

# Predictors of Relapse and Treatment Resistance in Antineutrophil Cytoplasmic Antibody–Associated Small-Vessel Vasculitis

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**Background:** Predictors of treatment resistance and relapse have not been well described in antineutrophil cytoplasmic antibody (ANCA)–associated small-vessel vasculitis.

**Objective:** To identify clinical, pathologic, and serologic predictors of treatment resistance and relapse in a community-based cohort of patients with ANCA-associated vasculitis.

**Design:** Cohort of patients identified at or near the time of biopsy diagnosis and followed as clinically indicated.

**Setting:** The Glomerular Disease Collaborative Network.

**Patients:** 350 patients who received a new diagnosis of ANCA-associated vasculitis between 1985 and 2003 and were followed for a median of 49 months.

**Measurements:** Patients were categorized according to whether they had antiproteinase-3 (anti-PR3) antibodies or antimyeloperoxidase (anti-MPO) antibodies. Organ involvement was determined by biopsy or by well-defined clinical criteria. Treatment resistance was defined as progressive decline in kidney function with active urine sediment or the persistence or appearance of extrarenal manifestations. Relapse was defined as the time to the resurgence of vasculitic symptoms.

**Results:** Treatment resistance affected 23% of 334 treated patients and was associated with female sex, black ethnicity, and presentation with severe kidney disease (odds ratio per serum

creatinine elevation of 100  $\mu\text{mol/L}$  [1.13 mg/dL, 1.28 [95% CI, 1.16 to 1.39]). The following factors were associated with relapse in 258 (77%) patients who attained remission: seropositivity for anti-PR3 antibodies (hazard ratio, 1.87 [CI, 1.11 to 3.14]) and disease of the lung (hazard ratio, 1.71 [CI, 1.04 to 2.81]) or upper respiratory tract (hazard ratio, 1.73 [CI, 1.04 to 2.88]). Relapses occurred in 26% of patients with no risk factors versus 73% of patients with all 3 risk factors (hazard ratio, 3.7 [CI, 1.4 to 9.7]). Among 143 patients attaining remission who subsequently stopped all immunosuppressant therapy, relapse rates were similar for those who had received cyclophosphamide therapy for 6 months or less (34%) compared with those treated for a longer duration (35%), even after adjusting for risk factors for relapse (hazard ratio, 1.41 [CI, 0.80 to 2.50]).

**Limitations:** The cohort mostly included patients with biopsy-proven kidney disease. Patients were not followed with uniform treatment protocols, and only limited information about their clinical course before diagnosis was available.

**Conclusions:** Female or black patients, or those with severe kidney disease, may be resistant to initial treatment more often than other patients with ANCA-associated small-vessel vasculitis. Increased risk for relapse appears to be related to the presence of lung or upper airway disease and anti-PR3 antibody seropositivity.

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Antineutrophil cytoplasmic antibody (ANCA)–associated small-vessel vasculitis includes microscopic polyangiitis, Wegener granulomatosis, the Churg–Strauss syndrome, and renal-limited vasculitis (ANCA-associated glomerulonephritis) (1, 2). The cornerstone of treatment for ANCA-associated vasculitis includes induction therapy with pulse corticosteroids and the prompt institution of daily oral glucocorticoids and cyclophosphamide (3–6). Approximately 85% of patients achieve remission with this therapy (5), but 11% to 57% of patients have a relapse (7–11). Some relapses are severe, resulting in worsening end-organ damage. Most relapses respond to therapy, but patients are subjected to additional immunosuppressive or cytotoxic drugs. Fear of relapsing disease has impelled physicians to prescribe prolonged maintenance therapies in most patients. Because 43% to 89% of patients may never have a disease relapse (7–11), use of long-term immunomodulating therapy often presents unnecessary risks and may well outweigh the benefits of preventing relapse. Little is known regarding predictors for relapse; identification of these risk factors would conceivably allow maintenance immunomodulatory therapy to be tailored to patients at high risk while sparing others unnecessary exposure to these drugs.

Over the course of almost 2 decades, we recruited a large cohort of patients with ANCA-associated glomerulonephritis and vasculitis. From this sample, we sought to ascertain the following: Which patients were more likely to be resistant to treatment; which patients were more likely to progress to end-stage kidney disease; the potential to determine which patients were more likely to relapse; the impact of relapse on long-term outcome; the correlation between length of immunosuppressive therapy and the

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**Context**

Patients with antineutrophil cytoplasmic autoantibody (ANCA)-associated small-vessel vasculitis sometimes experience relapses and resistance to glucocorticoid and cyclophosphamide treatment.

**Contribution**

This study followed 350 patients with ANCA-associated vasculitis for a median of 49 months. Of 258 patients attaining remission, 109 (42%) relapsed. Upper or lower respiratory tract disease and proteinase-3 ANCA seropositivity were associated with increased risk for relapse. Of 334 treated patients, 77 (23%) had progressive disease despite treatment. Severe kidney disease, black ethnicity, and female sex were associated with an increased risk for treatment resistance.

**Cautions**

The participants were primarily selected on the basis of their condition being identified by renal biopsy.

—The Editors

likelihood of relapse; and the viability of discontinuing immunosuppressive therapy in patients who have attained remission.

**METHODS****Patient Sample and Definitions**

Patients were eligible for this study if they had biopsy-proven vasculitis (diagnosed between 1985 and 2003) with positive ANCA determination by immunofluorescence microscopy or antigen-specific enzyme-linked immunosorbent assay (12); the patients were also required to be followed by physicians of the Glomerular Disease Collaborative Network (GDCN). The GDCN and a subset of the cohort were previously described elsewhere (4, 7), but the cohort was expanded to evaluate predictors of relapse. We used the University of North Carolina (UNC) Nephropathology Laboratory, which evaluates more than 1500 renal biopsies each year, to recruit participants for the GDCN's registry of patients with ANCA-associated vasculitis. All patients with a native kidney biopsy diagnosis of pauci-immune necrotizing and crescentic glomerulonephritis with or without granulomatous inflammation were eligible to enroll in the registry ( $n = 639$ ). Patients were invited to give informed consent to participate through their treating nephrologist. We then collected medical records dating back to the initial diagnosis of ANCA-associated vasculitis. A total of 307 patients (48% of eligible participants) with a biopsy-proven diagnosis were enrolled in this study. An additional 59 (9%) patients signed consent to participate but were deemed ineligible because of negative ANCA test results or overlapping disease. Another 43 patients who had not undergone renal biopsy were re-

cruited through the multidisciplinary UNC Vasculitis Clinic and through other GDCN nephrologists who work in collaboration with other medical specialists to care for patients with ANCA-associated vasculitis. Estimates of potentially eligible patients without a kidney biopsy-proven diagnosis were not available because no centralized service exists to evaluate nonrenal biopsy tissue. Initial biopsy diagnosis, whatever the organ, was used as each patient's start date in the registry. Detailed information on duration of symptoms before biopsy diagnosis was not always described in medical records and therefore was not available for analysis in this study. The Committee on the Protection of Human Subjects at UNC approved this study.

Patients in the cohort received clinically indicated care from their primary nephrologists, who were affiliated with 63 different GDCN private practice offices (1 to 12 nephrologists per office) and 5 academic medical centers, including UNC. Therapeutic interventions and frequency of clinical evaluations were not determined by protocol. Physicians were instructed to update GDCN records for patients on a yearly basis; follow-up calls and written reminders were provided if information was not received. Consequently, patient follow-up did not vary substantially across clinics.

Patients were categorized as having cytoplasmic ANCA, antiproteinase-3 (anti-PR3) ANCA, or both, or perinuclear ANCA, anti-myeloperoxidase (anti-MPO) ANCA, or both. Patients having only perinuclear ANCA were required to have a negative antinuclear antibody test. Categories of ANCA-associated vasculitis included Wegener granulomatosis, microscopic polyangiitis, and renal-limited disease (1, 2). The single patient with the Churg-Strauss syndrome was included with the microscopic polyangiitis group. Organ involvement was determined by biopsy or by previously described criteria (4, 7). For example, lung involvement was considered likely in the presence of hemoptysis; pulmonary hemorrhage; respiratory failure; or radiographic proof of infiltrates, nodules, or cavities without evidence of infection. Upper respiratory tract disease was considered likely with clinical or radiographic studies revealing sinusitis, otitis media, nasal crusting, or subglottic disease.

Treatment categories were determined by the first therapy regimen used at diagnosis (corticosteroids alone or in combination with cyclophosphamide, as previously described) (3). In brief, induction therapy was typically initiated with 3 daily pulses of methylprednisolone (7 mg/kg of body weight per day) followed by daily oral prednisone. Prednisone therapy was started at a dose of 1 mg/kg per day for the first month and was tapered over 3 to 4 months. Cyclophosphamide was administered by intravenous pulse (0.5 to 1 g/m<sup>2</sup> per month) or orally (1 to 2 mg/kg per day). Other immunosuppressive regimens included azathioprine, mycophenolate mofetil, and cyclosporine, usually after completion of induction therapy. The duration of therapy with various immunosuppressive med-

ications was recorded. Patients were considered to be treated if they received any immunosuppressive therapy, regardless of duration.

Medical records were reviewed on an ongoing basis. Drs. Falk and Nachman determined the outcomes, which included treatment resistance, remission while receiving therapy, remission without therapy, relapse, and end-stage kidney disease (4, 7). Treatment resistance was defined as progressive decline in kidney function with persistence of active urine sediment, or new or persisting extrarenal manifestations of vasculitis despite immunosuppressive therapy. Resistance to therapy was determined at least 1 month after the start of treatment. Remission was defined as stabilization or improvement of kidney function as measured by serum creatinine levels and resolution of hematuria and other manifestations of systemic vasculitis for more than 1 month. Remission without therapy was defined as remission while receiving only 7.5 mg of corticosteroids per day or less. Relapse could only occur in patients who reached remission (with or without therapy). Relapse was defined as vasculitic signs or symptoms in any organ system, as previously described (4, 7).

Histopathologic renal evaluations included assessment of disease activity, chronicity, and vascular sclerosis. Scores ranging from 0 to 4 were used to designate degrees of glomerular necrosis, cellular crescents, neutrophil infiltration, capillary wall thickening, glomerular hypercellularity, and interstitial leukocytes; the sum of these scores was used to grade overall renal activity (range, 0 to 24). Chronicity was quantified by the sum of the scores (0 to 4 for each) for glomerular sclerosis, fibrotic crescents, interstitial fibrosis, and tubular atrophy (range, 0 to 16). Vascular sclerosis was scored from 0 to 4.

The 4-variable Modification of Diet in Renal Disease equation (13, 14) was used to estimate glomerular filtration rate (GFR). Improvement or decline in GFR of 8 mL/min or more over 4 months was considered a clinically significant change in renal function.

### Statistical Analyses

Logistic regression was used to assess factors associated with treatment resistance. A time-to-event analysis was not used because actual time to resistance is not known and because outcomes occurred within a short time. Results were expressed as odds ratios with 95% CIs.

Kaplan–Meier estimators were used to estimate median survival times and probability of survival without end-stage kidney disease (15, 16). Cause-specific proportional hazards models were used to study, as competing risks, the 2 mutually exclusive outcomes of time to relapse (active disease outcome) and time to end-stage kidney disease without evidence of a relapse (chronic disease outcome) (15–17). Patients who had end-stage kidney disease or died at the time of an active relapse were placed into the former group. Patients were censored if they had not reached either outcome at their last follow-up. Patients who died

without evidence of disease activity were censored on the dates of their deaths. Cumulative incidence curves for relapse were used in a competing risk setting (with end-stage kidney disease without relapse as a competing event) to calculate the probability of relapse-free survival (15–18). To control for the wide variation in time to relapse, Cox regression models with time-dependent covariates were used to evaluate the impact of relapse on all-cause mortality and on end-stage kidney disease (15, 16). Assessment of model fit was done by plotting Martingale residuals (19). The proportional hazards assumption for all models was assessed by examining plots of  $-\log S(t)$  and Schoenfeld residuals (19, 20). Results were expressed as hazard ratios with 95% CIs.

Demographic characteristics and other variables to be assessed as potential predictors of treatment resistance, relapse, and end-stage kidney disease were determined before the study and are shown in **Table 1**. Selection of multivariable models was an iterative process that first included backward selection of variables that were statistically significant at an  $\alpha$  level of 0.05. These measures were retained in the model; each additional measure of interest was added to the model one at a time and was retained if the measure changed the outcome by 20% or more compared with the univariate impact of that measure. Models that controlled for serum creatinine did not control for renal biopsy variables, whereas models controlling for renal biopsy variables did not control for serum creatinine and only included patients who underwent a renal biopsy.

Missing data were uncommon. The 2 most common variables with missing values were serum creatinine at diagnosis (10 patients) and the renal biopsy variables (43 patients did not undergo renal biopsy and 2 were not measured by the pathologist). Because few data were missing, the effect measures were estimated from models that used the complete data.

The impact of treatment with or without cyclophosphamide was evaluated with respect to treatment resistance because some patients were treated with corticosteroids alone (4, 7). All models controlled for treatment. Effects associated with a *P* value of 0.05 or less were considered of interest. We performed data analyses using SAS statistical software, version 8.2 (SAS Institute, Inc., Cary, North Carolina).

### Role of the Funding Source

This study was supported in part by a grant from the National Institutes of Health, National Institute of Diabetes & Digestive & Kidney Diseases (P01-DK58335). Funding provided support for ongoing recruitment, sample acquisition, and follow-up of patients with ANCA-associated vasculitis for several research projects. The source of funding did not play a role in the design or interpretation of the results. All authors had unrestricted access to the data files for the study.

Table 1. Characteristics of the Total Cohort and Subgroups by Outcome

Characteristic	Total Cohort	Response among Treated Patients (n = 334)		Outcomes among Treatment-Responsive Patients (n = 258)		
		Treatment Resistant	Treatment Responsive	Relapse	Continued Remission	End-Stage Kidney Disease without Relapse
<b>Demographic</b>						
Patients, n	350	76	258	109	121	28
Mean age (SD), y	58 (18)	63 (17)	56 (18)	53 (17)	59 (18)	58 (20)
Men, n (%)	184 (53)	34 (45)	142 (55)	58 (53)	69 (57)	15 (54)
Black ethnicity, n (%)	33 (9)	13 (17)	17 (7)	8 (7)	6 (5)	3 (1)
Antiproteinase-3 seropositive, n (%)*	142 (41)	17 (22)	120 (47)	63 (58)	46 (38)	11 (39)
<b>Median follow-up, mo</b>	<b>49</b>	<b>2</b>	<b>45</b>	<b>44</b>	<b>45</b>	<b>106</b>
<b>Diagnosis category</b>						
Wegener granulomatosis, n (%)	59 (17)	6 (8)	53 (20)	33 (30)	16 (13)	4 (14)
Microscopic polyangiitis, n (%)	202 (58)	42 (55)	151 (59)	65 (60)	70 (58)	16 (57)
Kidney-limited, n (%)	89 (25)	28 (37)	54 (21)	11 (10)	35 (29)	8 (29)
<b>Organ involvement</b>						
Kidney, n (%)	307 (88)	66 (87)	226 (88)	89 (82)	109 (90)	28 (100)
Pulmonary, n (%)	172 (49)	35 (46)	131 (51)	69 (63)	47 (39)	15 (54)
Upper respiratory, n (%)	109 (31)	13 (17)	93 (36)	53 (49)	32 (26)	8 (29)
Skin, n (%)	88 (25)	14 (18)	73 (28)	41 (38)	29 (24)	3 (11)
<b>Serum creatinine level (SD)†</b>						
$\mu\text{mol/L}$	422 (324)	590 (344)	353 (282)	323 (271)	330 (245)	568 (375)
mg/dL	4.8 (3.7)	6.7 (3.9)	4.0 (3.2)	3.7 (3.1)	3.7 (2.8)	6.4 (4.2)
<b>Median serum creatinine level, <math>\mu\text{mol/L}</math> (mg/dL)</b>	<b>327 (3.7)</b>	<b>495 (5.6)</b>	<b>283 (3.2)</b>	<b>261 (3.0)</b>	<b>265 (3.0)</b>	<b>508 (5.7)</b>
<b>Renal biopsy measures (SD)</b>						
Chronicity score‡	5.0 (3.8)	6.2 (4.1)	4.6 (3.6)	3.9 (3.7)	4.6 (3.3)	6.8 (3.4)
Activity score§	5.2 (3.6)	5.8 (3.7)	5.0 (3.6)	4.5 (3.7)	5.0 (3.4)	7.1 (3.4)
Vascular sclerosis score	1.4 (1.0)	1.8 (0.9)	1.3 (1.0)	1.2 (1.0)	1.3 (1.0)	1.7 (1.1)

\* Includes all patients with cytoplasmic antineutrophil cytoplasmic antibodies, antiproteinase-3 antibodies, or both; all who were not in this category had perinuclear antineutrophil cytoplasmic antibodies, antimyeloperoxidase antibodies, or both.

† Peak serum creatinine level at diagnosis.

‡ Scores range from 0 to 16.

§ Scores range from 0 to 24.

|| Scores range from 0 to 4.

## RESULTS

### Cohort Description and Outcomes

During the trial, 350 patients were followed prospectively until censorship, death, or onset of end-stage kidney disease. Cohort characteristics are shown in Table 1. Ages ranged from 2 to 92 years (mean, 58 years). The sample was 53% male; 90% were white, 9% were black, and 1% were of other ethnic backgrounds. The demographics of the cohort were similar to those of the 639 patients originally invited to participate in the registry (mean age, 58 years; 52% male; 79% white, 12% black, and 1% of other ethnic backgrounds [8% with no reported ethnicity]). Of the 350 participants, 307 (88%) had biopsy-proven kidney involvement. The lungs, upper respiratory tract, and skin were other commonly affected organs. Fifty-nine patients (17%) had Wegener granulomatosis, 202 had microscopic polyangiitis (58%), and 89 (25%) had renal-limited disease. Anti-PR3 antibodies were present in 142 (41%) patients, and anti-MPO antibodies were detected in 208 (59%) patients. The median length of follow-up was 49

months and ranged from under 1 month (for those who presented with end-stage kidney disease or who died of disease complications) to 18 years.

Of the total cohort, 16 (5%) with advanced renal disease at diagnosis elected not to be treated with immunosuppressants (Figure 1). Among the 334 patients treated, 46 (14%) received corticosteroids alone and 288 (86%) received corticosteroids and concomitant immunosuppressive therapy with intravenous ( $n = 161$ ) or oral ( $n = 112$ ) cyclophosphamide. Fifteen patients were treated with other agents, including azathioprine and mycophenolate mofetil. Twenty-seven patients with pulmonary hemorrhage underwent plasmapheresis in conjunction with cyclophosphamide therapy.

Among those treated, 258 (77%) patients responded to initial therapy, whereas 76 (23%) were resistant (Figure 1). Among those who responded, 91 (35%) patients were in remission while receiving therapy and 167 (65%) achieved a sustained remission after cessation of therapy. Of the 258 patients who attained a remission, 109 (42%)

relapsed over a median of 44 months (median time to relapse among those who relapsed was 16 months) from the time therapy was initiated. Of the 167 patients who maintained remission after therapy, 63 relapsed; of the 91 who attained remission while receiving therapy, 46 relapsed. Throughout follow-up, 149 (58%) patients remained in remission for a median of 106 months (45 [30%] while still receiving therapy and 104 [70%] after therapy was discontinued).

### Predictors of Treatment Resistance

Of the 76 treatment-resistant patients, 60 developed end-stage kidney disease in a median of 2 months after starting therapy (Figure 2), 12 died of disease- or therapy-related complications in a median of 1 month, and 4 had continued disease symptoms during the first course of therapy. As previously reported (4, 7), cyclophosphamide therapy conferred a lower risk for treatment resistance compared with glucocorticoids alone. The adjusted odds ratio for resistance among cyclophosphamide recipients was 0.43 (CI, 0.25 to 0.74;  $P = 0.002$ ) compared with patients receiving corticosteroids alone, independent of age, sex, ethnicity, ANCA specificity, and renal function.

Female sex and black ethnicity were predictors of

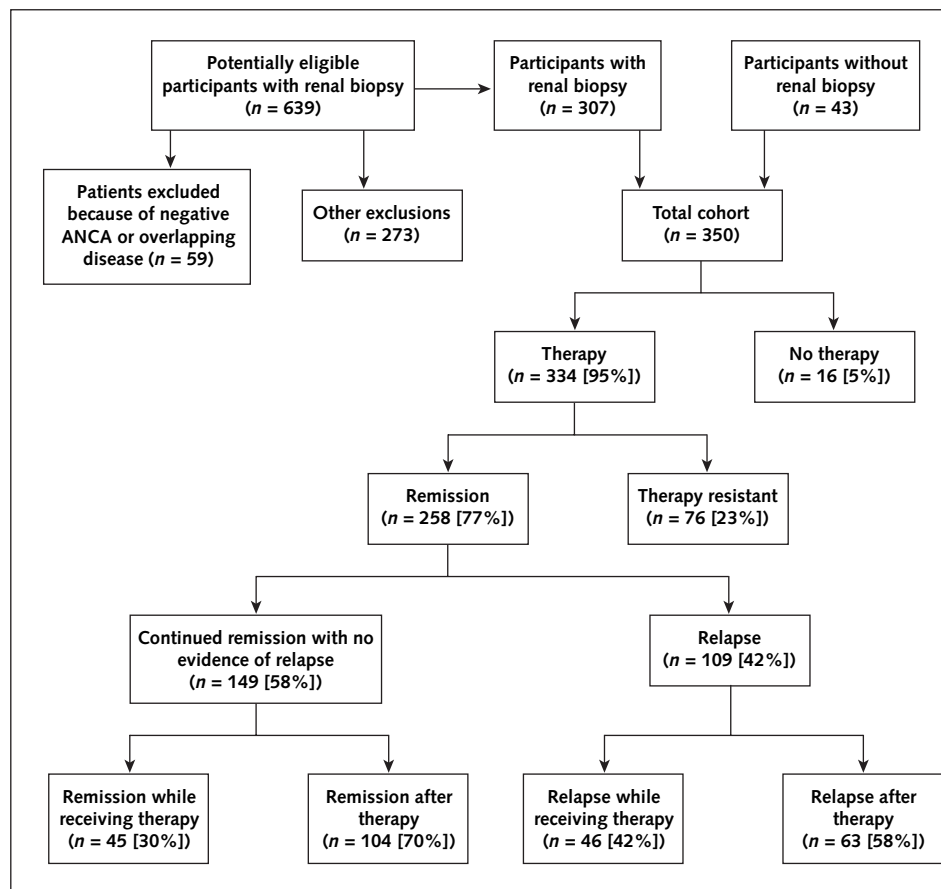
treatment resistance (Table 2). Advanced age also tended to be associated with resistance. Those patients with anti-PR3 antibodies were less likely to be treatment resistant, whereas specific diagnosis or organ involvement did not show evidence of influencing the risk for resistance.

For each serum creatinine elevation of 100  $\mu\text{mol/L}$  (1.13 mg/dL), risk for resistance increased by 1.28 (CI, 1.16 to 1.39;  $P < 0.001$ ) (Table 2). Renal biopsy findings with higher chronicity and vascular sclerosis scores were also associated with treatment resistance. Treatment-resistant patients had a higher mean serum creatinine level than that of patients who responded to treatment (590  $\mu\text{mol/L}$  [6.7 mg/dL] vs. 353  $\mu\text{mol/L}$  [4.0 mg/dL]); however, treatment was not futile regardless of the degree of renal dysfunction. Remission occurred in 172 of 240 (72%) patients with a GFR of 30 mL/min or less, in 128 of 188 (68%) patients with a GFR of 20 mL/min or less, and 55 of 96 (57%) patients with a GFR of 10 mL/min or less.

### Predictors of End-Stage Kidney Disease after Initial Response to Treatment

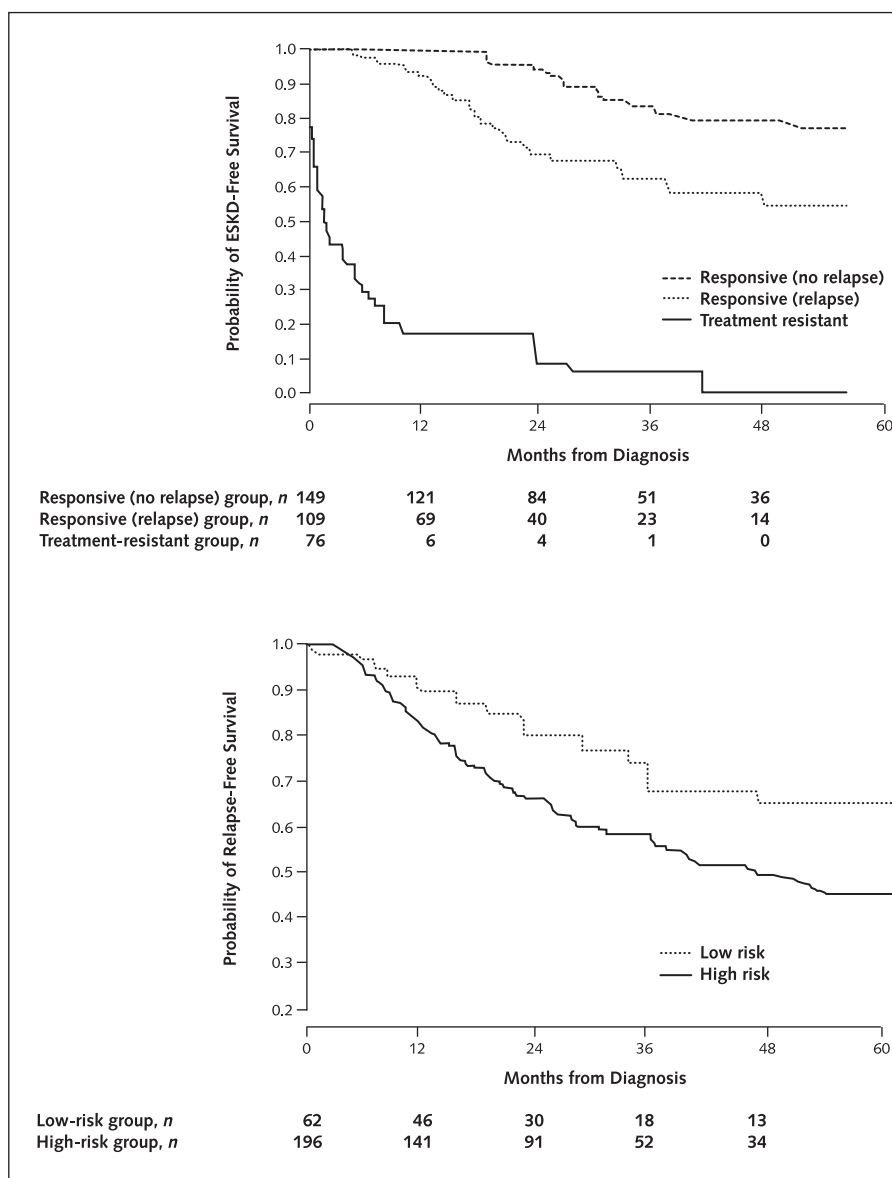
Among patients who responded to treatment, 28 patients progressed to end-stage kidney disease in a median of

Figure 1. Flow diagram of the study cohort.



ANCA = antineutrophil cytoplasmic antibody.

Figure 2. Probabilities of survival without end-stage kidney disease (ESKD) among treatment-resistant and treatment-responsive patients who did and did not relapse (top) and probability of relapse-free survival by risk group (bottom).



The high-risk group included patients with 1 or more of the 3 risk factors for relapse (anti-proteinase-3 [anti-PR3] antibodies, lung involvement, upper respiratory disease involvement). The low-risk group included patients with none of these 3 risk factors. The numbers represent the number of patients being followed in each subgroup at the beginning of the study and at 12, 24, 36, and 48 months.

more than 106 months without having a relapse (Table 1). These patients presented with degrees of renal dysfunction and chronicity scores on renal biopsy that were similar to those of the treatment-resistant patients. The only distinguishing feature in this group of patients was that skin involvement at onset was associated with a protective effect against end-stage kidney disease without relapse in the cause-specific hazard model (hazard ratio, 0.20 [CI, 0.06 to 0.75];  $P = 0.017$ ).

To assess how the patients' initial response to therapy affected their long-term renal outcome, we estimated the

effect of changes in GFR over the first 4 months of treatment. Controlling for baseline serum creatinine level, type of treatment, organ involvement, and ANCA specificity, we determined that patients with a GFR decrease of 8 mL/min or greater were 5.6 times more likely to progress to end-stage kidney disease (CI, 2.4 to 13.1;  $P < 0.001$ ) than those whose GFR was stable. In comparison, progression to end-stage kidney disease was 4.8 times less likely in patients with a GFR increase of 8 mL/min or greater (hazard ratio, 0.21 [CI, 0.1 to 0.6];  $P = 0.001$ ) than in those with a stable GFR.

## Predictors of Relapse

Among the 258 patients who attained a remission, those with anti-PR3 antibodies were 1.87 times more likely to relapse than patients who were anti-MPO seropositive (Table 2). Lung and upper respiratory tract involvement were each associated with an approximately 1.7-fold increase in risk for relapse, whereas disease involving other organs did not have a statistically significant impact. No other variable had a statistically significant impact on relapse. Black ethnicity was associated with a trend toward a higher risk for relapse.

In an effort to determine the impact of these risk factors on relapse in a more clinically relevant form, we compared the frequency of relapse and the time to relapse among patients presenting with none of the risk factors (defined as the low-risk group), at least 1 risk factor (high-risk group) or all 3 risk factors (multiple-risk group). Among 62 patients in the low-risk group, 16 (26%) relapsed in a median of 62 months (the median time to relapse among those who relapsed was 20 months) (Figure 2). In contrast, among 196 patients in the high-risk group, 93 (47%) relapsed in a median of 39 months (median time to relapse among those who relapsed was 16 months). This outcome corresponded to a 2.0-fold (CI, 1.1-fold to 3.9-fold) increase in risk for relapse ( $P = 0.038$ ). Among 44 patients in the multiple-risk group, 32 (73%) relapsed in a median of 17 months (median time to relapse among those who relapsed was 15 months). This finding corresponded to a 3.7-fold (CI, 1.4-fold to 9.7-fold) increase in risk for relapse ( $P = 0.007$ ) compared with those with no risk factors.

## Impact of Relapse on Long-term Outcome

Death from any cause was observed in 19% (21 of 109) of patients who relapsed and 33% (49 of 149) of

those who did not relapse in median times of 147 and 113 months, respectively. There was no statistical evidence for a difference in all-cause mortality between those who relapsed and those who did not, according to the Cox regression model with time-dependent covariates (hazard ratio, 1.5 [CI, 0.8 to 2.6];  $P = 0.180$ ).

End-stage kidney disease occurred in 28% of patients who relapsed (30 of 109) and 19% of those who did not relapse (28 of 149) in median times of 68 and over 106 months, respectively (Figure 2). The Cox model with time-dependent covariates revealed that the likelihood of progression to end-stage kidney disease was 4.7 times (CI, 2.7 to 8.4 times) higher among those patients who relapsed compared with those who did not ( $P < 0.001$ ). The increased risk for end-stage kidney disease associated with relapse was independent of age, sex, ethnicity, ANCA specificity, and renal function at time of biopsy. The increased risk was entirely attributable to the recurrence of nephritis because no patient with nonrenal relapse progressed to end-stage kidney disease.

## Impact of Length of Therapy on Relapse

We evaluated the outcomes of the 143 patients who were treated with cyclophosphamide and corticosteroids, attained a remission, and subsequently stopped all immunosuppressive therapy. These patients were representative of the overall cohort with respect to the frequency of ANCA subtype and the presence of lung and upper respiratory tract involvement (76% had at least 1 of the 3 risk factors for relapse). Of the 143 patients, 54% received intravenous cyclophosphamide and 46% received the drug orally. Median duration of treatment was 6 months (range, 1 to 31 months). The relapse rate was similar among patients who received therapy for 6 months or less (34%)

Table 2. Multivariable Predictors of Treatment Resistance and Relapse

Predictor	Prediction of Treatment Resistance (n = 334)*		Prediction of Relapse (n = 258)†	
	Odds Ratio (95% CI)‡	P Value‡	Hazard Ratio (95% CI)‡	P Value‡
Age per 10 years	1.20 (0.97–1.48)	0.093	0.94 (0.84–1.06)	0.31
Female versus male	1.80 (1.01–3.30)	0.048	1.05 (0.70–1.56)	0.97
Black versus nonblack	3.10 (1.19–7.85)	0.013	1.70 (0.83–3.90)	0.163
Antiproteinase-3 vs. antimyeloperoxidase antibody status§	0.47 (0.25–0.90)	0.023	1.87 (1.11–3.14)	0.022
Wegener granulomatosis vs. kidney-limited	0.49 (0.11–2.15)	0.34	1.28 (0.53–3.11)	0.45
Microscopic polyangiitis vs. kidney-limited	0.55 (0.22–1.39)	0.20	1.08 (0.51–2.27)	0.87
Lung involvement	1.46 (0.64–3.36)	0.37	1.71 (1.04–2.81)	0.034
Upper respiratory involvement	0.69 (0.29–1.63)	0.39	1.73 (1.04–2.88)	0.030
Skin involvement	0.89 (0.39–2.02)	0.78	1.41 (0.85–2.32)	0.182
Serum creatinine level per $\mu\text{mol/L}$ ¶	1.28 (1.16–1.39)	<0.001	1.01 (0.91–1.13)	0.82
Chronicity score per unit change (0 to 16)¶	1.14 (1.10–1.25)	0.010	0.99 (0.98–1.09)	0.98
Activity score per unit change (0 to 24)¶	1.11 (1.00–1.23)	0.052	1.00 (0.93–1.01)	0.97
Vascular sclerosis score per unit change (0 to 4)¶	1.55 (1.10–1.19)	0.013	1.00 (0.75–1.33)	0.97

\* Estimated using logistic regression.

† Estimated using cause-specific proportional hazards models.

‡ Evaluated in a model that controlled for all other measures identified by backward selection except where noted.

§ “Antiproteinase-3” also encompasses cytoplasmic antineutrophil cytoplasmic antibodies, and “antimyeloperoxidase” encompasses perinuclear cytoplasmic antibodies.

¶ Peak serum creatinine level at diagnosis.

¶ Models controlling for serum creatinine level did not control for renal biopsy variables; models controlling for renal biopsy variables did not control for serum creatinine level and included only patients who underwent a renal biopsy.

**Table 3. Relapse Rates among Patients in Sustained Remission after Therapy with Cyclophosphamide and Corticosteroids**

Category	Received Therapy for ≤6 mo	Received Therapy for >6 mo	Hazard Ratio (95% CI)	P Value
All patients, n/n (%)	26/77 (34)	23/66 (35)	1.41 (0.80–2.50)	0.145*
High-risk patients, n/n (%)†	24/59 (41)	20/50 (40)	1.50 (0.82–2.78)§	0.186
Low-risk patients, n/n (%)‡	2/18 (11)	3/16 (19)	2.17 (0.19–24.72)§	0.53

\* Multivariable proportional hazards model controlling for risk factors for relapse (antiproteinase-3 antibodies vs. antimyeloproteinase antibodies and lung and upper respiratory disease involvement) and age.

† Included patients with antiproteinase-3 antibodies and lung or upper respiratory disease involvement.

‡ Included patients with antimyeloperoxidase antibodies and no lung or upper respiratory disease involvement.

§ Hazard ratio estimates are from models limited to high-risk or low-risk patients.

compared with patients treated for a longer duration (35%) (hazard ratio adjusted for risk factors for relapse, 1.41 [CI, 0.80 to 2.50];  $P = 0.145$ ) (Table 3). Relapse rates by length of therapy were also similar within high- and low-risk groups (Table 3).

## DISCUSSION

This large observational cohort of patients with ANCA-associated vasculitis suggests many findings and implications. The 77% remission rate was comparable with previously reported rates of 70% to 92% (5, 8, 21–23). Treatment resistance was most common among patients presenting with higher serum creatinine levels, greater disease chronicity, and vascular sclerosis on renal biopsy. In previous reports, cumulative organ damage (measured by the Vasculitis Damage Index) (24), glomerular sclerosis, interstitial infiltrates, tubular necrosis, atrophy (25), and other markers of chronic disease were consistently labeled as predictors of treatment resistance, despite differences in statistical models and outcome definitions. These associations were independent of the level of disease activity, disease category, ANCA pattern or specificity, and demographic region. In this cohort, vascular sclerosis on biopsy was also an independent predictor of treatment resistance. We concluded that this association possibly resulted from chronic renal damage secondary to hypertension or other atherosclerotic processes; ANCA-associated nephritis may have also been a contributing factor. The impact of renal damage as a predictor of resistance emphasizes the importance of early diagnosis and prompt institution of therapy.

We found no threshold of renal dysfunction for which treatment was deemed futile; more than half of the patients presenting with a GFR of less than 10 mL/min reached remission and had substantial improvement in renal function. Therefore, we concluded that aggressive immunosuppressive therapy should be strongly considered in all patients with new diagnoses. However, the risk for progression to end-stage kidney disease was determined by the change in GFR within the first 4 months of treatment. In the absence of other disease manifestations, the decision to continue immunosuppressive therapy among patients with sharply declining GFR should be weighed against the diminishing chance of renal recovery.

Anti-MPO seropositivity, female sex, black ethnicity,

and advanced age were associated with a higher likelihood of treatment resistance after controlling for renal dysfunction and other factors. Information on socioeconomic indicators and access to care was not available; these factors will need to be explored to assess their potential role in delayed diagnosis and therefore in presumed treatment resistance among elderly, female, and black patients.

Disease relapse occurred in 42% of patients who reached a remission, which was within the range of previously reported relapse rates of 11% to 57% (7–11). A European study previously reported that patients with Wegener granulomatosis were more likely to relapse than patients with microscopic polyangiitis (26). In our study, the risk for relapse was increased in the presence of anti-PR3 antibodies and lung or upper airway involvement, whereas specific disease diagnoses (Wegener granulomatosis vs. microscopic polyangiitis) did not independently predict relapse. We concluded that this difference in the predictive values of specific disease diagnosis possibly reflected differences in the relative frequency of the 2 diseases between Europe and the southeastern United States. Conversely, focusing on a patient's clinical features may be more practical than assigning a specific disease diagnosis when estimating risk for relapse. This reasoning especially applies to patients with Wegener granulomatosis and microscopic polyangiitis, for which the recommended therapies are currently the same.

Previous research to determine whether changes in ANCA titers predict relapses has yielded conflicting observations (24, 27–37). Our cohort was recruited over 2 decades, during which time assays for ANCA changed substantially and titers were not systematically determined. For these reasons, we could not evaluate the predictive value of ANCA titers on relapse. Because ANCA pattern and antigen specificity were similar across different laboratories, we determined that anti-PR3 antibodies were associated with a 1.9-fold increase in risk for relapse; this finding was consistent with previous studies (24, 32–35, 38, 39).

An association between lung involvement and relapse was previously reported in 1 (33) of 2 studies of Wegener granulomatosis (24). Previous reports did not specifically identify upper respiratory tract disease as a risk factor for relapse; however, upper airway colonization with *Staphylococcus aureus* was associated with a higher relapse rate in

patients with Wegener granulomatosis (40), suggestive of a superantigen effect (41). Upper airway colonization with *S. aureus* was not determined in our study. Nonetheless, presence of active disease or chronic upper respiratory tract destruction from vasculitis may foster an environment for *S. aureus* infection.

One might reason that prevention of relapse confers a benefit to long-term outcomes, although earlier research did not demonstrate such a parallel with end-stage kidney disease or death (42). We found an association between relapse and subsequent progression to end-stage kidney disease, which was attributable to recurrent nephritis. Persistent undetected active nephritis may be an especially important risk factor among patients without overt signs of systemic vasculitis. As with previous reports (22), relapse did not affect long-term all-cause mortality.

The seminal work of Fauci and colleagues (43) began the use of cyclophosphamide as a life-saving treatment for patients with Wegener granulomatosis. The onerous adverse effects of this therapy fuel the search for strategies that reduce long-term cyclophosphamide exposure. Repeated courses of treatment for relapses are a major contributor to extended exposure to cyclophosphamide, but fear of relapse has also prompted prolonged maintenance immunosuppression therapy. The contention that prolonged immunosuppression prevents relapse has never been demonstrated. In our cohort of patients who discontinued all immunosuppressants after a course of cyclophosphamide and corticosteroids, we found similar relapse rates (34% and 35%) between patients treated for 6 months or less and those treated longer after taking into account risk factors for relapse (adjusted hazard ratio, 1.41 [CI, 0.80 to 2.50]). These results challenge the paradigm that prolonged immunosuppression is beneficial for relapse prevention. However, whether prolonged immunosuppression prevents relapses should be refuted or confirmed with additional studies.

Research has not conclusively demonstrated which medications are effective at preventing a relapse. In the only placebo-controlled trial of “maintenance” therapy, the use of etanercept did not reduce the high rate of relapse (8). Studies assessing azathioprine (22), methotrexate (10, 44, 45), leflunomide (46), and mycophenolate mofetil (47) have reported divergent rates of relapse during maintenance therapy. A direct comparison of these rates is difficult because the studies do not necessarily involve similar patient samples or define the concept of relapse uniformly.

Several limitations of the current study should be noted. The cohort was primarily identified by renal biopsy; therefore, patients without renal involvement may be underrepresented. Prevalence of renal involvement in ANCA-associated vasculitis has been reported in 75% to 90% of patients (48). Differences in the incidence of Wegener granulomatosis and microscopic polyangiitis by country have been described, with Wegener granulomatosis being more common than microscopic polyangiitis in northern

European countries and less common in Spain (49–51). The predominance of microscopic polyangiitis (83%) and common renal involvement (88%) in our cohort possibly represent the population of patients with ANCA-associated vasculitis in the southeastern United States. However, studies of incidence and prevalence in the study area have not been done. Other limitations inherent to community-based cohort studies conducted over a long period of time include nonuniform treatment protocols and general variations in patient care. Information about the clinical course before biopsy-proven diagnosis was limited. Tests for ANCA evolved with time and were not standardized across the entire cohort; however, there is good concordance between earlier ANCA test methods and the commercial kits that are currently available (52). In addition, we could not determine exactly when patients reached remission given the variable intervals between clinic visits. Despite these limitations, it is still critical to evaluate long-term studies in large samples to further the understanding of predictors of disease outcomes, especially in ANCA-associated vasculitis and other such rare diseases associated with increased morbidity.

In summary, current induction therapy for ANCA-associated vasculitis rests on the use of cyclophosphamide and glucocorticoids, with the addition of plasmapheresis for patients with pulmonary hemorrhage (53) or advanced renal failure (54). Although this approach affords a satisfactory remission rate, the frequent relapses pose a challenge in the long-term management of patients with the condition. The uniform use of prolonged immunosuppression exposes a large proportion of patients to the risks and costs of such treatment even if they are unlikely to relapse. In this context, the ability to prospectively distinguish patients likely to relapse opens the possibility to target more effective immunosuppressive therapy to those at higher risk. Likewise, the ability to identify patients at low risk for relapse may lead to less toxic treatment strategies for these patients. In our study, the presence of anti-PR3 antibodies or upper or lower respiratory tract disease constituted risk factors for relapse. The clinical utility of these risk factors for decisions regarding treatment needs to be prospectively validated. An effective and safe agent for the prevention of relapse remains to be identified. These challenges highlight the importance of careful patient education and vigilant physician monitoring to secure favorable clinical outcomes.

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## References

- Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum.* 1994;37:187-92. [PMID: 8129773]
- Jennette JC, Wilkman AS, Falk RJ. Anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and vasculitis. *Am J Pathol.* 1989;135:921-30. [PMID: 2683800]
- Falk RJ, Hogan S, Carey TS, Jennette JC. Clinical course of anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and systemic vasculitis. The Glomerular Disease Collaborative Network. *Ann Intern Med.* 1990;113:656-63. [PMID: 2221646]
- Hogan SL, Nachman PH, Wilkman AS, Jennette JC, Falk RJ. Prognostic markers in patients with antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol.* 1996;7:23-32. [PMID: 8808106]
- de Groot K, Adu D, Savage CO. The value of pulse cyclophosphamide in ANCA-associated vasculitis: meta-analysis and critical review. *Nephrol Dial Transplant.* 2001;16:2018-27. [PMID: 11572891]
- Briedigkeit L, Kettritz R, Gobel U, Natusch R. Prognostic factors in Wegener's granulomatosis. *Postgrad Med J.* 1993;69:856-61. [PMID: 8290430]
- Nachman PH, Hogan SL, Jennette JC, Falk RJ. Treatment response and relapse in antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol.* 1996;7:33-9. [PMID: 8808107]
- Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med.* 2005;352:351-61. [PMID: 15673801]
- Savage CO, Winearls CG, Evans DJ, Rees AJ, Lockwood CM. Microscopic polyarteritis: presentation, pathology and prognosis. *Q J Med.* 1985;56:467-83. [PMID: 4048389]
- Reinhold-Keller E, Fink CO, Herlyn K, Gross WL, De Groot K. High rate of renal relapse in 71 patients with Wegener's granulomatosis under maintenance of remission with low-dose methotrexate. *Arthritis Rheum.* 2002;47:326-32. [PMID: 12115164]
- Bacon PA. The spectrum of Wegener's granulomatosis and disease relapse. *N Engl J Med.* 2005;352:330-2. [PMID: 15673799]
- Hagen EC, Ballieux BE, van Es LA, Daha MR, van der Woude FJ. Antineutrophil cytoplasmic autoantibodies: a review of the antigens involved, the assays, and the clinical and possible pathogenetic consequences. *Blood.* 1993;81:1996-2002. [PMID: 8471761]
- Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med.* 1999;130:461-70. [PMID: 10075613]
- Levey AS, Green T, Kusek JW, Beck GJ, and MDRD Study Group. A simplified equation to predict glomerular filtration rate from serum creatinine [Abstract]. *J Am Soc Nephrol.* 2000;11:155A.
- Allison PD. Competing Risks. *Survival Analysis Using the SAS System: A Practical Guide.* Cary, NC: SAS Publishing; 1995:29-60, 185-209.
- Kalbfleisch JD, Prentice RL, eds. *The Statistical Analysis of Failure Time Data.* 2nd ed. Hoboken, NJ: J Wiley; 2002:1-29, 196-199, 247-77.
- Pepe MS, Mori M. Kaplan-Meier, marginal or conditional probability curves in summarizing competing risks failure time data? *Stat Med.* 1993;12:737-51. [PMID: 8516591]
- Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med.* 1999;18:695-706. [PMID: 10204198]
- Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model.* New York: Springer Publishing; 2000.
- Hess KR. Graphical methods for assessing violations of the proportional hazards assumption in Cox regression. *Stat Med.* 1995;14:1707-23. [PMID: 7481205]
- Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniene J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med.* 2003;349:36-44. [PMID: 12840090]
- Guillevin L, Cordier JF, Lhote F, Cohen P, Jarrousse B, Royer I, et al. A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. *Arthritis Rheum.* 1997;40:2187-98. [PMID: 9416856]
- Guillevin L, Cohen P, Mahr A, Arene JP, Mouthon L, Puechal X, et al. Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in sixty-five patients. *Arthritis Rheum.* 2003;49:93-100. [PMID: 12579599]
- Koldingsnes W, Nossent JC. Baseline features and initial treatment as predictors of remission and relapse in Wegener's granulomatosis. *J Rheumatol.* 2003;30:80-8. [PMID: 12508394]
- Bajema IM, Hagen EC, Hermans J, Noel LH, Waldherr R, Ferrario F, et al. Kidney biopsy as a predictor for renal outcome in ANCA-associated necrotizing glomerulonephritis. *Kidney Int.* 1999;56:1751-8. [PMID: 10571783]
- Booth AD, Almond MK, Burns A, Ellis P, Gaskin G, Neild GH, et al. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. *Am J Kidney Dis.* 2003;41:776-84. [PMID: 12666064]
- van der Woude FJ, Rasmussen N, Lobatto S, Wiik A, Permin H, van Es LA, et al. Autoantibodies against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosis. *Lancet.* 1985;1:425-9. [PMID: 2857806]
- Kerr GS, Fleisher TA, Hallahan CW, Leavitt RY, Fauci AS, Hoffman GS. Limited prognostic value of changes in antineutrophil cytoplasmic antibody titers in patients with Wegener's granulomatosis. *Adv Exp Med Biol.* 1993;336:411-4. [PMID: 8296645]
- Davenport A, Lock RJ, Wallington T. Clinical significance of the serial measurement of autoantibodies to neutrophil cytoplasm using a standard indirect immunofluorescence test. *Am J Nephrol.* 1995;15:201-7. [PMID: 7618644]
- Tervaert JW, Huitema MG, Hene RJ, Sluiter WJ, The TH, van der Hem GK, et al. Prevention of relapses in Wegener's granulomatosis by treatment based on antineutrophil cytoplasmic antibody titre. *Lancet.* 1990;336:709-11. [PMID: 1975893]
- Segelmark M, Phillips BD, Hogan SL, Falk RJ, Jennette JC. Monitoring proteinase 3 antineutrophil cytoplasmic antibodies for detection of relapses in small vessel vasculitis. *Clin Diagn Lab Immunol.* 2003;10:769-74. [PMID: 12965902]
- Girard T, Mahr A, Noel LH, Cordier JF, Lesavre P, Andre MH, et al. Are antineutrophil cytoplasmic antibodies a marker predictive of relapse in Wegener's granulomatosis? A prospective study. *Rheumatology (Oxford).* 2001;40:147-51. [PMID: 11257150]
- Kyndt X, Reumaux D, Bridoux F, Tribout B, Bataille P, Hachulla E, et al. Serial measurements of antineutrophil cytoplasmic autoantibodies in patients with systemic vasculitis. *Am J Med.* 1999;106:527-33. [PMID: 10335724]
- Tervaert JW, Stegeman CA, Kallenberg CG. Serial ANCA testing is useful in monitoring disease activity of patients with ANCA-associated vasculitides. *Sarcoidosis Vasc Diffuse Lung Dis.* 1996;13:241-5. [PMID: 8946592]
- De'Oliviera J, Gaskin G, Dash A, Rees AJ, Pusey CD. Relationship between disease activity and anti-neutrophil cytoplasmic antibody concentration in long-term management of systemic vasculitis. *Am J Kidney Dis.* 1995;25:380-9. [PMID: 7872315]
- Han WK, Choi HK, Roth RM, McCluskey RT, Niles JL. Serial ANCA titers: useful tool for prevention of relapses in ANCA-associated vasculitis. *Kidney Int.* 2003;63:1079-85. [PMID: 12631091]
- Langford CA. Antineutrophil cytoplasmic antibodies should not be used to guide treatment in Wegener's granulomatosis [Editorial]. *Clin Exp Rheumatol.*

- 2004;22:S3-6. [PMID: 15675126]
38. Boomsma MM, Stegeman CA, van der Leij MJ, Oost W, Hermans J, Kallenberg CG, et al. Prediction of relapses in Wegener's granulomatosis by measurement of antineutrophil cytoplasmic antibody levels: a prospective study. *Arthritis Rheum.* 2000;43:2025-33. [PMID: 11014352]
39. Jayne DR, Gaskin G, Pusey CD, Lockwood CM. ANCA and predicting relapse in systemic vasculitis. *QJM.* 1995;88:127-33. [PMID: 7704563]
40. Stegeman CA, Tervaert JW, Sluiter WJ, Manson WL, de Jong PE, Kallenberg CG. Association of chronic nasal carriage of *Staphylococcus aureus* and higher relapse rates in Wegener granulomatosis. *Ann Intern Med.* 1994;120:12-7. [PMID: 8250451]
41. Popa ER, Stegeman CA, Bos NA, Kallenberg CG, Tervaert JW. Staphylococcal superantigens and T cell expansions in Wegener's granulomatosis. *Clin Exp Immunol.* 2003;132:496-504. [PMID: 12780698]
42. Guillevin L, Lhote F, Cohen P, Jarrousse B, Lortholary O, Genereau T, et al. Corticosteroids plus pulse cyclophosphamide and plasma exchanges versus corticosteroids plus pulse cyclophosphamide alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome patients with factors predicting poor prognosis. A prospective, randomized trial in sixty-two patients. *Arthritis Rheum.* 1995;38:1638-45. [PMID: 7488285]
43. Fauci AS, Haynes B, Katz P. The spectrum of vasculitis: clinical, pathologic, immunologic and therapeutic considerations. *Ann Intern Med.* 1978;89:660-76. [PMID: 31121]
44. Langford CA, Talar-Williams C, Barron KS, Sneller MC. Use of a cyclophosphamide-induction methotrexate-maintenance regimen for the treatment of Wegener's granulomatosis: extended follow-up and rate of relapse. *Am J Med.* 2003;114:463-9. [PMID: 12727579]
45. Langford CA, Talar-Williams C, Sneller MC. Use of methotrexate and glucocorticoids in the treatment of Wegener's granulomatosis. Long-term renal outcome in patients with glomerulonephritis. *Arthritis Rheum.* 2000;43:1836-40. [PMID: 10943874]
46. Metzler C, Fink C, Lamprecht P, Gross WL, Reinhold-Keller E. Maintenance of remission with leflunomide in Wegener's granulomatosis. *Rheumatology (Oxford).* 2004;43:315-20. [PMID: 14963200]
47. Nowack R, Gobel U, Klooker P, Hergesell O, Andrassy K, van der Woude FJ. Mycophenolate mofetil for maintenance therapy of Wegener's granulomatosis and microscopic polyangiitis: a pilot study in 11 patients with renal involvement. *J Am Soc Nephrol.* 1999;10:1965-71. [PMID: 10477149]
48. Franssen CF, Stegeman CA, Kallenberg CG, Gans RO, De Jong PE, Hoorntje SJ, et al. Antiproteinase 3- and antimyeloperoxidase-associated vasculitis. *Kidney Int.* 2000;57:2195-206. [PMID: 10844589]
49. Watts RA, Lane SE, Scott DG, Koldingsnes W, Nossent H, Gonzalez-Gay MA, et al. Epidemiology of vasculitis in Europe [Letter]. *Ann Rheum Dis.* 2001;60:1156-7. [PMID: 11760724]
50. Watts RA, Scott DG. Epidemiology of the vasculitides. *Curr Opin Rheumatol.* 2003;15:11-6. [PMID: 12496504]
51. Cotch MF, Hoffman GS, Yerg DE, Kaufman GI, Targonski P, Kaslow RA. The epidemiology of Wegener's granulomatosis. Estimates of the five-year period prevalence, annual mortality, and geographic disease distribution from population-based data sources. *Arthritis Rheum.* 1996;39:87-92. [PMID: 8546743]
52. Lim LC, Taylor JG 3rd, Schmitz JL, Folds JD, Wilkman AS, Falk RJ, et al. Diagnostic usefulness of antineutrophil cytoplasmic autoantibody serology. Comparative evaluation of commercial indirect fluorescent antibody kits and enzyme immunoassay kits. *Am J Clin Pathol.* 1999;111:363-9. [PMID: 10078112]
53. Klemmer PJ, Chalermkulrat W, Reif MS, Hogan SL, Henke DC, Falk RJ. Plasmapheresis therapy for diffuse alveolar hemorrhage in patients with small-vessel vasculitis. *Am J Kidney Dis.* 2003;42:1149-53. [PMID: 14655185]
54. Gaskin G, Jayne DR, European Vasculitis Study Group. Adjunctive plasma exchange is superior to methylprednisolone in acute renal failure due to ANCA-associated glomerulonephritis [Abstract]. *J Am Soc Nephrol.* 2002;13:2A-3A.

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