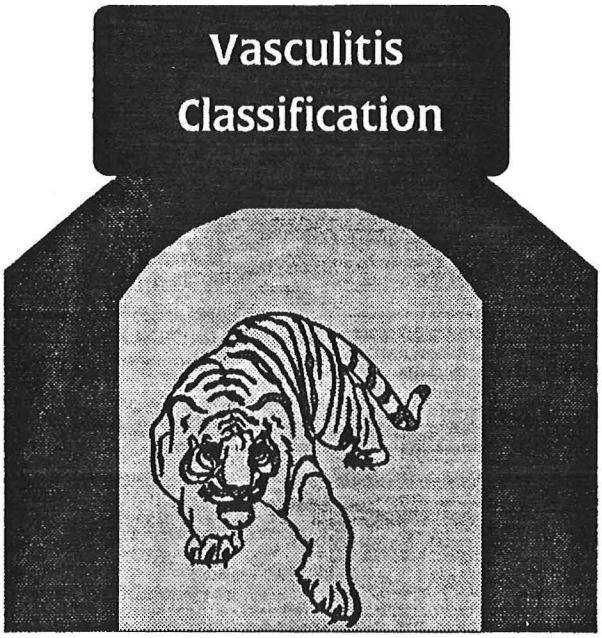
VASCULITIS: IT'S TIME TO RECLASSIFY



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Vasculitis is inflammation of blood vessels. Vasculitic disorders are relatively rare, and for many physicians it is unusual to encounter a patient with vasculitis. Nevertheless, it is important for these physicians to be familiar with the vasculitic syndromes. In most cases, patients with systemic vasculitis present to practitioners with nonspecific or mild symptoms and are followed for extended lengths of time prior to the occurrence of catastrophic events. Recent advances in the treatment of patients with vasculitis have demonstrated extraordinary success. However, the major determinant of successful treatment is the rapidity with which the diagnosis is made and treatment is initiated. When treatment is initiated in patients undergoing catastrophic life-threatening complications, the success rate is significantly less than when treatment is initiated prior to the occurrence of these events. Thus, it becomes essential that these diagnoses are made early.

In this article, I will review the systemic vasculitides. One of the major reasons why so many physicians are confused by the vasculitides is the inability to generate an acceptable classification and nomenclature scheme. Recent advances have provided a framework by which such a scheme can now be proposed. In addition, I will review the present state of the treatment of these disorders.

I would like to start the discussion by presenting a patient who was referred to me in September of 1993. E.H. is a 47 year old white male referred for acute leg swelling. The patient was healthy until 9 months previously when he developed weakness, recurrent ear infections, a "clogged up head," dizziness, dyspnea, and cough. He had seen multiple doctors who had treated him for diagnoses including sinusitis, congestive heart failure, and urinary tract infections. A few days prior to admission, the patient developed painful swelling of his thighs and profound weakness. On physical examination, blood pressure was 112/74, chest showed rales at the left base, thighs were swollen, erythematous, and tender, and neurologic exam showed profound lower extremity proximal weakness. Laboratory values were noteworthy for a hematocrit of 28.6 with an MCV of 79.1, a white blood cell count of 15.8 with 71% neutrophils, 8% bands and 2% metamyelocytes, a CPK of 2200, a serum creatinine of 3.6 mg% and a BUN of 55 mg%. It is noteworthy that two weeks earlier the serum creatinine was reported to be normal. Urine analysis showed many red blood cells and many granular casts. Chest x-ray showed multiple linear densities and a left pleural effusion.

On initial assessment this patient fit into the syndrome of rapidly progressive glomerulonephritis. This is based on the urine analysis findings of hematuria and casts suggesting glomerulonephritis, with a rapid increase in creatinine suggesting that it was rapidly progressive. In addition to rapidly progressive glomerulonephritis, patient E.H. had a number of more systemic symptoms, suggesting that we were not dealing with a simple renal disease, but more likely a systemic disease, probably a vasculitis.

CRESCENTIC GLOMERULONEPHRITIS

The term rapidly progessive glomerulonephritis refers to a clinical syndrome. When one considers patients with parenchymal renal disease, a glomerular syndrome is suggested by the presence of hematuria, proteinuria, and salt retention. Table 1 shows a nephrologist's approach to glomerular syndromes. In general, these can be divided into those that are dominated by hematuria and nephritis, and those that are dominated by proteinuria. The so-called hematuria/nephritic patients are divided into three syndrome categories based on the severity of their lesion. The first category, **recurrent hematuria**, refers to patients who manifest hematuria alone. This can be microscopic or macroscopic, and generally correlates with mild

renal disease confined to the glomerular mesangium. The most common cause of this is IgA nephropathy. **Acute glomerulonephritis** refers to the acute onset of hematuria with salt retention manifested by hypertension and congestive heart failure. It is noteworthy that although these patients develop mild azotemia, significant azotemia or acute renal failure is unusual. **Rapidly progressive glomerulonephritis or RPGN** includes all of the above plus the rapid onset of significant azotemia in weeks to months. Based on clinical findings, patient E.H. clearly fits into the syndrome of RPGN.

Table 1

GLOMERULAR SYNDROMES

Hematuria/Nephritic	Proteinuria/Nephrotic
1. Recurrent hematuria hematuria	
2. Acute glomerulonephritis above + salt retention: ↑BP, CHF mild azotemia	
3. RPGN above + rapid onset azotemia (weeks-months)	

The pathologic counterpart to the syndrome of RPGN is crescentic glomerulonephritis. Crescentic glomerulonephritis refers to the extracapillary proliferation of mononuclear cells within Bowman's space. It has been suggested that crescent formation occurs in response to disruption of glomerular capillary wall integrity. Thus, glomerular crescent formation can be considered to be a response to severe glomerulocapillary injury. Many different renal diseases can cause inflammation of the glomerulus. When any of these become very severe, crescents form. Because crescents indicate a severe glomerulonephritis, they correlate clinically with the syndrome of RPGN.

A major question relevant to vasculitis, is whether glomerulonephritis or crescentic glomerulonephritis represent forms of vasculitis. One could make the argument that all glomerulonephritis represents inflammation of capillaries, and since capillaries are blood vessels, that all glomerulonephritis should be considered a vasculitis. Such a usage of the term vasculitis, however, would be of little clinical utility. The clinical presentations of the majority of patients with glomerulonephritis is so distinct from that of vasculitis that inclusion of these patients would make the term vasculitis pathologically accurate but clinically useless. On this basis, all glomerulonephritis has been considered to **not** represent vasculitis.

However, I would argue that crescentic glomerulonephritis should be considered a vasculitis. First, as will be discussed below, crescentic glomerulonephritis is frequently part of a systemic vasculitis syndrome. When crescentic glomerulonephritis occurs in the absence of extrarenal involvement, it is generally referred to as idiopathic crescentic glomerulonephritis and is not considered a vasculitis. However, in this setting the disease represents a medical emergency very similar to that of the systemic vasculitides. In addition, when one compares patients with systemic vasculitis and patients with idiopathic crescentic glomerulonephritis, the distinctions are not as clear as were previously thought {1}. Constitutional symptoms can frequently be found with idiopathic crescentic glomerulonephritis. In addition, as will be discussed below, many of the serologies are similar between systemic vasculitis and idiopathic crescentic glomerulonephritis. Lastly, the treatment of idiopathic crescentic glomerulonephritis is very similar to that of vasculitis with respect to the urgency of treatment, the types of drugs

used, and the prognosis. Based on all of these, I would argue that crescentic glomerulonephritis should be classified as a vasculitis. I will return to this later.

Table 2

CRESCENTIC GN
Classification

	Type	IF	Serologies
I.	Anti-GBM	Linear	Anti-GBM
II.	Immune complex	Granular	Decreased complement
III.	Pauci-immune	Negative	ANCA

Table 2 shows a general classification of crescentic glomerulonephritis that has proven to be extremely useful. These have been divided based on their pattern of immunofluorescence. **Type I crescentic glomerulonephritis** has a linear immunofluorescence pattern with antibodies against immunoglobulin or complement. This reflects glomerular injury mediated by antibodies directed against the glomerular basement membrane (anti-GBM), and correlates with circulating anti-GBM antibodies. **Type II crescentic glomerulonephritis** has a granular immunofluorescence pattern with antibodies against immunoglobulin or complement. This is felt to reflect immune complex disease. The best serologic markers for these diseases are decreased levels of C3 and C4. **Type III crescentic glomerulonephritis** is referred to as **pauci-immune**, because immunofluorescence is negative. This suggests that these disorders are not mediated by anti-GBM antibodies or immune complexes, but does not provide a specific mechanism. As will be discussed extensively below, the presence of pauci-immune glomerulonephritis correlates well with the presence of anti-neutrophil cytoplasmic antibodies (ANCA).

As noted above, Type I crescentic glomerulonephritis refers to an entity associated with linear immunofluorescence and with the presence of anti-GBM antibodies. In general, this condition has been divided into two specific disease entities. The first is **Goodpasture's syndrome**, which includes the diagnostic triad of glomerulonephritis which is frequently crescentic, pulmonary hemorrhage, and anti-GBM antibody formation. In essence this entity involves pulmonary and renal disease occurring in response to antibodies against the basement membrane. **Type I idiopathic crescentic glomerulonephritis** refers to a similar entity where patients have once again a glomerulonephritis that is frequently crescentic and have circulating anti-GBM antibodies, but there is no evidence of pulmonary disease. Thus, these diseases are very similar, with the exception of whether there is pulmonary involvement. I would argue that the distinction between Goodpasture's disease and anti-GBM disease is of no practical use. First, the mechanism of disease is identical between the two diseases. Second, in certain patients with Goodpasture's, pulmonary symptoms may be subclinical leading to the diagnosis of the idiopathic disorder. Lastly, as will be discussed below, the treatment of these two entities is identical.

The antigen recognized by anti-GBM antibodies in these disorders has now been purified and cloned and is the NC1 (noncollagenous) domain of the $\alpha 3$ isoform of type IV collagen {2,3}. Type IV collagen represents the major collagen of basement membranes throughout the body. Most of these basement membranes contain $\alpha 1$ and $\alpha 2$ type IV collagen. $\alpha 3$ type IV collagen has been found to be present in renal glomerular basement membrane, lung, choroid plexus, lens capsule, choroid, and retina of the eye, and chochlea. This explains why Goodpasture's disease does not involve all basement membrane structures. There may be

subtle disease involving the choroid plexus, eye and ear, that is not clinically apparent.

Type 2 crescentic glomerulonephritis represents immune complex disease. In general, these disorders are frequently systemic and are very diverse. Common causes include **SLE, Henoch-Schoenlein purpura, IgA nephropathy, mixed cryoglobulinemia, infections, and drugs.** When none of these are found to be present and the kidney is the only organ involved, this entity is referred to as **type II idiopathic crescentic glomerulonephritis**. While disease mechanisms are similar, there may be some usefulness in separating out disease confined to the kidney, in that long term follow up does not involve treatment of other organs. In general it should be noted that a number of these disorders, including Henoch-Schoenlein purpura and mixed cryoglobulinemia typically represent vasculitic processes. Conditions such as SLE and immune complex disease secondary to infections cause vasculitis only in a small minority of cases representing the patients who are most severely affected. In these latter entities crescentic glomerulonephritis also is unusual and only occurs in the most severely affected patients.

Type III crescentic glomerulonephritis is the pauci-immune type. There is no evidence of immune complex disease or of anti-GBM antibody in this disorder. This category represents the most common category of crescentic glomerulonephritis. Its differential diagnosis includes three entities, **type III idiopathic crescentic glomerulonephritis** representing a disease confined to the kidney, **Wegener's granulomatosis** representing a granulomous vasculitis of the upper and lower respiratory tract along with crescentic glomerulonephritis, and **microscopic polyarteritis** representing a more diffuse vasculitis. While it was once believed that these entities had little in common with the exception that the consequent glomerulonephritis was not associated with immune complexes or anti-GBM antibody, this is no longer believed to be the case. As we will discuss extensively below, there is significant overlap between Wegener's granulomatosis and polyarteritis. In addition, there is significant overlap between these entities and type III idiopathic crescentic glomerulonephritis. All three of these entities have been found to be associated with circulating ANCA.

VASCULITIS: DEFINING CLINICAL ENTITIES

As noted above, patient E.H. had the syndrome of rapidly progressive glomerulonephritis, but in addition had a number of extrarenal findings which suggested a more systemic illness, possibly a vasculitis. These included sinusitis, problems with his ears, cough, and myositis. A number of questions arise when addressing patients such as this.

1. What are the specific diagnostic entities that should be considered?
2. What procedures are required in order to distinguish these diagnoses?
3. How does the establishment of the specific diagnostic entities affect treatment and prognosis?

To address the first question, we must define the specific vasculitic entities. In other words we need to generate a classification for vasculitis. Relevant to the remaining questions, such a classification should be as easily definable as possible based on clinical criteria and diagnostic tests. In addition such a classification should have relevance to treatment and prognosis. Ideally, such a classification should have relevance to pathophysiology.

Classification of the vasculitides has been extremely difficult. This has been based on the facts that clinical criteria have been inadequate and that there have been many overlaps between disease entities. Further compounding the problem has been the total lack of

knowledge related to pathogenesis of these disorders. In the section that follows, we will define some of the basic vasculitic disorders. This will be followed by a discussion of more recent findings related to these disorders, and data related to treatment and prognosis. Lastly, I will conclude by proposing a classification scheme that I believe provides the greatest degree of utility in the management and treatment of these patients.

Classic Polyarteritis Nodosa

Polyarteritis nodosa is a recurrent, progressive, necrotizing inflammatory disease of small and medium sized muscular arteries {4}. The lesions tend to be most pronounced at vessel bifurcations. Acutely, polymorphonuclear leukocytes infiltrate all layers of the vessel wall. Later, the inflammatory infiltrate is of a more chronic nonspecific nature. At autopsy there are grossly visible nodules, leading to the name of this disorder. On angiogram there are characteristic aneurysms typically occurring at the crotch of vessel bifurcations. In its classic form this disease does not affect smaller vessels and does not cause glomerulonephritis {4,5}. This entity was first described by Kussmaul and Maier in 1866 {6}. However, Zeek is given credit for providing the first initial classification of vasculitides in which this entity was precisely described {4}.

Most of the clinical manifestations of polyarteritis nodosa can be attributed to vessel stenosis with tissue ischemia. Thus, obstruction of arteries supplying the kidney leads to hypertension and renal insufficiency. Renal biopsy shows ischemic glomeruli. Urinalysis may show some degrees of hematuria and proteinuria, but these do not dominate the clinical presentation. GI involvement is due to bowel ischemia and frequently involves abdominal pain, nausea, vomiting, and may involve hematochezia and bowel infarction. Mononeuritis multiplex is common and is attributable to involvement of vessels supplying peripheral nerves. Involvement of vessels supplying muscle causes myositis. Coronary artery involvement can lead to congestive heart failure and myocardial infarction. Cutaneous vascular involvement causes painful nodules and livido reticularis. Testicular involvement causes pain, and when present provides a useful site for tissue diagnosis. In general, pulmonary involvement is unusual.

Allergic Angiitis and Granulomatosis of Churg-Strauss

While there is general agreement that the above definition applies to the entity of **classic polyarteritis nodosa**, there is significant disagreement as to whether this definition applies to the term polyarteritis nodosa in general. When one reviews the older literature and even in some cases the more recent literature on polyarteritis nodosa, it is not unusual to find a significant number of patients with asthma, eosinophilia, crescentic glomerulonephritis, and pulmonary vasculitis. Churg and Strauss defined an entity called allergic angiitis and granulomatosis, in which there is vasculitis of arteries similar to that seen in polyarteritis nodosa {7}. However, the vasculitis in these patients has a number of characteristic features. First, eosinophils predominate in the vascular inflammation. Second, macrophages and giant cells surround necrotic areas. Lastly, cardiac and pulmonary involvement are frequent. In addition, to vasculitis, these patients have stromal infiltrates in which eosinophils predominate acutely and macrophages and giant cells become more predominant chronically. Acutely, eosinophils can comprise up to 70-80% of the cells in the infiltrate. Although Churg-Strauss does involve medium-sized arteries, the vasulitis also involves smaller vessels.

Clinically, these patients have manifestations very similar to polyarteritis nodosa, including constitutional symptoms such as anemia, weight loss, weakness, and fever,

hypertension, abdominal pain, and peripheral neuropathy. In addition, patients with allergic angiitis and granulomatosis all have a history of asthma which precedes the onset of the vasculitis syndrome by a few months to many years. The patients also have pronounced eosinophilia and recurrent pneumonia. Glomerulonephritis is unusual in this syndrome. Because this picture is relatively distinct, most authors have separated the Churg-Strauss syndrome out as a distinct entity, and do not include cases under polyarteritis nodosa. However, it should be noted that some patients present with a syndrome of polyarteritis nodosa with eosinophilia or asthma but not both. Here the question of whether to call these patients Churg-Strauss syndrome or PAN is not totally resolved.

Microscopic Polyarteritis

Zeek in her original classification noted the necessity to separate out patients who had a PAN-like syndrome, but who presented with small vessel vasculitis and glomerulonephritis {4}. This point was emphasized in a classic paper by Davson et al {8}, and was named microscopic polyarteritis by Savage et al {5}. This syndrome likely includes many of the patients reported as having PAN, who present with crescentic glomerulonephritis and/or hemoptysis. This disease entity is a non-granulomatous necrotizing vasculitis of small vessels, including arterioles, capillaries, and venules. It may in addition involve small and medium sized arteries, leading to its confusion with the syndrome of PAN. The clinical presentation is in many respectes similar to PAN including constitutional symptoms, fever, arthralgia, myalgia, purpura, abdominal pain, diarrhea, hematochezia, and peripheral neuropathy. A number of features, however, are distinct from that of polyarteritis nodosa. First and foremost, is the frequent occurrence of a focal necrotizing crescentic glomerulonephritis of the pauci-immune type {5,8,9}. Also noteworthy is the presence of hemoptysis attributed to an alveolar capillaritis in 1/3 of patients. In contrast to patients with classic PAN, hypertension is infrequent, mild, and usually occurs later in the disease. Hepatitis B surface antigen, which frequently has been associated with classic polyarteritis nodosa, generally is not present in patients with microscopic polyarteritis {5}. There is a higher incidence of palpable purpura indicating a leukocytoclastic angiitis. Aneurysms and organ infarction are less frequent.

Wegener's Granulomatosis

Wegener's granulomatosis is a fairly distinct syndrome, in which there has been relatively little controversy over nomenclature. However, it should be noted that there remains a significant problem of overlap with other syndromes. Wegener's granulomatosis includes a classic triad of: 1) **upper respiratory tract inflammation** including sinusitis, otitis, rhinitis, ocular inflammation, epistaxis, proptosis, and oral ulcers; 2) **lower respiratory tract inflammation** including pulmonary infiltrates, cough and hemoptysis; and 3) **rapidly progressive glomerulonephritis** related to a pauci-immune crescentic glomerulonephritis {10-14}. Patients frequently present with fever, arthralgia, weight loss, peripheral neuropathy, and skin rash. Hypertension tends to be absent or mild, and generally evolves later in the course of the disease. The pathology in Wegener's granulomatosis is distinct in that there is granulomatous vasculitis affecting small and medium-sized vessels and granulomas. However, it is unusual to document granulomatous vasculitis with biopsies of the kidney or the upper respiratory tract. Lung biopsy usually will show granulomatous vasculitis, but an open lung biopsy is required. Bronchoscopic biopsy has a very low yield. Thus, it is not uncommon to see patients with crescentic glomerulonephritis, sinusitis, and pulmonary infiltrates, in whom a granulomatous

vasculitis has not been documented. While a significant fraction of these patients likely have Wegener's granulomatosis, many may also have microscopic polyarteritis.

Immune Complex-Associated Vasculitis

Lastly, it is worth noting that there are a number of immune complex mediated vasculitides that involve small vessels. The classic example of this is **Henoch-Schoenlein purpura** in which patients develop palpable purpura on their lower extremities and have abdominal pain, both attributable to a small vessel leucocytoclastic angiitis. In addition, these patients develop crescentic glomerulonephritis. The immune complexes are noted to include IgA. **Essential mixed cryoglobulinemia** also represents an immune complex disorder that frequently manifests as a small vessel vasculitis. There is also an entity referred to by various names including **cutaneous leucocytoclastic angiitis** or **hypersensitivity angiitis**, which involves small vessel vasculitis confined to the skin.

Classification

A number of specific classifications have been proposed by which to organize the vasculitic syndromes. These have been recently reviewed in an excellent editorial {15}. Perhaps one of the most popular classification schemes is that from the National Institutes of Health. This scheme organizes a number of the vasculitides under the heading of systemic necrotizing vasculitis. According to this scheme, the entity referred to here as microscopic polyarteritis would fit under classic polyarteritis nodosa. This would imply that microscopic polyarteritis is more similar to classic polyarteritis than it is to Wegener's granulomatosis. Nephrologists have long believed that this is not the case, given the fact that both microscopic polyarteritis and Wegener's granulomatosis cause a crescentic glomerulonephritis and are associated with pulmonary involvement. This scheme also utilizes the term hypersensitivity angiitis, which seems to mean different things to different people. It is certainly rare that any form of hypersensitivity is identified in this form of vasculitis. Particularly bothersome in this classification is the use of the overlap syndrome {16}. The overlap syndrome is defined as including any overlap between any two vasculitic syndromes. Thus, it is unlikely that these overlap syndromes have anything in common with each other such that one would want to classify them together. Based on recent advances in our understanding of the vasculitic syndromes, it may now be time to propose a new classification (see below).

ANTINEUTROPHIL CYTOPLASMIC ANTIBODY

Antibodies against neutrophil antigens that appear to have a cytoplasmic pattern were first described by Davies et al {17}. van der Woude et al were the first to describe the association between Wegener's granulomatosis and antibodies against neutrophils and monocytes {18}. These autoantibodies were detected in 25 of 27 samples from patients with active Wegener's granulomatosis and in only 4 of 32 samples from patients in whom Wegener's had become inactive. The antibodies recognize specific antigens that are components of the primary or azurophyllic granules. When indirect immunofluorescence is done on formalin-fixed cells, the antibodies show a diffuse granular cytoplasmic staining by indirect immunofluorescence. However, when indirect immunofluorescence is performed on ethanol-fixed cells, two patterns are seen. One pattern referred to as **c-ANCA** or **cytoplasmic ANCA**, is once again a diffuse cytoplasmic staining. A second pattern, referred to as **p-ANCA** or **perinuclear ANCA**, shows a perinuclear distribution of staining. The mechanisms responsible

for these two staining patterns have now been extensively worked out. The c-ANCA pattern corresponds to antibodies against proteinase 3, a component of the primary granules {19,20}. In most, but not all cases, the p-ANCA pattern is produced by antibodies against myeloperoxidase (MPO) {21}. Upon fixation in ethanol, myeloperoxidase migrates to the nucleus, leading to the perinuclear staining. While anti-myeloperoxidase antibodies are present in most patients with p-ANCA patterns, some patients have antibodies to other components of the primary granules such as elastase, or to undefined antigens.

Sensitivity and Specificity of ANCA

When one reviews the literature on ANCA specificity and sensitivity, it is clear that there is much variation. Before reviewing individual studies, it is worth discussing some of the variables which complicate these studies. First, the sensitivity and specificity of ANCA will depend on the **definition of disease entities**. In the case of the vasculitides, the definition of disease entities is not totally resolved. In that each study may utilize different disease definitions, they are likely to derive different sensitivity and specificities. An example of this is a patient with pauci-immune focal necrotizing crescentic glomerulonephritis and pulmonary vasculitis, but with no documented granulomatous vasculitis or granulomas, who has a positive c-ANCA. Some investigators would say that in the absence of granulomatous vasculitis and granulomas, this patient should be considered microscopic polyarteritis. This would then be a false positive c-ANCA when considered as diagnostic of Wegener's. On the other hand others could argue that given this clinical presentation, the positive c-ANCA indicates Wegener's and it is likely that clinicians have failed to find the granulomatous disease. These investigators would consider this a true positive.

A second point is that the sensitivity of these tests relies in many cases on the **disease activity**. It has been shown for Wegener's granulomatosis that ANCA is more frequently positive when the disease is active {18,22}. Patients with limited Wegener's confined to the lungs and upper respiratory tract, have a much lower rate of ANCA positivity than patients whose Wegener's also involves the kidney {23}. In addition, treatment which causes Wegener's to become inactive, decreases the ANCA titers and eventually leads to a negative ANCA {22}. A similar response has been found for ANCA positive patients in general {20}. Thus, if one obtains an ANCA early in the disease when it is relatively inactive, an ideal time to make the diagnosis, c-ANCA may be falsely negative.

Lastly, it should be noted that specificity depends on the **patient population** studied. An example of this comes from the studies of Ulmer et al, where 3000 sera from unselected patients were tested {24}. In this study, 620 patients had a positive p-ANCA pattern on indirect immunofluorescence. 85.6% of these p-ANCA patterns were attributable to anti-nuclear antibodies, and thus would be considered a false positive. It is important to be aware that the p-ANCA pattern looks very similar to a nuclear binding pattern, and thus one should be cautious in interpreting positive p-ANCA in the absence of a negative ANA. In this study, of the 9.8% of patients that had anti-myeloperoxidase antibodies by ELISA, 24 patients had pulmonary renal syndrome, 13 had a rapidly progressive glomerulonephritis syndrome, 1 had Churg-Strauss syndrome, 2 had Wegener's granulomatosis, 2 had systemic lupus erythematosis, and 1 had SLE with vasculitis. Eight patients had glomerulonephritis which was not rapidly progressive. These studies therefore showed that anti-MPO antibodies detected by ELISA are more specific than merely demonstrating a p-ANCA pattern. The magnitude of the discrepancy depends on the patient population.

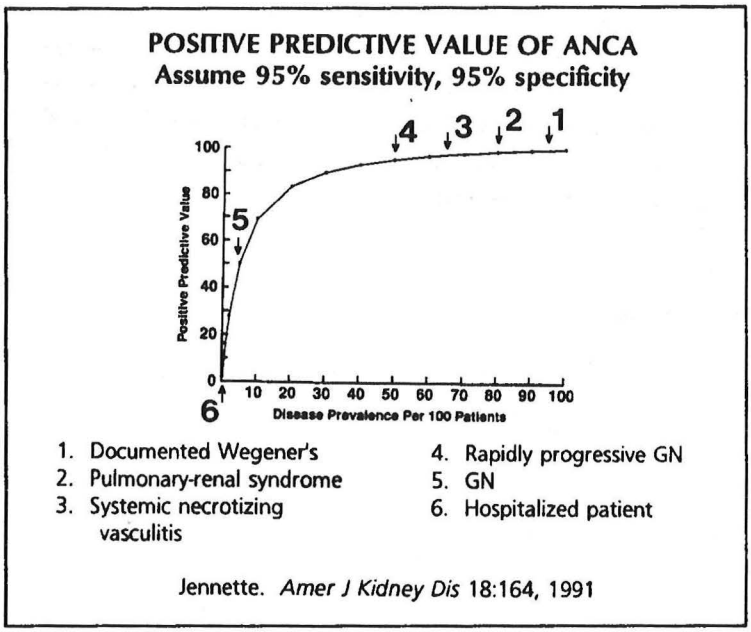


Figure 1

The importance of the patient population was illustrated in a mathematical formulation presented by Jennette {25}. This is shown in Figure 1. In this graph, it is assumed that a test such as the ANCA has a 95% sensitivity and a 95% specificity. The positive predictive value of the test is then plotted as a function of the disease prevalence in the population. The lower the disease prevalence, the less the positive predictive value. Number one on the far right represents patients with documented Wegener's granulomatosis in which the disease prevalence is very high. In this setting a positive ANCA should be diagnostic. In patients with pulmonary renal syndromes in general, the disease prevalence decreases somewhat, as indicated by #2. In patients with vasculitis, disease prevalence decreases again, but the test is still very useful (#3). As indicated in #4, in rapidly progressive glomerulonephritis there is about a 50% prevalence of the disease, and the test remains useful. Number 5 indicates patients with glomerulonephritis in general. Now the prevalence of the disease is down to less than 10%, and the positive predictive value of the test becomes somewhat dubious. The last point, #6, refers to all hospitalized patients, in which the value of the positive test is virtually worthless.

The relative specificities of a p-ANCA pattern versus anti-myeloperoxidase antibodies detected by ELISA has also been addressed by Velosa et al in a more limited group of patients who required a renal biopsy {26}. Utilizing the p-ANCA and c-ANCA by indirect immunofluorescence, there was 50% sensitivity and 79% specificity for the diagnoses of idiopathic necrotizing crescentic glomerulonephritis and renal vasculitis. A similar comparison performed with a combination of anti-myeloperoxidase antibodies and c-ANCA markedly increased sensitivity to 78% and somewhat increased specificity to 84% {26}. Thus, it would appear that anti-

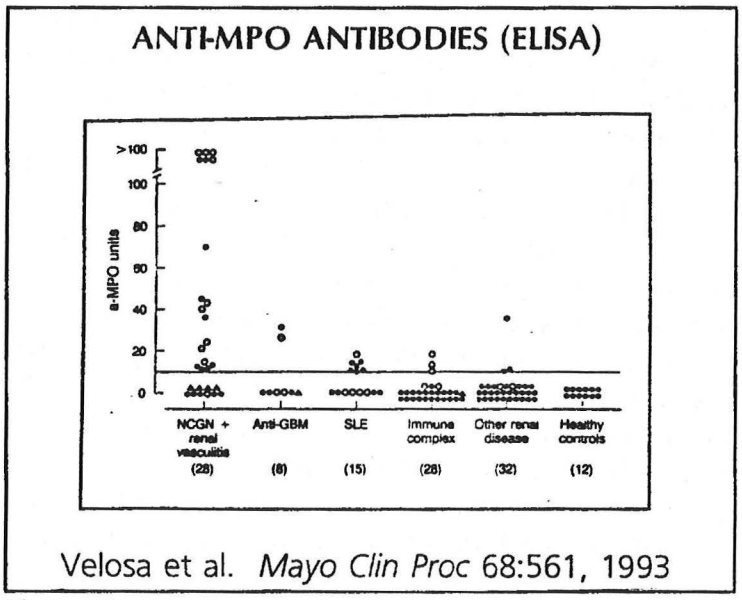


Figure 2

myeloperoxidase is more sensitive and more specific than a p-ANCA pattern. Figure 2 shows the anti-MPO titer in patients in this study. There were a significant number of patients with high titers of antibody in the group with crescentic glomerulonephritis and renal vasculitis. Two patients with antiglomerular basement membrane disease were positive. As will be discussed below, these likely do not represent false positives. There was also some positivity in lupus and in patients with immune complex disease, but titers were very low.

Table 3
ANCA

	c-ANCA	p-ANCA	MPO-ANCA
Generalized WG (25)	12	4	1
Localized WG (16)	4	0	0
PAN (47)	1	12	10
Idiopath. CGN (45)	5	32	32
Anti-GBM (37)	0	12	11
Isolated pulmonary hemorrhage (3)	0	3	3

Bosch et al, AJKD 20:231, 1992

A number of studies have examined the sensitivity and specificity of c-ANCA, p-ANCA and their respective antibodies. Bosch et al examined 651 patients with a variety of diseases. c-ANCA and p-ANCA were determined by indirect immunofluorescence {23}. Specificity for MPO was determined by repeating the ANCA using granulocytes from MPO-deficient patients. No patient with c-ANCA had MPO-ANCA. Table 3 shows results from this study. As can be seen, in generalized Wegener's granulomatosis, 16 out of 25 patients had a positive ANCA, and in 12 of these the pattern was c-ANCA. There were 4 patients with p-ANCA, one of whom had MPO-ANCA. In localized or limited Wegener's, ANCA was positive in only 4 of 16 patients. In polyarteritis, 13 out of 47 patients were ANCA positive. In 12 of these 13, the pattern was p-ANCA, and in 10 of these the p-ANCA corresponded with MPO-ANCA. It is worth noting that although listed as polyarteritis nodosa in this study, the MPO-ANCA patients were the only ones of the patients listed as PAN that had renal insufficiency. In 7 of these 10 patients, a renal biopsy was performed that showed necrotizing and crescentic glomerulonephritis in 6. In addition, of these 6 patients, 4 developed pulmonary hemorrhage. Lung biopsy was performed in 3 patients and showed necrotizing alveolar capillaritis. It should also be noted that 6 of the patients diagnosed as PAN had hepatitis B surface antigen and/or antibody, but none of these patients had a positive ANCA. In idiopathic crescentic glomerulonephritis, positive ANCAs were prevalent, and the majority of these were p-ANCA and MPO-ANCA. Approximately 1/3 of patients with anti-GBM disease were also ANCA positive. These patients were p-ANCA and MPO-ANCA positive. These results agree with results of other studies (see below). Lastly, three patients had isolated pulmonary hemorrhage. All three patients were ANCA positive. This ANCA corresponded with p-ANCA and MPO-ANCA. It should be noted that ANCA positivity occurred in only a small minority of patients with other disease processes.

Fienberg et al examined 68 patients in whom extrarenal tissue was available {19}. Of 44 patients in whom ANCA was positive, all had pathologic evidence of Wegener's granulomatosis, necrotizing arteritis, alveolar hemorrhage, or necrotizing crescentic glomerulonephritis. Patients with c-ANCA were positive for anti-proteinase 3 (anti-PR3) by ELISA. Patients with p-ANCA were positive for anti-MPO by ELISA. No patient was positive for anti-proteinase 3 and anti-MPO. Table 4 shows the results of the ELISAs in a number of patient groups. Of 30 patients with a definitive diagnosis of Wegener's, 18 had anti-proteinase 3 antibodies and 6 had anti-MPO antibodies. In 7 patients suspected of Wegener's 5 had anti-PR3 antibodies. In 2 patients with Churg-Strauss both were positive for anti-MPO. In 3 patients with necrotizing arteritis without granulomata, likely fitting into the category of microscopic polyarteritis, 2 were positive for anti-MPO. In 16 patients with alveolar hemorrhage, 9 were anti-PR3 and 5 were anti-MPO.

Table 4
ANCA
68 Patients in Whom Extrarenal Tissue Was Available

	n	PR3	MPO	Neg
Total	68	28	16	24
Wegener's granulomatosis				
Definite	30	18	6	6
Suspected	7	5	0	2
Churg-Strauss	2	0	2	0
Necrotizing arteritis without granulomata	3	0	2	1
Alveolar hemorrhage	16	9	5	2
No diagnostic extrarenal lesion	18	3	2	13

Fienberg et al, Hum Pathol 24:160, 1993.

Saxena et al examined 82 consecutive patients with crescentic glomerulonephritis defined as greater than 50% of biopsied glomeruli demonstrating crescents {27}. In patients with vasculitis and documented granuloma, there were 5 patients with anti-PR3. With vasculitis but without documented granuloma, 9 patients had anti-PR3 and 2 patients were anti-MPO. In patients with clinically suspected vasculitis, 11 were anti-PR3 and 5 were anti-MPO. Lastly, in patients with crescentic glomerulonephritis with extrarenal features 7 were anti-PR3 and 3 were anti-MPO. In the patients without extrarenal features 1 was anti-PR3 and 6 were anti-MPO. This study concluded that anti-MPO was more likely to be found in patients with isolated crescentic glomerulonephritis.

Cohen Tervaert et al examined 35 consecutive patients with crescentic glomerulonephritis (Table 5) {28}. Of 9 patients with biopsy-proven Wegener's granulomatosis, all were positive for c-ANCA and for antibodies against a 29 kDa antigen which has subsequently been shown to be proteinase 3. In 15 patients clinically suspected of Wegener's granulomatosis, 10 showed c-ANCA and anti-PR3, while 5 showed p-ANCA and anti-MPO. In

Table 5

ANCA

35 consecutive patients with crescentic GN

Diagnosis (*number of patients tested*)	c-ANCA by IIF *N*	29 kD-ANCA by ELISA *N*	(Peri)nuclear staining pattern by IIF *N*	MPO-ANCA by ELISA *N*
Biopsy proven WG (*N* = 9)	9	9	0	0
Clinically suspected WG (*N* = 15)	10	10	5	5
Idiopathic CGN (*N* = 8)	2	2	6	6
CGN of infectious origin (*N* = 3)	0	0	1	0
Different forms of CGN (*N* = 7)	0	0	4	0
Non crescentic SLE nephritis (*N* = 11)	0	0	9	0
IgA nephropathy (*N* = 12)	0	0	0	0
Membranoproliferative glomerulonephritis (*N* = 11)	0	0	0	0
Normal donors (*N* = 52)	0	0	0	0

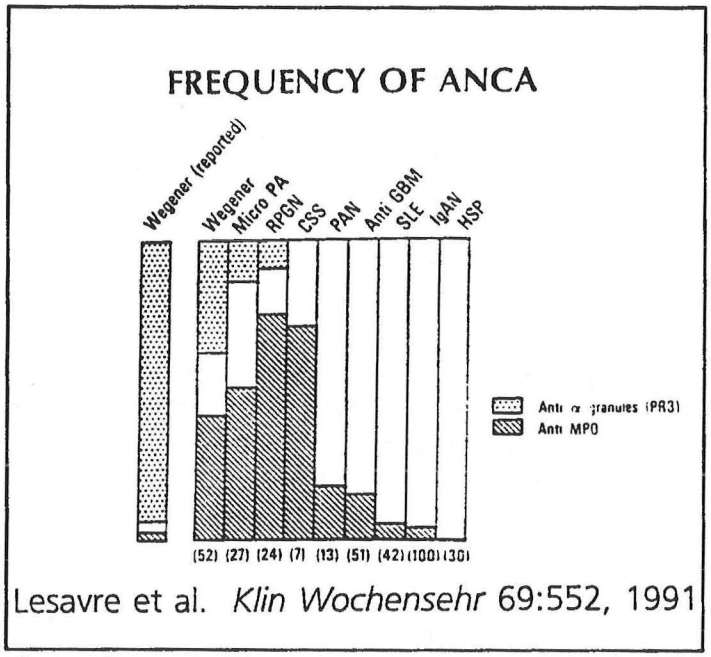
Abbreviations are: WG, Wegener's granulomatosis; CGN, crescentic glomerulonephritis.

Cohen Tervaert et al. *Kidney Int* 37:799, 1990

anti-MPO, and are occasionally negative. In other series (shown by the bar on the left), there is a higher incidence of anti-PR3, which may be attributable to the definition of Wegener's. It is likely that other investigators may consider some of the anti-MPO positive patients to be microscopic polyarteritis. In microscopic polyarteritis and RPGN, patients are more commonly positive for anti-MPO. On occasion these patients have anti-PR3. Patients with Churg-Strauss syndrome also tend to be positive for ANCA and when positive have anti-MPO. Only a minority of patients with polyarteritis nodosa are positive for anti-MPO. Similarly, there is some positivity in anti-GBM patients. In general, SLE, IgA nephropathy, and Henoch-Schoenlein purpura are negative.

8 patients with idiopathic crescentic glomerulonephritis, 2 were positive for c-ANCA and anti-PR3, while 6 were positive for p-ANCA and anti-MPO. A number of patients were also examined that had crescentic glomerulonephritis due to other causes, or SLE nephritis. In these patients there was a significant incidence of p-ANCA, but MPO-ANCA was negative by ELISA. Once again these studies show that anti-MPO antibodies are more specific than p-ANCA. In addition, in IgA nephropathy, membranoproliferative glomerulonephritis, and in normal patients, ANCA was negative.

Figure 3 shows the results of Lesavre and coworkers in a series of patients with various disease entities {29}. In general, their results agree with those of the above groups. Patients with Wegener's granulomatosis can have anti-PR3 or



Lesavre et al. *Klin Wochensehr* 69:552, 1991

Figure 3

In summary, a number of statements can be made. First, there are a number of disorders which can be considered ANCA-associated. These include Wegener's granulomatosis, microscopic polyarteritis, idiopathic crescentic glomerulonephritis of the pauci-immune type, the Churg-Strauss syndrome and one-third of anti-GBM patients. Based on this, it would seem that entities such as microscopic polyarteritis and Churg-Strauss are more similar to Wegener's granulomatosis than they are to classic polyarteritis. Thus, a classification scheme which places these entities in a polyarteritis group and places Wegener's in a separate group, is unlikely to be accurate.

A second important point is that the ANCA is of limited usefulness in distinguishing which one of these entities is present. While a c-ANCA is more suggestive of Wegener's and a p-ANCA is more suggestive of microscopic polyarteritis, idiopathic crescentic glomerulonephritis, or Churg-Strauss, there is sufficient overlap to prevent diagnosis based on ANCA alone. The possibility exists that indeed these four entities represent minor variations of one disease process. Indeed, in the literature one encounters patients with Wegener's or microscopic polyarteritis that have asthma or eosinophilia but not both, and thus have not been classified as Churg-Strauss. Similarly, occasionally patients are encountered with Churg-Strauss that have a necrotizing glomerulonephritis {30}. Jennette noted that when one considers the ANCA-associated disorders, there are a number of common pathologic features. In the acute phase, all demonstrate segmental distribution, fibrinoid necrosis, and influx of neutrophils.

Table 6

CLINICAL FEATURES OF PATIENTS WITH ANTI-PR3 AND ANTI-MPO ANTIBODIES

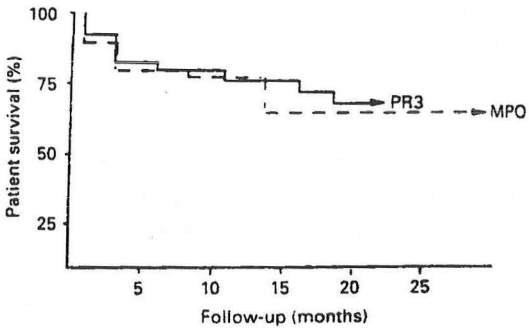
	MPO (n = 45)	PR3 (n = 38)	P
Kidney	42 (93%)	35 (92%)	NS
ENT*	25 (56%)	28 (74%)	NS
Lung	30 (67%)	21 (55%)	NS
-AH**	18 (40%)	7 (18%)	<0.05
Joints	16 (36%)	19 (50%)	NS
Skin	14 (31%)	16 (42%)	NS
Nerv Syst	11 (24%)	7 (18%)	NS
Muscle	7 (16%)	5 (13%)	NS
Eye	4 (9%)	12 (32%)	<0.01
Cardio	5 (11%)	2 (5%)	-
Cholestasis	4 (9%)	1 (3%)	-
Granulomas	5 (11%)	17 (45%)	<0.001

*ENT: ear, nose & throat. AH**: alveolar hemorrhage
Geffriaud-Ricouard et al. Clin Nephrol 39:125, 1993

Clinically when one compares patients with anti-PR3 and anti-MPO ANCAs, the similarities far outnumber the differences. Table 6 shows a comparison made by Geffriaud-Ricouard et al of organ involvement in patients with anti-MPO and anti-PR3 {20}. The only significant differences were that patients with anti-PR3 had a higher incidence of eye involvement and had granulomas. Patients with anti-MPO had a higher incidence of alveolar hemorrhage.

These investigators also noted a similar seasonal variation in the appearance of first symptoms, as has been noted by others {20}. The ANCA-associated disorders tend to start during the winter suggesting an infectious etiology. Lastly, as shown in Figure 4, survival is similar in patients with anti-PR3 and anti-MPO {20}.

One last point to be made is that as noted above, a number of patients with anti-GBM disease are also ANCA positive {26,27,29,31,32}. In fact, approximately 1/3 of anti-GBM positive patients are ANCA positive. Most studies find p-ANCA and MPO-ANCA in these patients. These patients have been studied in depth by Jayne et al and Bosch et al {31,32}. In general, a number of findings have been noted. Patients with both anti-GBM antibody and ANCA tend to have lower anti-GBM antibody titers. Patients with both anti-GBM antibodies and ANCA antibodies also tend to have evidence of extrarenal/extrapulmonary involvement suggesting a systemic vasculitis. Lastly, as will be discussed below, ANCA positive patients have



Geffriaud-Ricouard et al. *Clin Nephrol* 39:125, 1993

Figure 4

a better prognosis than anti-GBM antibody positive patients. Patients with anti-GBM and ANCA positivity also have a better prognosis than patients with anti-GBM antibody alone.

TREATMENT

It has been very difficult to evaluate the effectiveness of treatments for the vasculitic disorders. This is based on a number of factors. First, the low incidence of each of the specific vasculitic disorders has led to small numbers of patients in each study. Second, a lack of a universal nomenclature and classification has led to variable study populations. Lastly, the poor prognosis in most of the vasculitic disorders has caused an unwillingness to perform properly controlled, randomized studies. In many cases investigators have resorted to historical controls. These suffer because they do not consider advances in other aspects of treatment such as antibiotics and intensive care treatment. Many studies also use retrospective comparisons comparing patients who received two different treatment modalities. These studies are flawed because they do not take into account the reasons for the treatment decision. For instance, patients with Goodpasture's who are on dialysis have been shown to have a very poor response to treatment. Therefore, many of these patients are no longer treated. The net result is that these patients who do poorly would comprise the control group, and it is likely that any treatment regimen would be shown to do well.

There are a number of treatments which have been used for the various vasculitic disorders. Prednisone either as an oral dosage or as a pulse intravenous treatment has had extensive use in crescentic glomerulonephritis and for pulmonary hemorrhage. Cytotoxic drugs such as azathioprine and cyclophosphamide have been used extensively for the vasculitides. Plasmapheresis has become the mainstay of treatment for Goodpasture's disease and in many cases for vasculitis. At this point, I will review the current state of the art for treatment of a number of these disorders.

Goodpasture's Disease

Untreated, Goodpasture's and anti-GBM disease have been felt to carry an almost 100% incidence of renal failure and mortality. There have been reports that cytotoxic agents can improve mortality {33}. However, the bulk of the studies have examined the effect of treatment with prednisone, cytotoxic agents, and plasmapheresis. A number of reports have shown that this treatment strategy leads to preservation of renal function and longterm survival {34,35}. In a retrospective analysis, Simpson et al compared patients treated with immunosuppression alone versus immunosuppression plus plasma exchange {36}. While the patients did better in the plasma exchange group, it was difficult to compare the groups because of differences in clinical severity. The possibility was raised that plasma exchange

offered no advantage over immunosuppression alone and it was suggested that a prospective controlled trial be performed. In a similar retrospective analysis, Savage et al stratified patients

Table 7

RETROSPECTIVE COMPARISON OF PATIENTS WITH ANTI-GBM MEDIATED DISEASE RECEIVING FULL TREATMENT (GROUP 2) OR LESS TREATMENT

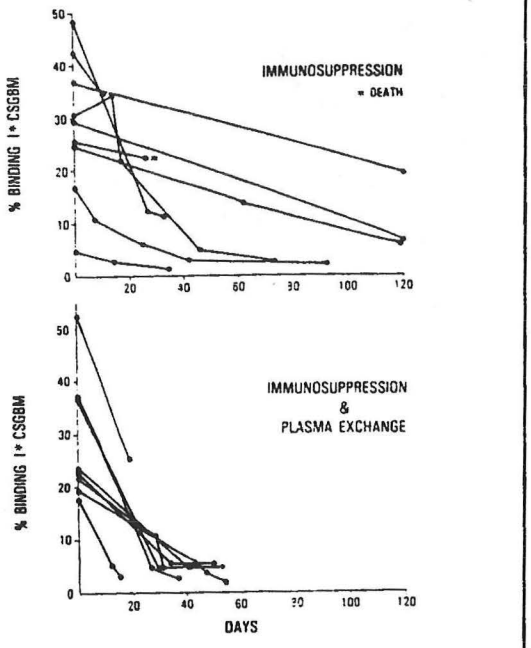
Presentation			Outcome at eight weeks		
Plasma creatinine (μmol/l)	No of patients	Received treatment	Improved	Required dialysis	Died
		Group 1 (n=59)			
Normal	3	2	3		
<600	5	5	2	2	1
>600	7	7		4	3
Dialysis dependent	44	33		33	11
		Group 2 (n=49)			
Normal	4	4	3		1
<600	15	15	13	2	
>600	5	5	1	4	
Dialysis dependent	25	25		18	7

Conversion: SI to traditional units—Plasma creatinine: 1 μmol/l=0·01 mg/100 ml.

Savage et al. *Brit Med J* 292:301, 1986

according to whether their renal function at the time of initiation of treatment was normal, creatinine was <600 μM, >600 μM, or the patients were dialysis dependent {37}. Table 7 shows results of this study. Group 2 refers to patients that received a full treatment, including prednisone, cytotoxic agents, and plasma exchange. Group 1 refers to patients who did not receive this complete treatment. As can be seen, in dialysis-dependent patients and patients with creatinine >600 μM, there was little recovery of renal function in either group. This result agrees with many reports showing that patients with Goodpasture's or anti-GBM disease rarely respond to treatment when they have become dialysis-dependent or have serum creatinine >600 μM {35,36,38}. In patients with lower creatinines the response to treatment was better. It should be noted that this was true in both treatment groups.

Only one prospective study has been performed comparing immunosuppression versus immunosuppression plus plasma exchange {39}. Seventeen patients with anti-GBM disease were prospectively randomized. Figure 5 shows that the levels of anti-GBM antibody decreased more rapidly in the plasma exchange group. Figure 6 shows the response of the patients. Solid symbols indicate that the patient ended up on dialysis, whereas open symbols indicate that the patient did not require dialysis. Circles indicate immunosuppression and squares indicate immunosuppression plus plasma exchange. Data points indicate the percent crescents and the entry serum creatinine. It can be seen that the higher the percentage of crescents on the initial renal biopsy the higher the entry serum creatinine. In general, the patients with >80% crescents all ended up on dialysis irrespective of the type of treatment. There was a



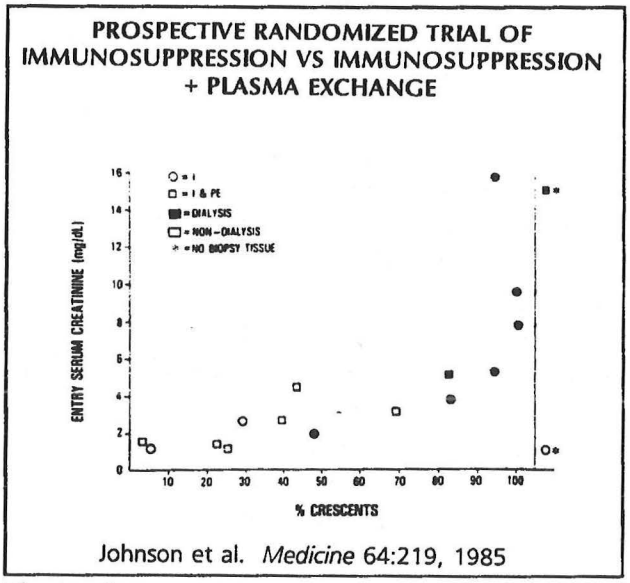
Johnson et al. *Medicine* 64:219, 1985

Figure 5

adapted. It also immediately became impossible to do a controlled trial with an untreated group. Pulse steroids generally means high doses of IV methylprednisolone, frequently 1 gram administered daily for 3-5 days, followed by a rapid taper. Table 8 shows a retrospective analysis by Bolton and Sturgill of patients treated with either pulse steroids or another form of conventional treatment {43}. Patients were divided into groups based on the type of crescentic glomerulonephritis they had. As can be seen, with conventional treatment (excluding pulse steroids), no patients that were already on hemodialysis recovered. There was one patient with immune complex (IC) disease and two patients with pauci-immune (PI) disease that improved. With pulse steroids, the results were better. Once again, patients tendency for patients treated with plasma exchange to do better, but this difference did not persist when the data was analyzed as a function of entry serum creatinine and % crescents. Thus these studies showed no benefit for plasma exchange. However, the small number of patients and the differences in entry serum creatinine and % crescents in the groups makes this data hard to interpret. What is required is a larger study where groups are stratified according to serum creatinine and % crescents at entry into the study. At present this is difficult given the bias by many people in the field that plasma exchange works.

Crescentic Glomerulonephritis

Historically, the prognosis for crescentic glomerulonephritis left untreated or treated with usual doses of oral prednisone, has been extremely poor. Thus, when it was initially reported that treatment with pulse methylprednisolone caused a significant recovery of renal function {40-42}, this treatment was immediately



Johnson et al. *Medicine* 64:219, 1985

Figure 6

with anti-GBM disease who were already on hemodialysis did not recover.

Table 8
PULSE METHYLPREDNISOLONE
IN CRESCENTIC GN

	N	HD Patients Who Recover	Total Improved %
Conventional Rx			
Anti-GBM	5	0/5	0
IC	7	0/6	14
PI	2	—	100
Vasculitis	3	0/3	0
Pulse			
Anti-GBM	12	0/10	17
IC	9	2/4	78
PI	21	10/15	76
Vasculitis	4	4/4	100

Bolton and Sturgill. Am J Nephrol 9:368, 1989

This agrees with the studies described above. Two patients who were not on hemodialysis did respond to treatment. Based on the small number of patients in this group, it is difficult to be certain whether pulse steroids work in anti-GBM disease. Patients with immune complex disease, pauci-immune disease, and vasculitis, all did well when treated with pulse steroids, as indicated by a 76-100% rate of improvement. In addition, even when these patients were on hemodialysis the majority recovered renal function. This ability to recover renal function even after requiring hemodialysis separates the non-anti-GBM related diseases from anti-GBM disease {39,43-46}.

There have been three prospective randomized controlled studies examining the effect of plasma exchange in crescentic glomerulonephritis. Pusey et al compared treatment with prednisone, cyclophosphamide, and azathioprine alone or in addition to plasma exchange in patients with Wegener's granulomatosis, microscopic polyarteritis, and idiopathic crescentic GN {47}. Patients who did not require dialysis at the time of treatment did well in both groups, and it was not possible to show an effect of plasma exchange. In patients who were dialysis dependent, plasma exchange appeared to improve recovery of renal function (10 of 11 vs 3 of 8 patients). Two other studies were designed similarly, and found no effect of plasma exchange in patients with non-anti-GBM crescentic GN {48} and in patients with idiopathic non-anti-GBM crescentic GN {49}. When data from all 3 controlled trials is combined, there is no effect of plasma exchange in patients not requiring dialysis, who generally do quite well (84% response) {44}. In patients requiring dialysis, plasma exchange appears to be beneficial (77% vs 42% response) {44}.

Wegener's Granulomatosis

In the absence of therapy, average survival in Wegener's granulomatosis was 5 months, and one year survival was 18% {50}. Oral steroids have been felt to offer some benefit, but large doses are required and it is rare to achieve a full remission. In addition, it has been difficult to stop the steroids and patients frequently develop many complications of steroid therapy. Cytotoxic agents have more recently become the main treatment for these patients {13,14,51-55}. Hoffman et al examined the outcome of treatment in 133 patients at the NIH {14}. Patients were treated with prednisone 1 mg/kg/day for 4 weeks, tapered to every other day steroids, and then tapered off steroids. In addition, patients were treated with cyclophosphamide 2 mg/kg/day. This was continued for one year after remission was obtained, and then was tapered in 25 mg increments every 2-3 months. Ninety-one percent of patients treated in this manner either improved or developed a partial remission. Seventy-five percent of patients developed a complete remission. Fifty percent of remissions were followed by relapses which occurred at 3 months to 16 years. This outcome is significantly superior to that which was achieved with no therapy or with oral steroids. Once again, it is unlikely that a controlled trial will be performed. The group at the NIH believes that cyclophosphamide is superior to azathioprine. However, other investigators have used azathioprine with good results. There are also reports that Wegener's granulomatosis responds to trimethoprim-sulfamethoxazole {56}.

A number of studies have noted that the most common cause for failure to respond to treatment in Wegener's and in vasculitis in general is a late diagnosis. Thus, most of the treatment failures are due to death or renal failure occurring early in the disease before treatment has had sufficient time to work. Also of concern is the high incidence of relapse in patients with Wegener's. However, given the responsiveness to therapy and the rapidity with which a relapse can be recognized, there is every reason to believe that these patients should do well if followed closely.

One approach which has recently been proposed is to utilize the ANCA to predict relapses. As noted above, in Wegener's granulomatosis ANCA levels decrease with treatment as the disease enters remission {22}. Most patients will eventually develop negative ANCA titers. It has also been noted in these patients that increases in ANCA titers precede relapses {22}. Thus, it is recommended to follow ANCA levels in Wegener's patients in remission. The frequency with which these are to be obtained has not been determined. A major question which arises is whether to treat a positive ANCA in these patients, or whether to wait for a clinical relapse to occur. Cohen Tervaert et al studied 20 patients with Wegener's granulomatosis in remission who developed a positive ANCA {57}. They were randomized to group 1 in which they were treated with cyclophosphamide 1 mg/kg/day for 9 months, and prednisone 30 mg/day for 3 months, irrespective of whether clinical relapse developed; or group 2 in which no treatment was instituted until a clinical relapse was diagnosed. Of 11 patients in group 2, 6 patients relapsed within 3 months. Three more patients relapsed within 6 months, and 2 patients never relapsed. In group 1, there were 9 patients and none of them showed a clinical relapse. Of note, the total treatment was greater in the patients randomized to no treatment. Thus, for the 9 patients who developed a clinical relapse, it probably would have been better to have initiated treatment at the time of the increase in ANCA. However, there were two patients who never developed a relapse who would have been treated unnecessarily if the positive ANCA was treated. This interesting question will require further study. At present, it is definitely indicated to follow ANCA levels in Wegener's patients in

remission. It is not clear whether this applies to all of the ANCA associated vasculitides.

Polyarteritis Nodosa

There have been a number of studies examining the treatment of patients with polyarteritis nodosa. Many of these studies have combined polyarteritis nodosa, Churg-Strauss syndrome and microscopic polyarteritis. Frohnert and Sheps performed a retrospective review of 130 patients with polyarteritis nodosa either untreated or treated with steroids {58}. They noted that 5 year survival increased from 13% in the untreated group to 48% in the group treated with steroids. Twelve years later, Leib et al performed a retrospective analysis of 64 patients with polyarteritis nodosa and found similar results {59}. Patients treated with supportive care had a mean survival of 3 months and a 5 year survival of 12%. Patients treated with steroids had a mean survival of 63 months and a 5 year survival of 53%. In addition, they found that patients treated with steroids and cytotoxic agents had a mean survival of 149 months and a 5 year survival of 80%. Fauci et al treated 17 patients with severe systemic necrotizing vasculitis with cyclophosphamide (16 patients) or azathioprine (1 patient) {60}. Fourteen patients achieved remission which was sustained from 2 to 61 months. None of these patients relapsed. These results are significantly superior to historical controls treated with supportive care or steroids alone.

Summary

In summary, it appears that studies on therapy have led to generally similar results for Wegener's granulomatosis, polyarteritis nodosa and related disorders, and crescentic glomerulonephritis. In general, for these studies steroids offer some benefit over supportive treatment. However, cytotoxic agents appear to have a significantly better outcome than steroids alone. Pulse methylprednisolone is beneficial in crescentic glomerulonephritis, whether idiopathic or whether associated with systemic vasculitis. Plasma exchange appears to offer no additional benefit over steroids and cytotoxic agents alone in crescentic glomerulonephritis and vasculitis, unless patients are on dialysis, in which case plasma exchange may offer a higher rate of cessation of dialysis.

In Goodpasture's and anti-GBM disease, the standard treatment is now steroids, cytotoxic agents, and plasma exchange. Although it is not clear that plasma exchange offers an additional advantage, there is little enthusiasm for a controlled trial given the poor prognosis for this disorder. In general, prognosis with Goodpasture's is dependent on the level of renal function at the time of initiation of treatment. Prognosis is far superior for patients whose creatinines are lower than 6 mg% than for patients whose creatinines are higher. Patients already initiated on dialysis in general do not respond to treatment. With non-Goodpasture's crescentic glomerulonephritis, prognosis is worse with worsened renal function, but patients from all categories are capable of a response.

A NEW CLASSIFICATION SCHEME

Based on all of the above information, it is now time to propose a new classification scheme that takes into account ANCA levels and similarities in treatment response between a number of different conditions (Table 9). The classification scheme I propose is based on the size of the vessel involved. Large vessel vasculitides involve the aorta or a branch of significant size. These arteritities include **giant cell arteritis** and **Takayasu's arteritis**. Medium vessel vasculitis includes only polyarteritis nodosa. In this case we are referring to the so-called **classic**

Table 9

VASCULITIS: CLASSIFICATION

Large Vessel
1. Giant cell (temporal) arteritis
2. Takayasu arteritis

Medium Vessel
1. Polyarteritis nodosa (classic)

Small Vessel
1. ANCA-associated: involves small vessels but may also involve arteries
   a. Wegener's granulomatosis
   b. Churg-Strauss syndrome
   c. Microscopic polyangiitis
   d. Idiopathic pauci-immune crescentic GN
2. Immune complex-associated
   a. Henoch-Schoenlein purpura
   b. Essential cryoglobulinemia
   c. Cutaneous leukocytoclastic angiitis
   d. Idiopathic immune complex crescentic GN
3. Anti-GBM-associated

polyarteritis nodosa in which there is no vasculitis of small vessels such as capillaries, venules, or arterioles. Therefore, there is no glomerulonephritis. This type of vasculitis is associated with hepatitus B surface antigen positivity.

The remaining category is small vessel vasculitis. I have divided up these vasculitides in a manner similar to that which has proven useful for the crescentic glomerulonephritities. Thus, these can be viewed as either ANCA-associated, immune complex-associated, or anti-GBM-associated. It should be noted that the small vessel vasculitides may also involve medium sized arteries, as proposed by the recent International Concensus Conference {61}. Since it appears that involvement of medium-sized arteries does not affect serologies, treatment, or outcome, we choose to keep these entities as small vessel vasculitides rather than naming them as an overlap syndrome. ANCA-associated vasculitides include **Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis,** and **idiopathic pauci-immune crescentic glomerulonephritis.** It should be noted that the term microscopic polyarteritis has been replaced by the term microscopic polyangiitis. This is as was recommended by the International Concensus Conference from North Carolina {61}, and represents the fact that the small vessels involved include arterioles, capillaries, and venules. It should be noted that this classification groups Churg-Strauss syndrome together with Wegener's and microscopic polyangiitis rather than with classic polyarteritis nodosa. This agrees with the observation that Churg-Strauss frequently involves small vessels in addition to medium-sized arteries. In addition, this classification is influenced by the fact that many patients with Churg-Strauss syndrome have an MPO-ANCA. Lastly, it is influenced by the fact that a number of patients with what appears to be Wegener's granulomatosis have eosinophilia or asthma, but not both suggesting that there may be overlaps between Churg-Strauss and Wegener's granulomatosis. The second category of small vessel vasculitis, the immune complex-associated ones include **Henoch-Shoenlein purpura, essential cryoglobulinemia, cutaneous leukocytoclastic angiitis,** and **immune complex crescentic glomerulonephritis.** The last category is the anti-GBM-associated disease. In this case there is only one cause which is **anti-GBM disease.** It is not felt that there is any reason to separate out Goodpasture's disease from anti-GBM disease.

Based on this classification, one can design a treatment strategy. Patients with large

vessel vasculitis are generally treated with steroids. Medium vessel vasculitis is treated with steroids plus cytotoxic agents. The ANCA-associated small vessel vasculitides should be treated with steroids and cytotoxic agents. If crescentic GN is present steroids should be administered initially utilizing a pulse protocol. If patients are dialysis-dependent at presentation, plasma exchange is likely indicated. Anti-GBM disease should be treated with steroids, cytotoxic agents and plasma exchange. The treatment of the immune complex-associated small vessel vasculitides is more complex, and depends in many cases on the specific disease entity. For instance, most patients with Henoch-Schoenlein disease need not be treated, while many patients with essential cryoglobulinemia are thought to respond to plasma exchange. Whatever the cause of vasculitis, early initiation of treatment and close patient follow-up are key.

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