdiagnosed as polymyalgia rheumatica (4,7). Notably, AAV in the elderly occurs on a background of more comorbidities (e.g., cardiovascular disease, diabetes, and malignancy), and there may be substantial CKD at baseline. The true frequency of CKD in the elderly is debated, as is the presence of myalgias and headaches which may be misdiagnosed as polymyalgia rheumatica (4,7). Notably, AAV in the elderly occurs on a background of more comorbidities (e.g., cardiovascular disease, diabetes, and malignancy), and there may be substantial CKD at baseline. The true frequency of CKD in the elderly is debated, partly related to difficulties with definitions, but creatinine clearance decreases by approximately 0.75 ml/min per year over the age of 40 years old in a normal population (8). Immunosuppressive therapy has been described to be equally efficacious in attaining remission in older populations, and relapse rates are similar (1,4,10) or lower (5) (Table 1). Prior studies have confirmed that older age is a strong risk factor for death and ESRD (1,4,5,11); however, older patients are more prone to the adverse effects of immunosuppressive therapy (1,4). It should, of course, be recognized that the overall health status of individuals with the same chronological age can vary considerably.

Despite being predominantly a disease of the elderly, many studies of AAV have excluded patients >75 years old. Indeed, in two recent studies of rituximab therapy in AAV, the mean age was 54 ± 16.8 years old (RAVE), and the median age was 68 (range = 56–75) years old (RITUXVAS). In this issue of C JASN, Weiner et al. (6) describe a retrospective observational study of 151 consecutive patients ages 75 years old or older with AAV who presented to one of six centers in Sweden, the United Kingdom, and the Czech Republic. The median age was 79 years old (46% were older than 80 years old), and the majority had advanced renal disease (mean creatinine of 3.2 mg/dl), with 31% of subjects requiring dialysis. Compared with younger patients, comorbidities were more common, particularly diabetes (15%), malignancy (15%), hypertension (46%), heart failure (8%), and stroke (13%).

As noted in prior studies of older patients, MPO-ANCA was more common (60%) than anti-proteinase 3 (PR3)-ANCA (39%), and the majority of subjects had a clinical pattern consistent with MPA (70%) according to the European Medicines Agency algorithm (12). AAV is more commonly classified according to the revised 2012 Chapel Hill criteria (13), but it should be recognized that there is substantial overlap in the phenotypes of MPA and GPA and that it is often difficult to confidently ascribe one of these diagnoses to an individual patient (14). We should also recognize that MPO-ANCA and PR3-ANCA are biomarkers that do not stratify perfectly with MPA and GPA (for example, GPA is anti-MPO positive in approximately 10% of patients) and that the clinical features associated with the presence of each of these antibodies are quite variable (15). Genetic susceptibility to AAV has been identified in two large genome wide association studies (GWAS) performed in cohorts from the United Kingdom (16) and North America (17). The United Kingdom study identified the strongest association of PR3-ANCA disease with variants in the MHC region HLA-DR and the genes SERPINA1 (encodes α1-antitrypsin) and PRTN3 (encodes proteinase 3) loci. MPO-ANCA disease was associated...
with the HLA-DQ locus. Notably, these associations were stronger for the antigenic specificity of the ANCA (PR3 versus MPO) than with the clinical syndrome (GPA versus MPA). Given the significant overlap in clinical presentations and prognosis and the separate genetic associations, consideration is being given to reclassifying AAV according to the type of antibody specificity (MPO versus PR3) rather than the traditional clinical phenotype (MPO versus GPA). A new endeavor, the Diagnostic and Classification Criteria for Vasculitis Study (DCVAS), aims to collect and analyze 2000 patients with primary systemic vasculitis and provide criteria of vasculitis validated in different populations (18).

The study by Weiner et al. (6) addresses the safety and potential benefits of immunosuppressive therapy for AAV in older patients. The overall 1- and 2-year survival rates were 71.5% and 64.6%, respectively, showing that most deaths occur within the first 1 year. It was noted that subjects in the Swedish cohort who survived to the second year had a similar death rate as the general age-matched population. As in previous studies, age and GFR were the strongest predictors of survival; however, the cause of death was not clearly defined. Studies from the European Vasculitis Study Group showed a 1-year mortality of 11.1% (in all age groups), which was attributed to active vasculitis in only 19% of patients but caused by adverse events from therapy in 59% of patients (11).

Subjects (n=102) who were treated with standard immunosuppressive regimens (oral or intravenous cyclophosphamide or intravenous rituximab) had a significantly better survival than those (n=28) who were treated with nonstandard or no immunosuppressive regimens. There were no obvious differences between these two groups in terms of age, renal function, or comorbidities, although, as discussed by Weiner et al. (6), it is very difficult to retrospectively compare these two heterogeneous groups because of the risk of confounding by indication (i.e., sicker or more frail patients may have been selected to receive nonstandard or no immunosuppressive therapy because of concerns over the risk of adverse events from therapy).

Similar findings to this study have been noted in the work by Bomback et al. (5), which described outcomes in a very elderly population (>80 years old) (6); 78 subjects were studied, of whom 72% were anti-MPO positive, and all had severe renal impairment (mean baseline creatinine = 4.3 mg/dl). The majority (n=50) was treated with immunosuppression (mostly steroids and either oral or intravenous cyclophosphamide). In the treated group, disease remission was achieved in 49%, although mortality was high (1-year survival was 53%), 36.2% reached ESRD at 1 year, and infectious complications were common (38%). Notably, relapse rates were low (4%); this was partly explained by the higher rate of MPO-ANCA–associated disease, which may permit a lower-dose maintenance therapy. The French MAINRITSAN Study (n=115) recently compared rituximab with azathioprine in patients with AAV who received induction therapy with pulse intravenous cyclophosphamide (19). The rate of relapse at 28 months was significantly better in the rituximab group (5%) versus the azathioprine group (29%) with similar adverse events.

What clinical lessons can we glean from these studies of AAV in older patients? There is a high death rate in the first 1 year of therapy, particularly in the first 3 months, with the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Harper and Savage (1)</th>
<th>Pagnoux et al. (9)</th>
<th>Chen et al. (4)</th>
<th>Bomback et al. (5)</th>
<th>Haris et al. (10)</th>
<th>Weiner et al. (6)</th>
</tr>
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<tbody>
<tr>
<td>Country</td>
<td>United Kingdom</td>
<td>United States</td>
<td>China</td>
<td>United States</td>
<td>Hungary</td>
<td>Europe</td>
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<td>No.</td>
<td>114</td>
<td>22</td>
<td>99</td>
<td>50</td>
<td>43</td>
<td>151</td>
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<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>&gt;65</td>
<td>&gt;75</td>
<td>&gt;65</td>
<td>≥80</td>
<td>&gt;65</td>
<td>&gt;75</td>
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<tr>
<td>Inclusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>70 (65–90)</td>
<td>78±3</td>
<td>72±5.6</td>
<td>83±2.7</td>
<td>72±6</td>
<td>79 (77–82)</td>
</tr>
<tr>
<td>Creatinine (mean), mg/dl</td>
<td>7.5</td>
<td>2.4</td>
<td>4.5</td>
<td>4.5</td>
<td>6.7</td>
<td>3.2</td>
</tr>
<tr>
<td>Proteinuria, g/24 h</td>
<td>—</td>
<td>—</td>
<td>1.67</td>
<td>1.5</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>GPA/MPA (%)</td>
<td>32/68</td>
<td>55/45</td>
<td>18/79</td>
<td>—</td>
<td>—</td>
<td>30/70</td>
</tr>
<tr>
<td>MPO/pANCA (%)</td>
<td>More common</td>
<td>—</td>
<td>—</td>
<td>94</td>
<td>68</td>
<td>63</td>
</tr>
<tr>
<td>PR3/cANCA (%)</td>
<td>Less common</td>
<td>—</td>
<td>5</td>
<td>21</td>
<td>24</td>
<td>36</td>
</tr>
<tr>
<td>Outcomes (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death (1 yr)</td>
<td>29</td>
<td>32</td>
<td>—</td>
<td>47</td>
<td>39</td>
<td>29</td>
</tr>
<tr>
<td>Death (2 yr)</td>
<td>—</td>
<td>36</td>
<td>48</td>
<td>56</td>
<td>—</td>
<td>35</td>
</tr>
<tr>
<td>ESRD* (1 yr)</td>
<td>30</td>
<td>—</td>
<td>31</td>
<td>36</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>Remission*</td>
<td>94</td>
<td>—</td>
<td>76</td>
<td>49</td>
<td>78</td>
<td>—</td>
</tr>
<tr>
<td>Relapse</td>
<td>26</td>
<td>—</td>
<td>15</td>
<td>4.3</td>
<td>19</td>
<td>—</td>
</tr>
<tr>
<td>Infection</td>
<td>40</td>
<td>—</td>
<td>—</td>
<td>38</td>
<td>39</td>
<td>—</td>
</tr>
</tbody>
</table>

Only data from elderly patients who were treated with immunosuppression are included. BVAS, Birmingham vasculitis score; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; pANCA, perinuclear ANCA; PR3, proteinase-3; cANCA, cytoplasmic ANCA.

*Surviving patients.
may further reduce these risks. Laxative, and appropriate modi-
tional support to the idea that selected elderly patients can
rates may be lower in the very elderly (5).
neutrophil cytoplasmic autoantibody vasculitides: The role of
for myeloperoxidase or proteinase 3 in disease recognition and
to optimize immunosuppressive therapy for AAV, despite the
higher risk of adverse effects from these medications in
this population. Careful attention to monitoring, prophyl-
axis, and appropriate modification of the treatment regime
may further reduce these risks.

Disclosures
None.

References
the end of the twentieth century—a disease of older patients.
Rheumatology (Oxford) 44: 495–501, 2005
2. Watts RA, Lane SE, Bentham G, Scott DG: Epidemiology of sys-
temic vasculitis: A ten-year study in the United Kingdom.
B, Radhakrishnan J, D’Agati VD: Renal biopsy in the very elderly.
autoantibody-associated vasculitis in older patients. Medicine
(Baltimore) 87: 203–209, 2008
LC, Stokes B, D’Agati VD, Markowitz GS: ANCA-associated
glomerulonephritis in the very elderly. Kidney Int 79: 757–764,
2011
CD, Tesar V, Salama AD, Segelmark M: Outcome and treatment
of elderly patients with ANCA-associated vasculitis. Clin J Am
7. Little MA, Nazar I, Farrington K: Polymyalgia rheumatica
preceding small-vessel vasculitis: Changed spots or misdiagnosis?
QJM 97: 289–292, 2004
8. Lindeman RD, Tobi JD, Shock NW: Association between blood
pressure and the rate of decline in renal function with age. Kidney
Int 26: 861–868, 1984
Nachman PH: Predictors of treatment resistance and relapse in
antineutrophil cytoplasmic antibody-associated small- vessel
vasculitis: Comparison of two independent cohorts. Arthritis
Rheum 58: 2908–2918, 2008
10. Haris Å, Polner K, Aråny J, Brunzitter H, Kaszás I, Mucsi I:
Clinical outcomes of ANCA-associated vasculitis in elderly
11. Little MA, Nightingale P, Verbrugh CA, Hauser T, De Groot K,
Savage C, Jayne D, Harper L: European Vasculitis Study (EUVAS)
Group: Early mortality in systemic vasculitis: Relative contribu-
tion of adverse events and active vasculitis. Ann Rheum Dis 69:
1036–1043, 2010
12. Watts RA, Lane S, Hansklik T, Hauser T, Hellmich B, Koldingnes W,
Mahr A, Segelmark M, Cohen-Tervaert JW, Scott D: De-
velopment and validation of a consensus methodology for the
classification of the ANCA-associated vasculitides and poly-
arteritis nodosa for epidemiological studies. Ann Rheum Dis 66:
222–227, 2007
13. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, Flores-
Suarez LF, Gross WL, Guillemin L, Hagen EC, Hoffman GS, Jayne
DR, Kallenberg CG, Lamprecht P, Langford CA, Luqmani RA,
Mahr AD, Matteson EL, Mearkel PA, Ozen S, Pusey CD,
K, Watts RA: 2012 Revised International Chapel Hill Consensus
Conference Nomenclature of Vasculitides. Arthritis Rheum 65:
1–11, 2013
Mearkel PA, Pagnoux C, Rasmussen N, Westman K, Jayne DR;
French Vasculitis Study Group (FVSG) and the European Vascu-
litis Society (EUVAS): Revisiting the classification of clinical
phenotypes of anti-neutrophil cytoplasmic antibody-associated
vasculitis: A cluster analysis. Ann Rheum Dis 72: 1003–1010,
2013
15. Lionaki S, Blyth ER, Hogan SL, Hu Y, Senior BA, Jennette CE,
Nachman PH, Jennette JC, Falk RJ: Classification of anti-
neutrophil cytoplasmic autoantibody vasculitides: The role of
antineutrophil cytoplasmic autoantibody specificity for myelo-
peroxidase or proteinase 3 in disease recognition and
16. Lyons PA, Rayner TE, Trivedi S, Holle JU, Watts RA, Jayne DR,
Baslund B, Brechley P, Bruchfeld A, Chaudhry AN, Cohen-
Tervaert JW, Deloukas P, Feighery C, Gross WL, Guillemin L,
Gunnarsson I, Harper L, Hrušková Z, Little MA, Martorana D,
Neumann Th, Olssohn S, Padmanabhan S, Pusey CD, Salama
AD, Sanders JS, Savage CO, Segelmark M, Stegeman CA, Tézary
V, Vagnlo A, Wieczorek S, Wilde B, Zwerina J, Rees AJ,
Clayton DG, Smith KG: Genetically distinct subsets within
17. Xie G, Roshandel D, Sherva R, Monach PA, Lu EY, Kung T,
Carrington K, Zhang SS, Pullit SL, Ripke S, Careette S, Dellaripa PF,
Edberg JC, Hoffman GS, Khalidi N, Langford CA, Mahr AD, St
Clair EW, Rees AJ, Farrington K, Chi, Amos CI, Mearkel PA,
Siminovitch KA: Association of granulomatosis with polyangiitis
(Wegener’s) with HLA-DPB1*04 and SELEMAA gene variants:
2468, 2013
18. Craven A, Robson J, Ponte C, Grayson PC, Suppiah R, Judge
A, Watts R, Merkel PA, Luqmani RA: ACR/EULAR-endorsed study
to develop Diagnostic and Classification Criteria for Vasculitis
Cohen P, Maurier F, Decaux O, Ninet J, Gobert P, Quéméneur T,
Blanchard-Delaunay C, Godmer P, Puech X, Carron PL,
Hatron PY, Limal N, Hamidou M, Ducret M, Daugas E, Papo T,
Bonnotte B, Mahr A, Ravaud P, Mouthon L: French Vasculitis
Study Group: Rituximab versus azathioprine for maintenance in
2014
CA, Savage CO, Segelmark M, Tesar V, van Paassen P, Walsh D,
Walsh M, Westman K, Jayne DR; European Vasculitis Study
Group: Rituximab versus cyclophosphamide in ANCA-
Kallenberg CG, St Clair EW, Turkiewicz A, Tchao NK, Weber B,
Ding L, Seijmsmundo LP, Mieras K, Weißenkamp D, Ikle D,
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