Small-vessel vasculitis (SVV) that is injurious to the kidney includes immune complex–mediated vasculitis, such as Henoch-Schönlein purpura and cryoglobulinemic vasculitis, and necrotizing vasculitis associated with anti-neutrophil cytoplasmic autoantibodies (ANCA), such as microscopic polyangiitis and Wegener’s granulomatosis. The most frequent renal lesion caused by SVV is glomerulonephritis, whereas large-vessel vasculitis (LVV) and medium-sized-vessel vasculitis (MVV) do not cause glomerulonephritis but may cause renal dysfunction secondary to ischemia.

In 1993, the Chapel Hill Consensus Conference for the Nomenclature of Systemic Vasculitis (1) agreed on the names and definitions of many vasculitides that affect the kidneys (Table 1). These names and definitions are used in this review. LVV, such as giant-cell arteritis and Takayasu arteritis, rarely cause clinically significant renal disease (2). When a LVV does cause renal dysfunction, it is usually in the form of the renovascular hypertension secondary to disease in the main renal arteries or in the aorta at the ostia of the renal arteries. MVV, including polyarteritis nodosa and Kawasaki disease, results in necrotizing inflammation of arteries without inflammation in vessels other than arteries, including no glomerulonephritis (2). MVV may cause aneurysmal dilation, thrombosis, and rupture of renal arteries, resulting in infarction and hemorrhage (1,2).

Patients with pauci-immune SVV, such as microscopic polyangiitis, Wegener’s granulomatosis, and Churg-Strauss syndrome, have a high frequency of ANCA (1,2). ANCA react with cytoplasmic constituents of neutrophils and monocytes (3,4). Approximately 90% of cytoplasmic-staining ANCA (C-ANCA) react with a serine proteinase called proteinase 3 (PR3-ANCA). In patients with SVV, approximately 90% of perinuclear-staining ANCA (P-ANCA) react with myeloperoxidase (MPO-ANCA). In ANCA-positive patients who do not have SVV or glomerulonephritis, such as patients with ulcerative colitis, primary sclerosing choleangiitis, or Felty’s syndrome, many P-ANCA have specificity for antigens other than MPO, such as lactoferrin and elastase.

PR3-ANCA are most common in patients with Wegener’s granulomatosis, but are not specific for this disease. Our own data, as well as that of a recent European vasculitis study group (E. Christiaan Hagen, personal communication), indicate that approximately 65% of patients with Wegener’s granulomatosis have PR3-ANCA and approximately 20% have MPO-ANCA (Table 2). PR3-ANCA are also found in patients with microscopic polyangiitis and necrotizing glomerulonephritis without evidence for systemic SVV, although MPO-ANCA are more common in these diseases. MPO-ANCA and PR3-ANCA occur in patients with Churg-Strauss syndrome, but relative frequencies are poorly defined because of the small numbers of patients who have been studied. Thus, although there are different frequencies of PR3-ANCA and MPO-ANCA among different types of SVV, neither ANCA subtype provides a diagnostic test that allows for the diagnostic differentiation among different phenotypes of ANCA-SVV. However, in a patient with signs and symptoms of SVV, ANCA positivity does confirm the presence of some form of ANCA-associated SVV, which is often useful for directing management even if the specific type of ANCA-SVV has not yet been determined.

### Pathologic Features

The characteristic acute vascular lesion of ANCA-SVV is focal fibrinoid necrosis of vessels with associated leukocyte infiltration, frequently with leukocytoclasis. In a given patient, this lesion may affect any or all of the following vessels: arteries, arterioles, venules, and capillaries, especially glomerular capillaries and pulmonary alveolar capillaries (2,5). The major clinicopathologic categories of systemic ANCA-vasculitis are microscopic polyangiitis, Wegener’s granulomatosis, and Churg-Strauss syndrome. Crescentic glomerulonephritis is a frequent component of systemic ANCA-vasculitis, and also occurs as a renal-limited form of ANCA-vasculitis (ANCA-GN). Microscopic polyangiitis, Wegener’s granulomatosis, and Churg-Strauss syndrome all share pathologically identical necrotizing inflammation in small vessels. Wegener’s granulomatosis is distinguished by the presence of necrotizing granulomatous inflammation, Churg-Strauss syndrome by the presence of asthma and eosinophilia, and microscopic polyangiitis by the absence of granulomatous inflammation and asthma (Table 1). Severe necrotizing glomerulonephritis is a frequent component of the vascular inflammation in Wegener’s granulomatosis and microscopic polyangiitis, but necrotizing glomerulonephritis is less frequent and usually less severe in Churg-Strauss syndrome.

In the kidneys of patients with any type of ANCA-SVV, glomerular capillaries are affected most often, resulting in necrotizing glomerulonephritis, usually with crescent formation (Figure 1, A and B). Arterioles, arteries, and interstitial capillaries/venules (especially medullary vasa recta) may also be involved (Figure 1, C and D). Interlobular and arcuate...
Table 1. Names and definitions of vasculitis adopted by the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis *

<table>
<thead>
<tr>
<th>Large-vessel vasculitis</th>
<th>Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. Often involves the temporal artery. Usually occurs in patients older than 50 and is often associated with polymyalgia rheumatica.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takayasu arteritis</td>
<td>Granulomatous inflammation of the aorta and its major branches. Usually occurs in patients younger than 50.</td>
</tr>
<tr>
<td>Medium-sized vessel vasculitis</td>
<td>Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules.</td>
</tr>
<tr>
<td>polyarteritis nodosa</td>
<td>Arteritis involving large, medium-sized, and small arteries, and associated with mucocutaneous lymph node syndrome. Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children.</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small- to medium-sized vessels, e.g., capillaries, venules, arterioles, and arteries. Necrotizing glomerulonephritis is common.</td>
</tr>
<tr>
<td>Wegener's granulomatosis</td>
<td>Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels, and associated with asthma and blood eosinophilia.</td>
</tr>
<tr>
<td>Churg-Strauss syndrome</td>
<td>Necrotizing vasculitis with few or no immune deposits, affecting small vessels, i.e., capillaries, venules, or arterioles. Necrotizing arteritis involving small- and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.</td>
</tr>
<tr>
<td>microscopic polyangiitis</td>
<td>Vasculitis with immunoglobulin A-dominant immune deposits, affecting small vessels, i.e., capillaries, venules, or arterioles. Typically involves skin, gut, and glomeruli, and is associated with arthralgias or arthritis.</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
<td>Vasculitis with cryoglobulin immune deposits, affecting small vessels, i.e., capillaries, venules, or arterioles, and associated with cryoglobulins in serum. Skin and glomeruli are often involved.</td>
</tr>
<tr>
<td>essential cryoglobulinemic vasculitis</td>
<td>Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis.</td>
</tr>
</tbody>
</table>

* The ANCA-associated vasculitides are Wegener’s granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome. (Modified from Jennette et al. [1] with permission.).

Table 2. Approximate frequencies of PR3-ANCA (C-ANCA) and MPO-ANCA (P-ANCA) in patients with glomerulonephritis caused by Wegener’s granulomatosis (WG), microscopic polyangiitis (MPA), and pauci-immune necrotizing and crescentic glomerulonephritis without systemic vasculitis (NCGN)

<table>
<thead>
<tr>
<th>ANCA Result</th>
<th>WG</th>
<th>MPA</th>
<th>NCGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive PR3-ANCA/C-ANCA</td>
<td>65 to 75%</td>
<td>35 to 45%</td>
<td>30 to 40%</td>
</tr>
<tr>
<td>Positive MPO-ANCA/P-ANCA</td>
<td>15 to 25%</td>
<td>45 to 55%</td>
<td>60 to 70%</td>
</tr>
<tr>
<td>Negative ANCA</td>
<td>10 to 20%</td>
<td>10 to 20%</td>
<td>10 to 20%</td>
</tr>
</tbody>
</table>

arteries are affected more often than larger arteries, but a few patients with ANCA-SVV will have involvement of interlobar and even main renal arteries. The renal necrotizing arteritis of ANCA-SVV is indistinguishable histologically from that of necrotizing MVV, such as polyarteritis nodosa; however, the absence of inflammation in vessels other than arteries (e.g., glomerular capillaries) distinguishes the MVV from ANCA-SVV. Necrotizing leukocytoclastic angiitis in medullary vasa recta may be very severe, and can result in papillary necrosis and hemorrhage. The frequency of the medullary angiitis is difficulty to know because it is not always sampled in renal biopsy cores, which purposefully have more cortex than medulla.

ANCA-SVV typically has an absence or paucity of immu-
nohistologic staining for immunoglobulins at sites of vasculitis and glomerulonephritis. This “pauci-immune” appearance is in contrast to the characteristic granular immunoglobulin staining of immune complex–mediated disease and the linear immunoglobulin staining of anti-glomerular basement membrane (anti-GBM) antibody–mediated disease. Although ANCA are much more common in patients with pauci-immune necrotizing glomerulonephritis and vasculitis, patients with anti-GBM glomerulonephritis (6) and immune-complex crescentic glomerulonephritis (7) have a higher frequency of ANCA than healthy control subjects. Approximately 20% to 30% of patients with either crescentic immune-complex glomerulonephritis or anti-GBM glomerulonephritis have ANCA. In patients with anti-GBM disease, the presence of ANCA correlates with the development of vasculitis that is not seen with anti-GBM disease alone, such as arteritis, arterioliitis, and venulitis in a distribution typical for ANCA-vasculitis. In patients with immune-complex glomerulonephritis, the presence of ANCA correlates with a greater likelihood of crescent formation and systemic vasculitis. For example, membranous glomerulopathy patients with ANCA often develop crescent formation and rapidly progressive disease. This suggests that ANCA can synergize with immune-complex localization to induce more severe inflammation.

How “pauci-immune” is the glomerulonephritis in patients with ANCA-SVV and ANCA-GN? In a recent evaluation of 213 patients with glomerulonephritis and crescent formation (excluding patients with lupus nephritis and anti-GBM disease), we concluded that, to be at least 80% predictive of ANCA disease, “pauci-immune” should be defined as 2+ or less staining for any immunoglobulin (on a scale of 0 to 4+) and absence of immune complex–type electron-dense deposits by electron microscopy (Figure 2) (7).

During the acute phase of disease, ANCA-SVV is characterized by fibrinoid necrosis and neutrophilic infiltration. This manifests in glomeruli as segmental necrosis and crescent formation. If the patient survives, these acute lesions evolve into chronic sclerotic lesions with predominantly mononuclear leukocyte infiltrates. For example, acute glomerular injury evolves into focal segmental glomerular scarring or diffuse

Figure 1. Renal histologic manifestations of ANCA-SVV. (A) Early segmental glomerular fibrinoid necrosis with slight adjacent epithelial proliferation (periodic acid-Schiff stain). (B) Large cellular crescent with focal disruption of Bowman’s capsule at the bottom of the photograph (periodic acid-Schiff stain). (C) Necrotizing inflammation involving two interlobular arteries (arrow, fibrinoid necrosis; Masson trichrome stain). (D) Leukocytoclastic angiitis affecting the medullary vasa recta (hematoxylin and eosin stain).
global glomerular scarring, depending on the severity of the acute injury (Figure 3).

The lungs are frequently affected by ANCA-SVV. Acute pulmonary lesions that occur in all types of ANCA-SVV include necrotizing inflammation of alveolar capillaries, arteries, arterioles, veins, and venules (8,9). Necrotizing granulomatous inflammation occurs in patients with Wegener’s granulomatosis and Churg-Strauss syndrome, and may involve vessels and airways. The acute inflammatory pulmonary injury evolves into more chronic lesions, such as interstitial fibrosis and bronchiolitis obliterans—organizing pneumonia. No particular pulmonary lesion is specific for either C-ANCA or P-ANCA–positive patients; however, necrotizing granulomatous inflammation is more commonly found in C-ANCA patients.

The tissue distribution of the inflammatory lesions of ANCA-SVV is extremely varied among patients, resulting in a wide variety of clinical manifestations. In addition to nephritis caused by glomerular inflammation and pulmonary hemorrhage caused by alveolar capillaries or granulomatous inflammation, patients may have purpura caused by dermal leukocytoclastic angiitis, mononeuritis multiplex caused by perineural and epineurial arteriolitis and arteritis, myalgias caused by arteriolitis and arteritis in skeletal muscles, and abdominal pain caused by venulitis, arteriolitis, and arteritis in abdominal viscera, such as the gut, liver, pancreas, and spleen.

Clinical Features

ANCA-SVV is more common in Caucasians than African Americans, with a ratio of approximately 7.5:1. Women and Men are equally affected, and although patients are usually 55 yr of age or older, patients of any age may develop ANCA-SVV (10–12). The clinical renal manifestations vary according to the severity and stage of the underlying renal injury (Figure 3). Hematuria with dysmorphic red blood cells and red blood cell casts is a frequent clinical feature. Proteinuria tends to be in the subnephrotic range, with a mean of 2 to 3 g/day, although some patients have as little proteinuria as 0.5 g/day and as much as 20 g/day. Although the presentation of ANCA glomerulonephritis is frequently that of rapidly progressive glomerulonephritis, the syndrome of asymptomatic hematuria with minimal amounts of proteinuria or acute nephritis is common as well. Unfortunately, at their first presentation, many patients already require dialysis because of chronic glomerulonephritis and severe glomerular sclerosis, and interstitial fibrosis indicative of ESRD. This circumstance is often the result of a delay in referring the patient to a nephrologist for management.

Nephrologists are confronted with the diagnostic dilemma of whether a renal biopsy is essential for the management of ANCA-GN and ANCA-SVV. The answer to this question is predicted on several variables, including the features of the clinical syndrome, the accuracy of the ANCA serologic methodology, and most importantly, the form of therapy that will be used. Some investigators have concluded that PR3-ANCA and MPO-ANCA assays can have a sensitivity for pauci-immune necrotizing and crescentic glomerulonephritis ranging between 95% and 100%, with a specificity in excess of 99% (13). If patients who have strong clinical evidence for ANCA-SVV are tested with such a high-quality assay system, the positive predictive value of the ANCA result is greater than 99% (14). Thus, expert ANCA testing may obviate pathological confirmation of ANCA-SVV or ANCA-GN especially in some emergency situations. For instance, in a patient who presents with pulmonary hemorrhage who requires ventilator support, and who has red blood cells and red blood cell casts in the urine, a rapidly rising creatinine concentration, and palpable purpura, renal biopsy may be unnecessary if the ANCA test is positive. However, despite the contention by some that ANCA serological testing has "come of age," not all laboratories perform antigen-specific ANCA assays, and the sensitivity and speci-
ficity for PR3-ANCA and MPO-ANCA testing vary among assay systems. Therefore, clinicians must have knowledge of the capabilities of the laboratory that is performing their ANCA testing before they can decide how much weight to give the test result in their management decisions.

If patients with ANCA-SVV and ANCA-GN could be treated effectively with innocuous drugs, theoretically, the clinician could decide to treat the patient empirically without exhaustive confirmation of the diagnosis. However, because ANCA-SVV and ANCA-GN are typically treated with potent anti-inflammatory and immunosuppressive drugs that predispose to life-threatening infections and risk of mutagenesis, it is our contention that a renal biopsy or other tissue confirmation is called for whenever possible. An integration of clinical manifestations, pathologic findings, and serologic data is required in order to provide optimum information for meaningful patient-informed consent and for treatment decisions.

In addition to ANCA-SVV, the differential diagnosis for patients with signs and symptoms of a systemic disease affecting small vessels often includes systemic immune-complex diseases, such as systemic lupus erythematosus, Henoch-Schönlein purpura, and cryoglobulinemic vasculitis, as well as the thrombotic microangiopathies and atheroembolization. Careful clinical, pathologic, and serologic evaluation should distinguish among these systemic vasculopathies.

Pulmonary-Renal Vasculitic Syndrome

ANCA-SVV has a predilection for the capillary beds of the respiratory tract (2.9.15). At least 50% of patients with ANCA-GN have pulmonary disease spanning the spectrum from severe life-threatening pulmonary hemorrhage to fleeting alveolar infiltrates. Among patients with ANCA-GN, 10% have massive pulmonary hemorrhage, with a mortality of 50%. The majority of patients with ANCA-SVV present with focal or diffuse pulmonary infiltrates with variable amounts of hemoptysis. In other patients—especially those with Wegener’s granulomatosis—pulmonary nodules, cavities, alveolar opacities, or diffuse ground-glass opacities are observed radiographically. Because these parenchymal opacities are ill-defined at times, routine chest x-rays miss smaller nodular or cavitary lesions that are best seen on fine-cut computed tomography. This form of imaging is a more sensitive approach to unravel the pulmonary manifestations of ANCA-SVV. Fiberoptic bronchoscopy with transbronchial lung biopsy is a useful procedure in patients in whom a pathological confirmation of a SVV cannot be made by kidney or upper respiratory tract biopsy. There may be no renal involvement at the onset of a SVV. For example, among the first 158 patients studied at the National Institutes of Health, only 18% of those with Wegener’s granulomatosis presented with evidence for glomerulonephritis; however, renal involvement eventually occurred in 77% of patients, usually in the first 2 yr of illness (16).

Upper respiratory tract symptoms of ANCA-SVV include necrotizing lesions of the nose, sinus, and ear (17). These lesions are found not only in patients with Wegener’s granulomatosis, but also in patients with microscopic polyangiitis. Granulomatous inflammation of the trachea, usually in the subglottic region, results in unilateral or bilateral edema, inflammation, fibrosis, and tracheal stenosis. The clinical picture is that of stridor and dyspnea that requires persistent long-term immunosuppressive therapy.

The differential diagnoses of pulmonary-renal vasculitic syndromes other than ANCA-SVV includes anti-GBM disease (Goodpasture’s syndrome) and some forms of immune-complex diseases, such as systemic lupus erythematosus. Renal histology is a definitive means of separating the diagnostic possibilities. Serological studies—including tests for antinuclear antibodies, anti-double-stranded DNA, low serum complement levels, cryoglobulins, hepatitis C antibodies, and anti-GBM antibodies—are useful for suggesting the appropriate diagnosis. One should bear in mind that 20% to 30% of patients with anti-GBM disease also are ANCA-positive and are at risk for developing any of the manifestations of ANCA-SVV. Thus, patients with pulmonary-renal vasculitic syndrome who have anti-GBM antibodies should also be tested for ANCA, and vice versa.

A difficult differential diagnosis occurs in patients with ANCA-SVV or ANCA-GN who, during treatment, develop pulmonary infiltrates with or without hemoptysis. Recurrent vasculitis must be differentiated from infection, especially fungal or mycobacteria tuberculosis. A high ANCA titer in such a patient is not definitive evidence for pulmonary vasculitis. A negative ANCA result makes pulmonary vasculitis less likely. Bronchoscopy, including bronchial alveolar lavage, may help differentiate infection from vasculitic alveolar hemorrhage. Similarily, infections of the upper respiratory tract can mimic vasculitic lesions in the nose, sinus, and ear. Fiberoptic translumination of the upper airways with biopsy is useful for identifying infections and vascular inflammation.

Renal-Dermal Vasculitic Syndrome

Renal-dermal vasculitic syndromes include Henoch-Schönlein purpura, cryoglobulinemia vasculitis, systemic lupus erythematosus, and ANCA-SVV (18). Common dermal vasculitic findings in ANCA-SVV are palpable purpura (usually in the lower extremities), petechia, ulcers, nodules, ecchymoses, and bullae. Urticaria is a much more common manifestation of SVV in the skin than was previously realized. The clinical syndrome of palpable purpura, nephritis, and ANCA is nearly diagnostic for ANCA-SVV, although tissue confirmation of vasculitis is comforting before the institution of toxic immunosuppression treatments. In a patient with renal-dermal vasculitic syndrome, biopsy demonstration of immunoglobulin A-dominant immune deposits in either dermal vessels or glomeruli is diagnostic for Henoch-Schönlein purpura. A renal biopsy will include or exclude cryoglobulinemic glomerulonephritis or lupus nephritis. The resolution of the differential diagnosis in patients with renal-dermal vasculitic syndromes is very important because the prognosis and appropriate treatments are quiet different among the diagnostic possibilities, i.e., Henoch-Schönlein purpura, cryoglobulinemic vasculitis, systemic lupus erythematosus, and ANCA-SVV. For example, a 25-yr-old patient with purpura and nephritis who has Henoch-Schönlein purpura usually does not require aggressive immunosuppression, whereas a patient with the same clinical
presentation who has ANCA-SVV is at risk for life-threatening organ injury if not promptly and appropriately treated.

**Other Organ System Involvement**

The most common neurological manifestation of ANCA-SVV is peripheral neuropathy, typically manifesting as mononeuritis multiplex. Occasionally, patients have central nervous system inflammation, especially granulomatosis meningial inflammation, which may be observed on magnetic resonance imaging. Patients may develop seizures, which will respond to immunosuppressive treatment.

Gastrointestinal disease, found in one third of patients with ANCA-SVV, may present with gastric or peptic ulcers detected by endoscopic examination. Vasculitis of the small and large intestine results in gastrointestinal bleeding, or—if severe—perforation of the vescas as a consequence of transmural infarction.

Iritis, uveitis, and episcleritis result in painful, red eyes. These lesions are frequently present in a "subclinical" fashion and require slit-lamp ophthalmologic evaluation for recognition.

Almost all patients have a prodrome of a “flu-like illness” with malaise, myalgias, and arthralgias, which is probably mediated by the increased systemic levels of cytokines released from the sites of inflammation. The arthralgias often migrate from joint to joint.

**Outcome**

Several studies have examined prognostic factors in ANCA-SVV (11,19). These studies point to the entry-level serum creatinine value, the presence of pulmonary disease, the severity of renal disease, and even the initial white blood cell count as important predictors of outcomes. In our own studies (11), the most important determinant of patient survival was the presence or absence of pulmonary hemorrhage (Table 3). The presence of any pulmonary symptoms—that is, pulmonary infiltrates, nodules, or cavities—did not increase the risk of death. The risk of ESRD was largely attributable to the entry-level serum creatinine value, even when such variables as the presence or absence of extrarenal disease and the presence or absence of pulmonary findings were incorporated into the model. Crescents and necrosis found on renal biopsy did not add to the predictive power of the model. Interstitial fibrosis on renal biopsy was an independent risk factor in individuals with an entry-level creatinine concentration of <3 mg/dL, whereas in individuals with serum creatinine concentrations greater than 4.5 mg/dL, tubulointerstitial injury was present.

**Treatment**

**Induction Therapy**

Because renal prognosis appears to be determined by early treatment, it is reasonable to induce suppression of the vascular inflammation promptly with aggressive therapy that usually includes high-dose corticosteroids and cyclophosphamide. Our approach is to give patients 7 mg/kg per day of methylprednisolone for 3 days, followed by daily oral prednisone. Whether plasmapheresis and methylprednisolone are equally good induction therapies, or whether plasmapheresis adds additional benefit to methylprednisolone as a means of induction therapy is currently under study (20). Cyclophosphamide is administered either intravenously or orally. Intravenous cyclophosphamide is administered on a monthly basis beginning at a dose of 0.5 g/m², with adjustment of the dose upward to 1 g/m² on the basis of 2-wk leukocyte counts (10,12). Oral cyclophosphamide should begin at a dose of 2 mg/kg per day (21). Prednisone is administered at a dose of 1 mg/kg for the first month, which is tapered to alternate-day therapy in the second month, with cessation of prednisone therapy at the end of the third to fourth months. All forms of cyclophosphamide dosage should be titrated to the leukocyte count. Special attention to the leukocyte count must be monitored while the patient is on tapering doses of prednisone, because cyclophosphamide dosage may need to be adjusted downward as the prednisone dose is decreased. This induction therapy can be initiated while clinicians wait for renal biopsy or serologic study results.

The optimal length of cyclophosphamide therapy has not been determined. It is clear that indefinite treatment with cyclophosphamide is associated with prohibitive risks, including a 15% incidence of transitional cell carcinoma in the bladder in those patients treated with long-term oral cyclophosphamide (22). In patients achieving complete remission within 6 months of therapy, treatment can be stopped under the provision that there is close patient follow-up. In those individuals with persistently active disease at 6 months, it is

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Relative Risk of Death</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary hemorrhage (present versus absent)</td>
<td>8.64</td>
<td>(3.36 to 22.19)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Any pulmonary symptoms (present versus absent)</td>
<td>2.36</td>
<td>(0.80 to 6.95)</td>
<td>0.16</td>
</tr>
<tr>
<td>Disease category (MPA versus NCGN alone)</td>
<td>1.68</td>
<td>(0.48 to 5.82)</td>
<td>0.61</td>
</tr>
<tr>
<td>ANCA pattern (C-ANCA versus P-ANCA)</td>
<td>3.78</td>
<td>(1.22 to 11.70)</td>
<td>0.031</td>
</tr>
<tr>
<td>Race (African American versus Caucasian)</td>
<td>2.41</td>
<td>(0.75 to 7.77)</td>
<td>0.34</td>
</tr>
<tr>
<td>Treatment (cyclophosphamide versus corticosteroids alone)</td>
<td>0.18</td>
<td>(0.05 to 0.66)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

* Reprinted from Hogan et al. (11) with permission.
reasonable to continue cyclophosphamide therapy for a full 12 months. Another possible protocol utilizes cyclophosphamide as the immunosuppressive agent for the first 3 months of treatment and then azathioprine (2 mg/kg) for the duration of the therapy (23). Most patients may stop this form of therapy after a total of 6 to 12 months of treatment.

Intravenous and oral cyclophosphamide appear to have equal efficacy in inducing remission. Whether oral cyclophosphamide treatment results in a decrease in the relapse rate when compared with intravenous cyclophosphamide remains an issue for study. Intravenous cyclophosphamide allows for a smaller total dose of cyclophosphamide than the oral regimen. As a consequence, there is a threefold decrease in both minor and major infections. The most bothersome feature of cyclophosphamide therapy, however, is the long-term mutagenic risk, especially the risk of induction of transitional cell carcinoma of the bladder (22). Gonadal toxicity in women over the age of 35 yr results in premature menopause.

Because cyclophosphamide is toxic, the question arises whether prednisone is an adequate treatment option; however, the requirement of cyclophosphamide as a necessary adjunct to prednisone has been appreciated for years (21). In our own studies, we have determined that treatment with prednisone alone resulted in a three-fold increased risk of relapse when compared with treatment with cyclophosphamide (12). Thus, patients with ANCA-SVV who are not dialysis-dependent should be treated with combination therapy including cyclophosphamide.

Alternative Treatment Strategies

DeRemee and colleagues suggested that local-regional disease of the upper respiratory tract should be treated first with trimethoprim-sulfamethoxazole and then with corticosteroid therapy in the event of unsuccessful antibiotic therapy (24). The rationale for this approach is based largely on empirical data, but is supported by the fact that chronic nasal carriage of Staphylococcus aureus is a risk factor for relapse in Wegener’s granulomatosis (25). In 1985, DeRemee et al. described their results in treating patients with Wegener’s granulomatosis (24). One hundred new patients with Wegener’s granulomatosis were treated with trimethoprim-sulfamethoxazole. Eleven of these patients improved, four of them without concurrent or previous immunosuppressive treatment. Most recently, Reinhold-Keller et al. (26) studied 19 patients with Wegener’s granulomatosis restricted to the upper and lower airways, and found similar results. A prospective placebo-controlled trial with trimethoprim-sulfamethoxazole (960 mg twice daily) was performed in 81 patients with Wegener’s granulomatosis (27). In 19% of these patients, therapy was stopped because of side effects. A statistically significant reduction in the number of relapses was observed in the groups assigned to trimethoprim-sulfamethoxazole, although the decrease in relapse rate was limited to relapse in the upper respiratory tract, and not to relapse in the lower respiratory tract or the kidney.

Conflicting data are beginning to emerge, however, in that a randomized trial comparing methotrexate and trimethoprin-sulfamethoxazole for maintenance of remission in 65 patients with Wegener’s granulomatosis was recently completed (25).

In this study, generalized Wegener’s granulomatosis was brought into remission by treatment with cyclophosphamide and prednisone. The maintenance of remission was much more effective with methotrexate therapy than with either trimethoprin-sulfamethoxazole or prednisone. In fact, trimethoprin-sulfamethoxazole and prednisone together seemed to increase the chance of relapse. Thus, the use of trimethoprin-sulfamethoxazole in patients with Wegener’s granulomatosis is still controversial.

Methotrexate may be a useful form of therapy for SVV, especially in individuals with normal or near-normal renal function, and in patients with vasculitis predominantly confined to the kidneys (29). Methotrexate should not be used if the patient’s serum creatinine concentration is greater than 2 mg/dL. Pooled intravenous γ-globulin has been tried anecdotally, not only for induction therapy but also for individuals resistant to cyclophosphamide and azathioprine therapy. The long-term role of these agents in the treatment of ANCA-SVV awaits further investigation.

Remission and Relapse

The terms “remission” and “relapse” for ANCA-SVV patients are defined in Table 4 (11). ANCA-SVV and ANCA-GN patients treated with either intravenous or oral cyclophosphamide have a long-term remission rate of between 60% and 85%. Relapse occurs in up to 40% of patients within a mean of 18 months after therapy has stopped. Relapse typically occurs in the same organ system initially affected by the disease.

Table 4. Criteria for evaluating treatment responses in patients with ANCA-SVV and ANCA-GN

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>Stabilization or improvement of renal function (as measured by serum creatinine concentration), resolution of hematuria, and resolution of extrarenal manifestations of systemic vasculitis. Persistence of proteinuria was not considered indicative of persistence of disease activity.</td>
</tr>
<tr>
<td>Treatment resistance</td>
<td>(1) Progressive decline in renal function with the persistence of an active urine sediment or (2) persistence of new appearance of any extrarenal manifestation of vasculitis despite immunosuppressive therapy.</td>
</tr>
<tr>
<td>Relapse</td>
<td>Occurrence of at least one of the following: (1) rapid rise in serum creatinine concentration, accompanied by an active urine sediment; (2) a renal biopsy demonstrating active necrosis or crescent formation; (3) hemoptysis, pulmonary hemorrhage, or new or expanding nodules without evidence for infection; (4) active vasculitis of the respiratory or gastrointestinal tracts as demonstrated by endoscopy with biopsy; (5) iritis or uveitis; (6) new mononeuritis multiplex; or (7) necrotizing vasculitis identified by biopsy in any tissue.</td>
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although new organ system involvement occurs as well. Relapses in the kidney are heralded by the recurrence of microscopic hematuria, red blood cell casts, and worsening renal function. Fluctuations in the amount of proteinuria are not good indicators of active disease, and may be related to glomerular sclerosis. Relapse in the lungs tends to occur in the same locus as the site of original injury. Many patients’ relapses are heralded by a recurrence in a migratory polyarthritis.

How to best diagnose and treat relapse is a matter of substantial investigation. Table 4 provides some clinical indicators that relapse is occurring. There is no consensus on the value of ANCA titers for monitoring remission. Full-blown vasculitic relapse should be treated with a repeat course of prednisone and cyclophosphamide. In general, these patients require maintenance on long-term immunosuppression with cyclophosphamide, azathioprine, or methotrexate. Less ominous relapse of the upper respiratory tract may be treated with prednisone alone or perhaps with trimethoprin-sulfamethoxazole.

Serial ANCA Testing

The value of ANCA titers for disease monitoring has been the subject of several investigations. ANCA titers rise during relapse in 23% to 77% of patients (30,31). ANCA titers may increase without overt clinical relapse, and in some patients, persistently high ANCA titers are found during clinical remission. In addition, some patients have a clinical relapse that is not associated with any rise in ANCA titers. At the very least, however, a rise in ANCA titer should raise the possibility of a relapse. The disappearance of ANCA is at least suggestive of remission. Many serologic tests, including ANCA titers, may have greater importance in some patients than in others. For instance, in some patients, the ANCA titers may closely follow the clinical disease course, whereas in other patients, ANCA titers may not correlate well at all with clinical events. Perhaps serial monitoring of different ANCA isotypes or affinities will prove to be a useful approach in the future. As of now, ANCA titers should not be used as a determinant for beginning or altering immunosuppressive therapy.

Treatment of Dialysis-Dependent Patients

At least 20% of patients with ANCA-SVV and ANCA-GN will require dialysis at the time of diagnosis. Half of these patients may come off dialysis within 8 to 12 wk of therapy. Which patient will remain on long-term dialysis or will have a dialysis-free response is not clear at the initiation of dialysis. The dialysis-free interval may last from as little as a few weeks to 3 to 4 yr. The degree of immunosuppression warranted during the first 12 wk of dialysis depends on the risk-to-benefit ratio. It is our practice to treat dialysis-dependent patients for at least 8 to 12 wk with pulse methylprednisolone and oral prednisone. If patients’ renal functions improve, we continue corticosteroid treatment and institute cyclophosphamide therapy. Whether plasmapheresis is a more effective way of inducing dialysis-free intervals than methylprednisolone is not yet known.

Transplantation

ANCA-GN and ANCA-SVV rarely recur after renal transplantation. Recurrence is not confined to the transplanted kidney, but may also recur in nonrenal sites, such as the upper and lower respiratory tracts. The question of whether ANCA titers need to normalize before renal transplantation has not been resolved. In those patients who are in clinical remission with a negative ANCA titer, transplantation should proceed. Delay of transplantation may be warranted in patients who have had a persistently negative ANCA titer, but who then develop a marked rise in titer. In patients who have persistently high ANCA titers but no clinical evidence for SVV, it is reasonable to proceed with renal transplantation.

References


