The Kidney in Systemic Diseases

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Introduction

When the kidney is involved in a systemic disease process, it may either be the most conspicuously damaged organ or play a minor role in diseases that affect other tissues. The kidney may be injured at the outset of the disease or affected relatively late in the course of the disease. For instance, in some patients with systemic lupus erythematosus (SLE), nephritis is a presenting manifestation of disease. In others, dermatologic and serologic evidence of SLE may predate the onset of renal disease by months to years. In some systemic disorders, the kidney is one of many affected organs, as in primary amyloidosis, which simutaneously affects the heart, liver, and kidney. In some patients, the extra-renal manifestations of systemic injury mirror the course of renal injury, whereas in others, the extra-renal disease may differ with respect to onset, severity, and course. This chapter will consider systemic diseases that frequently involve the kidney, including diseases due to vascular inflammation, infections, liver disease, paraneoplastic syndromes, and dysproteinurias. The systemic diseases that result in tubulointerstitial disease, thrombotic microangiopathy, and cancers of the kidney are discussed in other chapters.

Presentation of Systemic Diseases in the Kidney

The clinical manifestations of many systemic diseases involving the kidney can be divided into major clinical and pathological syndromes, including

- nephrotic syndrome,
- nephritic syndrome,
- tubulointerstitial disorders (covered in Chapter I.8),
- renal-pulmonary syndrome,
- renal-dermal syndrome, and
- liver disorders.

Some systemic disorders consistently present with nephrotic syndrome (e.g. the dysproteinemias) (Table 1), others consistently with the nephritic syndrome (e.g. antineutrophil cytoplasmic autoantibodies (ANCA) small-vessel vasculitis), and still others with features of both syndromes (e.g. SLE).

The clinician should first assess the patient with history and physical examination to determine the scope and nature of the systemic disease process. Laboratory studies, including serological findings, and assessment of complement cascade activation, may increase or decrease the likelihood of certain diseases (Tables 2 and 3). Some diseases activate complement primarily through the classical pathway, resulting in diminution of C4 to a greater

Table 1.

Systemic Diseases that Usually Present with Nephrotic Syndrome

Systemic lupus erythematosus
Dysproteinemias
- Amyloidosis (AL and AA)
- Light chain deposition disease
- Fibrillary glomerular diseases
- Immunotactoid glomerulonephritis

Paraneoplastic syndromes

Cirrhosis
- Focal segmental sclerosis

Infections
- Human immunodeficiency virus (especially in African Americans)
- Syphilis
- Malaria
- Leprosy
- Filariasis
- Toxoplasmosis
- Schistosomiasis (especially *S. mansoni*)

Systemic Diseases that Usually Present with Glomerulonephritis

Systemic lupus erythematosus

ANCA small vessel vasculitis

Henoch-Schönlein purpura

Cryoglobulinemia

Infections
- Hepatitis B, C
- Bacterial pneumonias: Pneumococcus, Staphylococcus, Legionella, Klebsiella, Mycoplasma
- Human immunodeficiency virus (especially in Caucasians)
- Viral infection with Coxsackie, Epstein-Barr, Rubella
- Toxoplasmosis
- Trichinosis

Paraneoplastic Syndromes

Cirrhosis
- IgA glomerulonephritis

extent than C3. In contrast, other disease processes result in activation of the alternative complement pathway, resulting in near-normal levels of C4 but a diminution of C3 (Table 3) [53].

Many systemic diseases that have renal involvement can be grouped in recognizable syndromes, such as renal-pulmonary, renal-dermal, renal-cardiac, or renal-liver syndromes (Table 4). For instance, patients with glomerulonephritis and pulmonary infiltrates or nodules and hemoptysis may fall into the spectrum of a small-vessel vasculitis that affects both the kidney and the lung. In other patients, the presentation of palpable purpura in the lower extremities and nephritis raises the possibility of Henoch-Schönlein purpura (HSP) in a young child, or microscopic polyangiitis or cryoglobulinemia in an adult. Thus, these syndromes provide clinicians with clues to the nature of the systemic disorder.

The clinician should approach a patient who may have a systemic disorder affecting the kidney with the following questions in mind:

- What is the renal presentation of the clinical disorder? Is it predominantly nephrosis, nephritis, or tubulointerstitial disease?
- Are there serologic findings that increase or decrease the likelihood of a specific systemic disease?
- What are the predominant extra-renal organ systems involved by the systemic disease process?
- Is the kidney the dominant organ involved?
- Would a kidney biopsy provide a pathological diagnosis of the disorder?

Frequently, patients with systemic disease are not cared for primarily by nephrologists. When a systemic disease affects the kidney, it may do so in an explosive fashion resulting in a rapid, sometimes irreversible, decline in re-

Table 2. Serologic Findings in Patients with Renal Disease and Systemic Illness

Systemic Illness	Serologic Findings
Systemic lupus erythematosus	ANA/Anti-double-stranded DNA
Small-vessel vasculitis	ANCA
Wegener's granulomatosis	PR3-ANCA > MPO-ANCA
Microscopic polyangiitis	MPO-ANCA > PR3-ANCA
Churg-Strauss syndrome	MPO-ANCA
Cryoglobulemic vasculitis	Mixed cryoglobulins
	Anti-Hepatitis C antibodies
Amyloid (primary amyloidosis)	Lambda monoclonal immunoglobulins
Light chain deposition disease	Kappa monoclonal immunoglobulins
Membranous nephropathy	Infections
	Anti-Hepatitis B antibodies
	Antitreponemal antibodies
HIV nephropathy	Anti-human immunodeficiency virus antibodies
Post-infectious glomerulonephritis	Anti-streptococcal antibodies/anti-DNAse b
Goodpasture's syndrome	Anti-GBM antibodies
Polyarteritis nodosa	Anti-Hepatitis B antibodies
Thrombotic microangiopathy	Anticardiolipin antibodies
Systemic sclerosis	Anti-DNA topoisomerase
Sjögren's syndrome	Anti-RO, anti-LA antibodies
Mixed connective tissue disease	Anti-RNP

Table 3. Complement Profiles in Systemic Disease

Disorders that activate complement primarily through the classical pathway (low C4)
– Systemic lupus erythematosus
– Cryoglobulinemia

Disorders that activate complement through the alternative pathway (low C3)
– Post-infectious disorders
– Post-streptococcal glomerulonephritis
– Infective endocarditis
– Partial or total lipodystrophy
– Atheroembolic emboli

nal function. This is especially true of the small-vessel vasculitides and SLE. In these cases, the nephrologist must ask yet another question.

– Does the rapid decline in renal function require urgent diagnosis and emergency therapeutic intervention?

Vascular Inflammatory Disease

Systemic Lupus Erythematosus (SLE)

Pathology

The diagnosis of SLE is based on combined clinical, pathological, and laboratory findings. The classification of patients with lupus is based on criteria established by the Ameri-

Table 4. Clinical Pathological Syndromes in Systemic Diseases

Renal-pulmonary syndromes
– ANCA small-vessel vasculitis
– Goodpasture's syndrome
– Systemic lupus erythematosus
– Cryoglobulinemic vasculitis
– Progressive systemic sclerosis
Renal-dermal syndromes
– ANCA small-vessel vasculitis
– Henoch-Schönlein purpura
– Systemic lupus erythematosus
– Cryoglobulinemic vasculitis
– Progressive systemic sclerosis
– Infective endocarditis
– Visceral abscesses
Renal-cardiac syndromes
– Infective endocarditis
– Amyloidosis
– Systemic lupus erythematosus
– ANCA small-vessel vasculitis
Renal-liver disorders
– Hepatitis B
– Hepatitis C
– Cirrhosis with:
IgA nephropathy
Focal sclerosis

can Rheumatism Association [97]. To establish a diagnosis of SLE, patients must exhibit at least 4 of the 11 signs or symptoms listed in Table 5. The clinical diagnosis of renal lupus is most likely made following a renal biopsy diagnostic of lupus nephritis in the presence of positive serology and characteristic extrarenal manifestations of disease.

Lupus nephritis is the prototypic immune complex glomerulonephritis. Most, if not all, lupus patients have deposition of immunoglobulin and complement, even if there is no clinically significant renal dysfunction. The location and quantity of immune reactants and the host response to these immune reactants results in a spectrum of renal lesions categorized by the World Health Organization (WHO) into different classes of lupus nephritis.

WHO class I (absence of pathologic lesion) is the mildest pathologic expression of lupus nephritis. Class II lupus nephritis is a consequence of immune complex localization confined to the mesangium. The deposits are readily identified in all mesangial regions by immunofluorescence and electron microscopy. By light microscopy, there may be no identifiable glomerular lesions (class IIA), or varying degrees of focal to diffuse mesangial hypercellularity (class IIB). Class II lupus nephritis usually causes only a mild nephritic picture with asymptomatic hematuria and proteinuria.

When nephritogenic immune complexes are deposited not only in mesangial but also in subendothelial regions of the glomeruli, they result in increased inflammation. This results in focal proliferative (class III) or diffuse proliferative (class IV) lupus nephritis. The glomerular lesions are characterized by complex endocapillary hypercellularity caused not only by mesangial and endothelial proliferation, but also by leukocyte infiltration. The most active lesions are complicated by necrosis and crescent formation. Because SLE is often a persistent, although relapsing and remitting, disease, inflammation usually results in chronic changes, such as glomerular sclerosis, adhesions, fibrous crescents, interstitial fibrosis, and arteriosclerosis. The relative histologic markers of active inflammation and chronic injury can be expressed as activity and chronicity scores, the prognostic importance of which is controversial [4].

When capillary wall immune complexes are localized predominantly in the subepithelial zone rather than the subendothelial

Table 5. ACR Criteria for Systemic Lupus Erythematosus

Criteria	Description
Malar rash	Flat or raised erythema
Discoid rash	Scaly, erythematous plaques
Photosensitivity	Sun-induced or exacerbated rashes
Oral ulcers	Ulcerations of mucous membrane
Arthritis	Nonerosive, nondeforming arthritis of small joints
Serositis	Pericarditis or pleuritis
Renal disorders	Proteinuria greater than 500 mg/day or cellular casts
Neurological disorders	Seizures or psychosis
Hematologic disorders	Hemolytic anemia, leukopenia, lymphocytopenia, or thrombocytopenia
Immunologic disease	Positive LE test, anti-double-stranded DNA antibodies, anti-SM antibody, or false-positive serologic test for syphilis (STS)
Anti-nuclear antibody	Abnormal titer (in absence of predisposing drugs).

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zone, they are not in direct contact with circulating inflammatory mediators, and a membranous glomerulonephritis results (class V lupus nephritis). Class V lupus nephritis tends to cause more nephrotic than nephritic disease, unless there is a substantial proliferative component along with the membranous pattern. Specimens with exclusively membranous changes are sometimes designated class Va, those with concurrent mesangial hypercellularity Vb, those with concurrent focal endocapillary proliferative changes Vc, and those with concurrent diffuse proliferative changes as Vd. In essence, so-called class Vd lesions are a combination of class IV and class V lesions and thus have massive accumulations of mesangial, subendothelial, and subepithelial immune complexes. Patients with class Vc and Vd lupus nephritis follow a clinical course resembling that of focal or diffuse proliferative lupus glomerulonephritis (class III and IV), whereas patients with class Va and Vb have a predominantly nephrotic course. Therefore, it is our bias to treat patients with combined membranous and proliferative lesions (class Vc and Vd) as if they had class III or IV lupus nephritis.

Several types of vascular abnormalities can be found in the setting of lupus nephritis. The most common is an arteriolopathy caused by accumulation of immune complexes in the walls of hilar arterioles without induction of overt vasculitis. True vasculitis with mural infiltration by leukocytes is rare. The presence of hypertension, which may reach the malignant range in aggressive lupus nephritis, leads to typical hypertensive arterial and arteriolar changes. Some lupus patients develop a thrombotic microangiopathy, possibly associated antiphospholipid antibodies or an overlap with systemic sclerosis. This complication is characterized by subendothelial expansion in glomerular capillaries, fibrinoid necrosis of arterioles, and edematous intimal expansion in arteries. The resultant narrowing of lumens, as well as superimposed thrombosis, can cause severe and rapid renal failure and microangiopathic hemolytic anemia.

One difficulty of managing a patient with lupus nephritis is that the pathological lesion may change from one form of glomerular injury to another. It is common for a class III lupus nephritis to progress to a class IV lupus nephritis. Both class III and class IV lesions can transform into membranous lupus nephritis, either spontaneously or with immunosuppressive therapy. It is less common, but possible, for membranous lesions to transform into more proliferative lesions. Even repetitive clinical evaluations may not be sufficiently insightful, and repeated renal biopsies are sometimes needed.

The Role of Renal Biopsy

The pathologic manifestations of lupus nephritis span the spectrum from mild mesangial proliferation to severe necrotizing and crescentic glomerulonephritis. The array of clinical findings may range from intermittent episodes of hematuria and proteinuria to acute nephritis with renal insufficiency, and from mild elevations of creatinine, proteinuria, hypertension, and hematuria (with or without red cell casts) to a picture compatible with rapidly progressive glomerulonephritis. As progressive glomerular sclerosis and interstitial fibrosis ensue, fixed proteinuria develops, as does reversible renal insufficiency. The nephrotic syndrome commonly occurs and is usually associated with either class V lupus nephritis or with chronic proliferative disease that has developed focal glomerular sclerosis, which is also typically associated with renal insufficiency. In fact, the nephrotic syndrome may be the predominant clinical manifestation of disease in fully half of lupus patients with renal involvement. At the time of initial presentation, 20 – 25% of patients with SLE already have some degree of renal insufficiency. The clinician faces the question of whether proteinuria is a consequence of membranous nephropathy, diffuse proliferative glomerulonephritis, or chronic disease with extensive glomerular sclerosis. Furthermore, in some patients, there is a dissociation between the pathological and clinical features of the disease. Patients may present with severe extra-renal SLE and a picture of acute nephritis, but only have mild class II lesions by biopsy. In others, a diffuse proliferative glomerulonephritis may present clinically with only minimal degrees of hematuria and proteinuria.

One of the most difficult clinical pictures is that of a patient with long-standing lupus nephritis and a history of intermittent episodes of nephritis, who develops a rising serum creatinine. In these individuals, it is not always clear whether the renal insufficiency is caused by progressive glomerular and interstitial scarring or by the recrudescence of active nephritis.

The role of a renal biopsy in the evaluation of patients with systemic lupus erythematosus and nephritis has been extremely controversial. Extensive debate continues concerning the correlation between pathologic findings of classic lupus nephritis, the activity of the injury, the degree of chronic changes, and long-term outcome [6]. In our view, the renal biopsy helps to clarify the clinicopathologic syndrome. The biopsy allows for a reasonable separation of membranous lupus from predominantly proliferative disease. It may also restrain the impulse for immunosuppressive therapy in individuals with marked renal insufficiency and proteinuria, who on pathologic examination have only chronic disease with extensive glomerular sclerosis, but no active inflammation. The renal biopsy can be a key factor in determining if a rise or decline in renal function is a consequence of recrudescence of active inflammation or of progressive glomerular sclerosis. Similarly, it

is important to perform a renal biopsy for a patient with lupus nephritis who suddenly develops acute decompensation in renal function. The biopsy will determine whether this sudden deterioration is caused by worsening of the lupus nephritis (e.g. with extensive crescentic formation), the development of a thrombotic microangiopathy (possibly associated with antiphospholipid antibodies), or the development of a process not directly caused by lupus (e.g. tubulointerstitial nephritis caused by the use of an antibiotics or nonsteroidal anti-inflammatory drug (NSAID)).

Laboratory Studies

Antinuclear antibodies (ANA) are more than 90% sensitive for SLE but are only 70% specific. These antibodies are also found in patients with other rheumatic diseases, with infections, and in older age groups. In contrast, up to 10% of patients who fulfill the ACR criteria for lupus do not have a positive ANA. A proportion of ANA-negative patients actually have a positive ANA, if HEp-2 or Kb culture cell lines are used as the target substrate.

Tests for antibodies to nuclear or cytosolic antigens other than DNA are more specific for SLE. For example, antibodies to the SM antigen, one of the so-called extractable nuclear antigens (ENA), are very specific for lupus but found in only 25% of patients. It has been suggested that patients with anti-Sm antibodies have a higher risk of severe lupus, renal disease, CNS disease, cutaneous vasculitis, and death [7, 8].

Complement studies are frequently performed in patients with lupus, both for diagnosis and to measure disease activity. The total hemolytic complement (CH50), as well as C4 and C3, are typically low during active disease. Because decreased synthesis of complement components also results in depressed complement levels, a depressed complement value may not always indicate active disease. Repeated analysis of these factors may provide an insight into the relative state of complement activation.

Prognosis

There is a general assertion that the long-term survival of patients with SLE has improved over last 50 years. Some of this progress is a consequence of the broadened appreciation of the picture of SLE, and some may be attributed to the judicious use of corticosteroids and the introduction and refinement of the use of cyclophosphamide and azathioprine. Overall, lupus mortality is still more likely to result from cerebritis or myocarditis than a loss of renal function, largely due to the availability of dialysis and transplantation. The other major cause of death is overwhelming infection after immunosuppressive therapy.

Certain prognostic factors affect the long-term outcome of renal disease. In a recent study of patients with diffuse proliferative glomerulonephritis treated with cyclophosphamide, poor outcome was more likely for black patients and for those whose biopsies revealed interstitial fibrosis [32]. Using multivariate analysis, black race was a more significant predictor of poor outcome than the entry serum creatinine. From the available data, it was not clear why black patients fared poorly. Hypertension and the rapidity of diagnosis do not appear to be critical variables in these analyses. Whether the poor prognosis is a consequence of a genetic factor or of a lower socioeconomic status is not certain and is the subject of ongoing investigation.

In other studies, the entry serum creatinine [6] and the biopsy findings have been suggested as predictors of eventual renal failure. While no specific numerical cutoff on the chronicity index scale is invariably associated to long-term outcome, it is reasonable to suggest that individuals with substantial interstitial fibrosis, glomerulosclerosis, and tubular atrophy will progress to end-stage renal disease (ESRD) over the course of years, especially if they suffer additional episodes of active inflammation.

Patients with lupus membranous glomerulonephritis (WHO class Va and b) appear to follow a similar course to that of patients with idiopathic membranous nephropathy [82]. Patients with WHO class Vc and d with proliferative glomerulonephritis, necrosis and crescent formation have a similar course to those with aggressive Class IV disease. In our view, classifying cases of severe diffuse proliferative glomerulonephritis in the setting of lupus membranous nephropathy as Class V (c and d) lupus has only served to confuse the nomenclature and clinical evaluation of the disease process. Certainly, membranous nephropathy can transform to a diffuse proliferative glomerulonephritis and result in a worse prognosis for the patient. In a study by Sloan [92], a group of 79 patients with lupus membranous nephropathy were examined and divided into 3 groups:

- (1) WHO class Va and Vb,
- (2) WHO class Vc (with <50% glomeruli involved), and
- (3) WHO class Vc (with >50% glomeruli involved) and Vd.

At the end of five years, the renal survival was 86%, 72%, and 49% in each of these 3 groups respectively, and 72%, 48%, and 20% at 10 years. The entry serum creatinine was the only clinical predictor of renal outcome.

Treatment Issues

Few areas of medicine generate as much discussion and controversy as does the subject of therapy for SLE and lupus nephritis. Whether patients should be treated only with corticosteroids, with intravenous cyclophosphamide, or with oral cyclophosphamide or azathioprine has never been truly resolved. Nor is it resolved whether corticosteroids should be used in high-dose oral form, as some have asserted a role for parenteral methylprednisolone (pulse methylprednisolone). Rarely has an identical protocol been employed in different uncontrolled – or even controlled – trials. Despite the morass of conflicting literature, the general practice of nephrologists has been altered by several investigations from the National Institutes of Health in the mid-1980s. These studies promulgated the beneficial effects of combined prednisone with parenteral cyclophosphamide, oral cyclophosphamide or oral cyclophosphamide and azathioprine [6]. More recently, Boumpas et al. [13] conducted a prospective trial treating patients with severe diffuse proliferative glomerulonephritis with either pulse methylprednisolone alone or either a long or short course of cyclophosphamide. The short course involved either three pulses of intravenous methylprednisolone or monthly pulses of intravenous cyclophosphamide for six months. In the long course, six months of monthly pulses of intravenous cyclophosphamide were followed by a dose every three months for two years. Similar amounts of corticosteroids were used. After 5 years of follow-up, the pulse methylprednisolone group experienced a doubling of the serum creatinine in almost half of the patients, and 25% developed ESRD. In the short-course cyclophosphamide group, the serum creatinine doubled in one third of the patients; 25% also developed ESRD. In the long-

course cyclophosphamide group, the serum creatinine doubled in only 15% of the patients and only 10% developed ESRD.

The most prominent side effects of this form of therapy are infection, ovarian failure (especially inpatients treated with long-course cyclophosphamide), bone disease, and cataract formation. The incidence of malignancies (especially bladder cancer) with this form of therapy is not known. Studies of long-term oral cyclophosphamide treatment for patients with Wegener's granulomatosis suggest that 15% of patients will develop transitional cell carcinoma of the bladder over the course of 5 to 10 years [100]. The rate at which patients with lupus nephritis treated with intravenous cyclophosphamide (which is associated with a smaller incidence of hemorrhagic cystitis than the oral form) will develop bladder cancer is not yet ascertained.

Our own studies of patients with diffuse proliferative glomerulonephritis reveal that Caucasian patients treated with intravenous cyclophosphamide have an excellent 5-year survival rate (95%), compared to only 57% at 5 years in blacks [32]. It is thus likely that the controversy about optimal treatment of patients with lupus nephritis stems in part from the enrollment of patients of different ethnicity, degrees of renal insufficiency, and WHO classifications of nephritis [5].

Because patients with lupus nephritis are frequently young women, the development of ovarian failure is of a substantial worry [72]. Whether there are forms of therapy that can protect the ovary is not yet known. Studies using leuprolide acetate to induce a temporary state of ovarian shutdown are under way. The results, and the usefulness of high-dose estrogen and progesterone are still unknown.

The best approach to therapy relies on an assessment of several factors. The clinician should assess disease activity, disease severity, the patient's previous history of disease activity, and the patient's own response to corticosteroid and immunosuppressive drugs.

The clinician must differentiate between disease severity and disease activity. Disease severity may be a consequence of previous organ system dysfunction, e.g. previous glomerular crescent formation and subsequent glomerular scarring. There can be severe renal damage that is no longer amenable to immunosuppressive therapy. In contrast, active disease may respond to corticosteroids and immunosuppressive activity. There have been several attempts at quantitating organ system dysfunction, including the development of a damage index [44].

There are several markers of disease activity. The clinical history is usually most helpful for assessing overall symptomatology. Renal disease activity may be indicated by numerous red cells and red cell casts found on urinalysis. The presence of proteinuria may relate to previous renal damage rather than to an acute process, except in cases of membranous nephropathy and its attendant nephrotic syndrome. Overall lupus activity may be ascertained by using serological markers as adjunctive tests. Rises in the anti-double-stranded DNA titer, or declines in complement levels, especially CH50, are particularly helpful. Nonspecific markers of disease activity, such as erythrocyte sedimentation rate or the C-reactive protein, are probably no more useful than an overall "sick index". There has been some interest in differentiating rises in C-reactive protein levels during infections from rises that occur during episodes of inflammation. Nonetheless, there are patients with clear evidence of renal exacerbation who do not have hypocomplementemia or elevated levels of anti-DNA antibodies. When there is a progressive rise in serum creatinine and development of significant hematuria, patients more than likely have aggressive renal disease. A renal biopsy is particularly useful for patients

with a history of a prior episode of glomerulonephritis and immunosuppressive treatment. The finding of widespread glomerular scarring, interstitial fibrosis, and tubular atrophy in a patient with moderate renal insufficiency may result in a less aggressive approach then when active inflammation is found with lesser amounts of sclerosis.

Treatment Recommendations

Our treatment strategy is based on persistent supportive management, including careful attention to blood pressure and nutrition, and a prophylactic approach to the surveillance and treatment of infections. Attention to the development of osteoporosis is considered in all patients. In nonrenal-failure patients having received any prednisone at all, specific recommendations include 1.2 grams of calcium/day. If the patient then has evidence of osteoporosis by bone densitometry scanning (T scores that are 2 standard deviations below the mean), use of an antiresorber (alendronate or calcitonin) is recommended. However, if the creatinine clearance is less than 50mL/min, alendronate would not be used. The specific recommendation for treatment of musculoskeletal complaints is the use of nonsteroidal anti-inflammatory agents and an anti-malarial (plaquenil) for mild to moderate arthritis or dermatitis.

We treat major episodes of Class III and IV glomerulonephritis with cyclophosphamide and prednisone. Prednisone is given at a dose of 1 mg/kg/day for the first month, leading to alternate-day doses in the second month. Each week, the prednisone dose is lowered by 10 mg every other day, (e.g. 60 mg alternating with 50 mg every other day, followed by 60 mg alternating with 40 mg one week later). Frequently, extra-renal manifestations of the disease require the continued use of daily oral prednisone at doses between 5 and 10 mg/day. Once patients reach a dose of 10 mg/day, the dose of prednisone is decreased by 1 mg/month until the corticosteroid dose is zero.

In the patient presenting with crescentic lupus diffuse proliferative glomerulonephritis (WHO class IV), pulse methylprednisolone is given at 7 mg/kg on 3 consecutive days. Intravenous cyclophosphamide is given according to the National Institutes of Health protocol, once a month for 6 consecutive months. The dosage is determined on the basis of the leukocyte nadir; the white count should not sink below 3000 cell/mm^3. The dosage is titrated upward during the first 6 months, starting at a dose of 0.5 g/m^2 body surface area and increasing by 0.25 g/m^2 on successive treatments, provided that the 2-week leukocyte count is acceptable. The dosage never exceeds 1 g/m^2. After the first 6 months, the NIH long-course therapy is used; then consolidating treatments, every 3 months for a total of 24 months. Patients with significant renal impairment (serum creatinine > 4 mg/L) may need a reduction in the first dose of parenteral cyclophosphamide.

For patients with focal proliferative glomerulonephritis (WHO class II and III), it is most difficult to determine when treatment is needed. Most patients are treated with corticosteroids for their extra-renal manifestations of disease. Whether additional high-dose prednisone, cyclophosphamide, or azathioprine is indicated for focal proliferative disease is not clear. However, when there is necrosis or crescent formation in addition to the focal proliferative disease, and when 50% of glomeruli are affected, the long-term outcome is probably similar to that of diffuse proliferative glomerulonephritis (Class IV) and should be treated in the same fashion.

Since the renal prognosis of membranous WHO Class Va or b lupus is usually excellent, a trial of corticosteroid therapy should only be considered in certain individuals. In patients with severe debilitating nephrotic syndrome or declining renal function, it may be useful to employ both corticosteroid and even cyclophosphamide therapy. It is not clear whether the degree of proteinuria represents an additional risk. The role of cyclosporine is under investigation. In our experience, patients treated with cyclosporine have a high relapse rate when therapy is discontinued.

Careful attention must be paid to the development of serious infection during the first few weeks of treatment. The results of a recent study by Ward [105] evaluated the cause of death in a cohort of 408 patients with systemic lupus erythematosus, 144 of whom died. Deaths were a consequence of lupus activity in 34%, 22% died of infections, 16% of cardiovascular disease, 6% of cerebral vascular disease, and 6% of cancer. Alarmingly, deaths due to lupus and to infection were more common in the younger age groups, whereas deaths due to cancer were more common in older patients. Patients at substantial risk for infection are those treated with pulse methylprednisolone, corticosteroids, and cyclophosphamide. Careful attention is given to avoid side effects of gastric complaints by avoiding the concomitant use of nonsteroidal anti-inflammatory drugs and corticosteroids, with or without the use of H_2 receptor blocking agents. The association of lupus with cancer is not solely attributable to the use of immunosuppressive agents; there may be a risk of lymphoma and other cancers in patients with lupus who have not received immunosuppressive therapy. The most effective way to diminish the side effects of therapy is to terminate the immunosuppression as soon as possible.

Ascertaining the effectiveness of immunosuppressive therapy may be difficult. Evidence for a substantial reduction in the number of urinary red blood cells or red cell casts, or at least stabilization of renal function, are the best indicators of response. Whether there is value to normalizing the CH50 or anti-double-stranded DNA antibodies is a matter of debate, although such normalization portends a favorable long-term outcome.

Plasmapheresis

Plasmapheresis is clearly not indicated in this population. The national cooperative prospective study randomly assigned patients to receive prednisone or cyclophosphamide, with or without plasma exchange [70]. The study failed to demonstrate any benefit of plasma exchange with respect to renal survival or overall survival. Whether other approaches using plasma exchange are efficacious, such as the synchronous use of plasmapheresis with pulse cyclophosphamide, is under investigation [34].

Treatment of Resistant Lupus

In many patients, existing treatment protocols with prednisone and cyclophosphamide are less successful, particularly patients of the black race [32]. One approach has been to use mycophenolate mofetil by itself or with corticosteroid treatment. The efficacy of this drug has been evaluated in two uncontrolled pilot studies, including one of our own for patients with resistant lupus nephritis [52, 77]. Some degree of clinical stabilization has been observed, but these studies are too small and too preliminary to draw conclusions. Two other

approaches have been evaluated in an anecdotal fashion. Pooled intravenous immunoglobulin and total lymphoid irradiation are promising approaches that have not been systematically evaluated.

There are several novel therapies currently under investigation, including lupus tolerogens, anticytokine antibodies, antibodies to the CD40 ligand, and antibodies to the fifth component of complement (anti-C5 antibodies). At this time, these trials are either beginning or are under way, and the utility of any of these agents remains to be determined.

Antiphospholipid Syndrome

In some patients, the antiphospholipid antibody syndrome is associated with SLE [38, 43]. Three types of antiphospholipid antibodies have been characterized, including lupus anticoagulants, anticardiolipin antibodies, and antibodies that cause a false-positive Venereal Disease Research Laboratories (VDRL) test. Patients with these antibodies may develop both arterial and venous thrombosis, thrombocytopenia, or thrombotic microangiopathy. (The diagnosis may be elicited on careful past history of patients who have experienced recurrent fetal loss.) In addition to their lupus, these patients develop glomerular and vascular thrombi. Renal involvement is characterized by fibrin thrombi in small arteries, and glomerular capillaries. Unfortunately, immunosuppresive therapy is usually not effective in reducing the level of antiphospholipid antibodies. Therefore, it is useful to continue long-term anticoagulation therapy with Warfarin, especially for patients with pathological confirmation of glomerular thrombi. It is not clear whether there is a correlation between the use of anticoagulants and renal outcome for patients with lupus.

Small-Vessel Vasculitis (SVV)

Nomenclature of SVV

The nomenclature of small-vessel vasculitis (SVV) has a rich and interesting history and has recently been reviewed [106]. The most recent approach is that proposed by the Chapel Hill Nomenclature Conference, the details of which can be seen in Table 6 [61]. Pauci-immune forms of SVV are microscopic polyangiitis, Wegener's granulomatosis, or the Churg-Strauss syndrome. These different forms of SVV have several similarities, not only on the basis of the blood vessels that they involve (predominantly capillaries, venules, arterioles, and small arteries), but also with respect to the clinical phenotype of the diseases and their association with ANCA.

Pathology

The characteristic feature of the glomerular lesion in SVV is a focal necrotizing glomerulonephritis. Associated with the necrotizing lesions are cellular or fibrocellular crescents that usually involve 50 – 100% of glomeruli. The glomerulonephritides associated with ANCA SVV and antiglomerular basement membrane (anti-GBM) disease are characterized predominantly by necrosis rather than hypercellularity. The reverse is true for immune complex glomerulonephritis, which tends to have prominent proliferative changes. Identification of vasculitis in vessels other than glomerular capillaries is seen in only approximately 10% of renal biopsies from patients with ANCA SVV. Occasionally, "sausage-shaped" pseudoaneurysms are observed within the small arteries of patients with small-vessel vasculitis. Interstitial necrotizing granulomatous inflammation is

Table 6. Names and definitions of vasculitis adopted by the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis

	Large-Vessel Vasculitis
Giant cell (temporal) arteritis	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery.
Takayasu arteritis	Granulomatous inflammation of the aorta and its major branches. Usually occurs in patients younger than 40.
	Medium-Vessel Vasculitis
Polyarteritis nodosa (classic polyarteritis nodosa)	Necrotizing inflammation of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries or venules.
Kawasaki disease	Arteritis involving large, medium 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.*
	Small-Vessel Vasculitis
Wegener's granulomatosis	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small-to medium-sized vessels (capillaries, venules, arterioles and arteries).
Churg-Strauss Syndrome	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.
Microscopic polyangiitis (microscopic polyarteritis)	Necrotizing vasculitis with few or no immune deposits affecting small vessels (capillaries, venules or arterioles). Necrotizing arteritis involving small- and medium-sized arteries may be present.
Henoch-Schönlein purpura	Vasculitis with IgA-dominant immune deposits affecting small vessels (capillaries, venules, or arterioles).
Essential cryoglobulinemic vasculitis	Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis.

Modified from Jennette JC, Falk RJ, Andrassy K et al. Nomenclature of systemic vasculitides: the proposal of an international consensus conference. Arthritis and Rheumatism 37:187-192, 1994, with permission.

rarely observed in renal biopsies from patients with Wegener's granulomatosis. Bowman's capsule is frequently disrupted in the inflammatory process and induces a somewhat granulomatous periglomerular inflammation. However, this is a relatively nonspecific reaction that occurs with any form of severely necrotizing glomerulonephritis. Some patients do not have any identifiable glomerular lesions, but rather have tubulointerstitial nephritis or a medullary peritubular leukocytoclastic angiitis.

The necrotizing glomerulonephritis heals with regions of focal sclerosis. In any biopsy specimen, it is possible to observe both acute necrotizing lesions and chronic lesions asso-

ciated with focal sclerosis. The cellular crescents first heal in fibrocellular and then fibrous crescents, resulting at times in complete obliteration of the glomerular tuft. The tubulointerstitial compartment develops interstitial fibrosis and tubular atrophy along with interstitial infiltration by chronic inflammatory cells.

Most patients with ANCA glomerulonephritis and SVV have little or no glomerular staining for immunoglobulin by immunofluorescence microscopy (i.e., they have pauci-immune disease). On electron microscopy, there are often no electron-dense deposits or only a few scattered small deposits within the mesangium. However, it is important to realize that some patients appear to have necrotizing ANCA-glomerulonephritis concurrent with anti-GBM disease or immune complex disease, in which case there is a well-defined background linear or granular staining for immunoglobulins.

Clinical Manifestations

Most patients with ANCA SVV present with constitutional findings such as fever, myalgias, arthralgias, and malaise. The majority of patients describe a flu-like prodrome early in the course of their disease that may occur within days or weeks prior to the onset of their illness. The flu-like prodrome is statistically more frequent in late fall, winter, and spring than in the summer months [35]. Arthralgias, especially a migratory polyarthropathy involving small and large joints, is a frequent prodrome to the clinical presentation of SVV. About 10% of patients will have a frank arthritis with synovial thickening and erythema of the joint.

The renal manifestations of necrotizing glomerulonephritis are hematuria, with or without red cell casts, and proteinuria that can at times be mild to moderate (< 1 to 2 g), or of nephrotic range (as much as 16 g) [90, 91]. Patients may first present with an acute nephritis that is manifested by hematuria, proteinuria, hypertension and renal insufficiency. One of the most common presentations of necrotizing glomerulonephritis is a rapidly progressive glomerulonephritis associated with rapidly-rising creatinine, hematuria, proteinuria, and hypertension. These cases will progress to ESRD if the individuals are not treated emergently.

Alternatively, some patients have clinically undetectable episodes of focal necrosis and hematuria, undergo a remitting and relapsing course which results in the development of substantial glomerulosclerosis and a picture most compatible with chronic glomerulonephritis. Episodes of focal necrosis may resolve by themselves with a loss of hematuria (and red cell cast formation), resulting in proteinuria associated with the pathological finding of focal sclerosing glomerulonephritis. These individuals usually do not respond well to immunosuppressive therapy and eventually require dialytic support.

Some patients present with a renal-dermal vasculitic syndrome. The most common lesion consists of a leukocytoclastic angiitis with purpuric lesions in the lower extremities. However, several other cutaneous lesions have been observed, including ecchymoses, erythematous tender nodules, focal necrosis, ulceration, and livido reticularis. Interestingly, a picture of urticaria that may have been previously treated with antihistamines is also a manifestation of ANCA SVV. This must be differentiated from hypocomplementemic urticarial vasculitis in which there is a depression of C3 and C4.

Pulmonary disease is found in 50% of patients with ANCA SSV and glomerulonephritis. The spectrum of pulmonary lesions varies

from focal infiltrates that wax and wane, to alveolar infiltrates associated with hemoptysis and, in the extreme, to fulminate hemorrhagic alveolar capillaritis resulting in life-threatening massive pulmonary hemorrhage. In many instances, a prodrome of waxing and waning infiltrates, with or without hemoptysis, may antedate the more fulminate phase of disease by months to years. Patients may have been treated with antibiotics with the presumption of bacterial pneumonia, only to discover that the pulmonary process was not affected by this form of therapy. In patients who have a granulomatous component to their disease (that is, Wegener's granulomatosis or Churg-Strauss syndrome), more nodular and occasionally cavitary lesions are found. These nodules and cavities may be very small and only found on spiral CT scans, but they are frequently large enough to be observed by routine chest x-rays. In Churg-Strauss syndrome, pulmonary involvement is the most predominant form of the disease and is associated with asthma and eosinophilia. The acute inflammatory and necrotizing pulmonary lesions evolve into chronic, nonspecific, sclerotic lesions, such as interstitial fibrosis, organized intra-alveolar fibrosis, and bronchiolitis obliterans.

Of the clinical manifestations of ANCA SVV, the upper respiratory tract is the most difficult to diagnose and treat. The vascular inflammation of upper respiratory tract lesions may include nasal erosions, ulcers, and necrosis of the nasal septum. Patients may have serous otitis with involvement of the middle ear and entrapment of the seventh nerve, resulting in facial paralysis. Sinusitis is found in one-third of patients, typically involving more than one sinus cavity, resulting in a picture of pansinusitis. Patients with Wegener's granulomatosis may have bony erosion into surrounding areas, including the orbit. The encrusting of the nasal cavity is difficult to differentiate from concomitant infection, especially in those who have been treated with immunosuppressive therapy. Patients with Wegener's granulomatosis may also have tracheal inflammation, especially in the subglottic region, resulting in stridor. When this subglottic region is profoundly inflamed, critical airway narrowing may ensue, requiring emergency tracheotomy. These lesions are difficult to treat with corticosteroids and cyclophosphamide and may have a relapsing course.

Approximately one-third of patients with ANCA SVV and glomerulonephritis have abdominal complaints, largely similar to those of patients with peptic ulcers that are not amenable to conventional ulcer disease management. In fact, some of these patients have nonhealing gastric ulcers due to vasculitis that only respond to immunusuppressive therapy. These lesions raise a diagnostic challenge for clinicians in differentiating whether they are the result of vasculitis or of corticosteroid therapy. Biopsy of the affected tissue may provide an insight into the pathogenesis. Other sources of abdominal complaints are due to pancreatic inflammation with elevations of amylase and lipase.

The most catastrophic abdominal complication of small-vessel vasculitis is involvement of small arteries or arterioles in the small or large bowel. Such involvement causes transmural ischemic ulcers and bowel perforation resulting in polymicrobial sepsis and bacterial peritonitis. It is important to note that ANCA SVV may also involve the renal, celiac, and mesenteric arteries. Thus, some patients may have aneurysmal formation of these vessels, resulting in bowel wall, renal, or liver infarction.

One quarter of patients with ANCA SVV and glomerulonephritis will develop a neurological disease. This may be a mononeuritis multiplex that results in focal peripheral neu-

ral lesions with either sensory or motor deficits. Rarely, patients may present with seizures as a result of central nervous system vasculitis.

Cardiac disease is uncommon in patients with small vessel vasculitis, but when it does occur, there are two different clinical phenotypes. One is the development of pericarditis with the clinical picture of a serositis-type chest pain. The other phenotype is coronary artery disease as a consequence of vasculitis that results in either subendocardial or transmural myocardial infarctions. Since the average age of patients with ANCA SVV is 55 years, it is difficult to differentiate atherosclerotic coronary artery lesions from those attributable to vasculitis. Other vascular beds can also be affected by ANCA SVV, including the eye. Patients may have iritis or uveitis resulting in red eyes that may or may not be painful. These subtle changes are discernible only by slit lamp examination by an ophthalmologist.

Serology

Approximately 90% of patients with ANCA SVV have either a myeloperoxidase ANCA (MPO-ANCA) or a proteinase 3 ANCA (PR3-ANCA) [48]. MPO-ANCA is predominant in patients with microscopic polyangiitis and the Churg-Strauss syndrome, or with necrotizing and crescentic glomerulonephritis without extrarenal manifestations. PR3-ANCA predominates in patients with Wegener's granulomatosis. Nonetheless, 20 – 30% of patients with Wegener's granulomatosis will have an MPO-ANCA, and approximately 20 – 30% of patients with necrotizing glomerulonephritis with no obvious extrarenal manifestations will have a positive PR3-ANCA. Most patients have normal complement levels, and approximately 10% of patients have a positive ANA.

Prognosis

The long-term prognosis of patients with ANCA SVV depends on two different variables. Mortality is largely related to the occurrence of massive pulmonary hemorrhage, which accounts for at least half of all deaths in the fulminant phase of disease. The long-term renal prognosis is largely associated with the entry serum creatinine [54]; the higher the serum creatinine, the higher the risk of developing ESRD. The combined pathological activity and chronicity indices may also play a prognostic role in patients with substantial active disease.

Treatment Recommendations

Treatment of ANCA SVV can be divided into three phases: induction, maintenance of remission, and treatment of relapse before tissue destruction occurs [78].

Several protocols have been used for induction therapy. Our approach is to use intravenous methylprednisolone at a dose of 7 mg/kg on 3 consecutive days, especially for patients with renal and pulmonary involvement. The use of plasmapheresis has been promulgated largely in Europe, especially in Great Britain, where the vast majority of patients with SVV receive this form of therapy [84]. The relative benefits of intravenous methyl prednisolone versus plasmapheresis are the subject of an ongoing clinical investigation.

To complete the induction therapy, all patients are given 1 mg/kg/day of prednisone for one month. Corticosteroids are then tapered

to an alternate-day regimen during the second month of treatment and eventually discontinued by the end of the fourth or fifth month.

Once induction therapy is complete, there are 3 options for immunosuppressive therapy. The first approach is to use intravenous cyclophosphamide on a monthly basis, given at a dose of 0.5 g/m^2. The dosage is adjusted on the basis of the 2-week leukocyte nadir in order to affect a leukocyte count of 4000 cells/mm^3. In some cases of especially severe systemic vasculitis, the initial dose may be repeated at week 3 if the symptoms of the vasculitis are breaking through high-dose prednisone therapy. A second alternative is to use oral cyclophosphamide, given at a dose of 2 mg/kg/day [55]. To prevent severe leukopenia, careful attention to the leukocyte count must be maintained throughout this therapy. The patient must be admonished to drink plenty of fluids, because adequate diuresis is essential to avoid hemorrhagic cystitis. A third alternative, largely used in Great Britain, is to treat with cyclophosphamide for 3 months and then to switch to oral azathioprine [84]. The use of prednisone alone for the treatment of ANCA SVV is no longer justified on the basis of a lower remission rate and a 3-fold higher incidence of relapse [78].

The optimal duration of alkylating therapy is still very much a matter of controversy. Some investigators suggest 6 months, provided the patient is in clinical remission, while others recommend a full year of therapy. If the patient no longer has any evidence of microscopic hematuria, mild to moderate amounts of proteinuria (less than 2 g/24 hours), and no extrarenal manifestations of disease at 6 months, the treating physician may comfortably cease alkylating therapy. Conversely, additional therapy is warranted if the patient has persistent signs of ongoing glomerulonephritis with red cells and red cell casts, or if there are signs and symptoms of extrarenal manifestations of disease (especially in the upper respiratory tract, the nose, and subglottic region). Alkylating therapy should be continued, either intravenously on a monthly basis or with daily oral cyclophosphamide. Continuation of oral azathioprine is considered a matter of course in Great Britain.

For some individuals, the usual induction therapy is not successful. These individuals are primarily those who have massive pulmonary hemorrhage. In our own experience, the institution of plasma exchange, in addition to pulse methylprednisolone, is warranted in these individuals. The consequence of early and aggressive institution of plasma exchange has substantially diminished the mortality associated with massive pulmonary hemorrhage; the plasma exchange is given on a daily basis for the first week and then every other day for a total of 14 days. The role of pooled intravenous gammaglobulin for this disease is largely anecdotal, although some investigators feel that this drug enhances early induction therapy by diminishing pulmonary symptoms.

The conventional therapy for treatment of relapse is to reinstitute the same form of therapy used in the initial induction and remission protocol. Whether intravenous methylprednisolone is necessary again depends upon the total amount of corticosteroid that has been administered to the patient over the course of the disease, as well as the severity of the relapse. Six months of cyclophosphamide, either intravenously or orally, is again recommended. If the patient is in remission, the question becomes whether long-term immunosuppressive therapy is indicated. Some investigators would suggest that no additional therapy should be used, while others suggest that low-dose prednisone and azathioprine should be maintained for the long term.

With the use of alkylating agents of any kind, remission rates of between 70% and

85% have been noted. Individuals who relapse will either do so immediately after therapy is stopped or within a mean of 13 months. The value of ANCA titers in predicting relapse is a matter of controversy, although most investigators would suggest that they are, at best, adjunctive to clinical history and physical and laboratory examination of the patient. If a patient has an ANCA titer that becomes negative and then suddenly becomes positive again at sufficient titer, it is wise to follow those patients vigilantly to detect early relapse. The treatment of frequent relapse can be particularly challenging in patients with nasal or subglottic vasculitis and destruction. In fact, it may be impossible to withdraw patients with this phenotype from long-term therapy.

Patients who require dialysis at the onset of their disease may or may not respond to induction treatment. Whether plasma exchange or pulse methylprednisolone improves the chances of a dialysis-free interval is a matter of conjecture. In our own experience, only half of the patients who began dialysis responded to treatment. When response did occur, dialysis-free intervals lasted from 3 months to 3.5 years. Half of the patients did not respond to any form of therapy and remained dialysis dependent. There were untoward complications of the treatment regimen, including death.

Alternative Treatment Strategies

There has been substantial interest in alternative therapy to prevent the recurrence of vasculitis. This has been most demonstrated with the use of trimethoprim-sulfamethoxazole combinations. In a study by Stegeman et al. [95], the prophylactic use of cotrimoxazole resulted in a significant decrease in the relapse rate of patients with ANCA SVV. Close inspection of the data reveals that the significant diminution of the vasculitis relapse rate was entirely attributable to the amelioration of the nasal and upper respiratory tract relapse. These data would support those derived from DeRemee et al. [107] who suggest that trimethoprim-sulfamethoxazole combinations are the best forms of therapy for local disease of the head and neck. At this time, there is no apparent benefit associated with the use of these antibiotics for disease outside of this area.

Methotrexate has been evaluated in the treatment of SVV as well. Its use is primarily for individuals without substantial renal involvement, because the risk of mucositis is greatly increased when the creatinine is above 2 mg/dL [93]. Preliminary data suggest that methotrexate might be a useful agent to prevent relapse of SVV outside the kidney. Further studies are necessary in this regard.

On an experimental basis, mycophenolate mofetil has recently been tried as an alternative therapy to maintain remission and treat relapse. This form of therapy has not undergone extensive evaluation, but may be of specific benefit in lesions of the subglottis.

Renal Transplantation

Currently, the value of ANCA tests should not alter the timing of renal transplantation. In renal transplant recipients, there is a 15 – 20% incidence of relapse in the transplanted kidney or elsewhere. Whether newer immunosuppressive therapy, e.g. mycophenolate mofetyl, decreases the risk of relapse is not known. In patients with relapse, substitution of cyclophosphamide for other immunosuppressive therapy is warranted.

Medium- and Large-vessel Vasculitis

Polyarteritis Nodosa and Takayasu Arteritis

Classic polyarteritis nodosa, by the definitions of the Chapel Hill consensus conference, affects arteries but not other vessels. Therefore, by this definition, patients with polyarteritis nodosa do not have glomerulonephritis. Thus, the renal vascular disease is largely that of aneurysm formation in renal arteries resulting in infarction and/or hemorrhage. In some studies, most patients with polyarteritis nodosa have hepatitis B infection (considered later in this chapter) [47].

Patients with Takayasu arteritis may have disease involvement at the origin of the renal artery, resulting in renal artery occlusion and decline in renal function or, in rare individuals, precipitous infarction of an entire kidney. The most common presentation, however, is that of renal vascular hypertension associated with mild renal insufficiency.

Henoch-Schönlein Purpura (HSP)

HSP is mostly seen in children, although adults may also be affected. The clinical picture includes leukocytoclastic vasculitis of the skin, abdominal pain, arthralgias, arthritis, and glomerulonephritis. The skin lesions are similar to those of other renal-dermal vasculitic syndromes. There are typically crops of macular and palpable purpuric rashes on the lower extremities, buttocks and flanks, as well as urticarial lesions. The rash may be accompanied by constitutional symptoms such as malaise and fever, especially in children. The abdominal symptoms are vomiting, abdominal pain, frequent colic, melena, and hematochezia. Patients may present with arthralgias, and occasionally with frank arthritis of the large joints. The percentage of patients with HSP who develop clinically significant renal disease varies. When renal disease occurs, it is typically noted within days to weeks after the onset of symptoms. Most patients present with microscopic or, at times, macroscopic hematuria with red cell casts. Proteinuria is typically mild, although some patients may have the nephrotic syndrome. While there is usually a correlation between the clinical manifestations of disease (including urinalysis and serum creatinine) and the pathologic findings, the light microscopic features of the disease appear more severe in some individuals.

Pathology

The glomerular picture of HSP is identical to that of IgA nephropathy, with a spectrum of lesions ranging from mild mesangial proliferation to diffuse endocapillary proliferation, with or without crescent formation (see Chapter 7). By immunofluorescence microscopy, there is IgA deposition, as well as complement components such as C3. By electron microscopy, electron-dense deposits are found, almost always in the mesangium. Capillary wall deposits are most common in patients with severe glomerulonephritis.

Skin biopsy typically reveals a leukocytoclastic vasculitis involving postcapillary venules. While this finding is present in other renal-dermal vasculitic syndromes, the presence of IgA deposition in vessels is relatively specific for IgA nephropathy.

No specific laboratory tests are either sensitive or specific markers of HSP.

Clinical Course and Treatment Recommendations

In most children, HSP is a self-limited disorder. This is especially true of the dermal and joint complaints. The gastrointestinal symptoms may be severe and prompt numerous diagnostic studies and even exploratory laparoscopy. Corticosteroids clearly improve the extrarenal manifestations of the disease, including the abdominal pain.

In general, the disease process follows a relapsing and remitting course. The renal lesions vary as well. In individuals with mild mesangial hypercellularity, it is unlikely that any anti-inflammatory or immunosuppressive therapy is appropriate. Because a large number of patients develop spontaneous remission, there is limited enthusiasm for the use of corticosteroids and cyclophosphamide. However, among patients who have acute nephritis or rapidly progressive glomerulonephritis, a substantial proportion (up to 44%) have persistant hypertension or a decline in GFR [45]. Nephrologists tend to use therapies similar to those used in other forms of crescentic glomerulonephritis, including pulse methylprednisolone and cytotoxic drugs.

One of the critical issues concerning HSP is whether the disease process is different in adults than children. In a recent study of 162 patients, including 46 adults, cutaneous lesions were the main clinical presentation in both [11]. Upper respiratory tract infection was more frequent in children, whereas adults had a statistically lower frequency of abdominal pain and fever, and a higher frequency of joint pain. Adults were significantly more severely affected with renal disease and required the use of corticosteroids and/or cytotoxic agents. The outcome was good in both groups, with complete recovery in 94% of the children and in 89% of the adults.

Progressive Systemic Sclerosis (PSS)

Pathology

The histologic findings in the acute renal crisis of PSS are those of a thrombotic microangiopathy. There is glomerular consolidation caused by subendothelial expansion and capillary thrombosis, fibrinoid necrosis of arterioles and edematous intimal expansion in arteries. The chronic changes of PSS resemble chronic hypertensive injury and include fibrotic intimal thickening in arteries and glomerular sclerosis. As a consequence of the vascular changes, there may be signs of chronic tubulointerstitial disease, including interstitial fibrosis, tubular atrophy, and glomerular obsolescence. Some of the tubulointerstitial and glomerular disease may be a consequence of the thrombotic microangiopathy, whereas others are a consequence of hypertension.

The Role of Kidney Biopsy

The kidney biopsy may not provide a definitive diagnosis of PSS, for the findings may be that of hypertensive changes without indicating an underlying thrombotic microangiopathy or acute artery changes. A renal biopsy is indicated in patients with acute renal failure who do not have extrarenal manifestations of PSS, and those for whom the diagnosis is uncertain. A renal biopsy may also be of value in those patients who have an overlap syndrome of PSS and SLE, ANCA SVV, or other forms of mixed connective tissue disease [31, 71]. The clinical dilemma occurs in those patients who have evidence of SLE, dermatomyositis, or a clinically nonspecific manifestation of PSS. In these individuals, a renal biopsy may be most useful.

Laboratory Findings

A positive ANA reponse with a speckled or nucleolar pattern occurs in 70% of scleroderma patients. More specific autoantibodies found in these patients react with DNA topoisomerase I (anti-Scl-70). These more specific antibodies are found in up to 30% of patients with diffuse cutaneous disease. Anticentromere autoantibodies are relatively specific for the CREST syndrome. Antibodies to double-stranded DNA or other nuclear antibodies are uncommon.

Clinical Syndromes

The clinical picture of PSS includes involvement of the skin and subcutaneous tissues with localized or diffuse thickening of the extremities, face, and trunk. This thickening results in hardening of the skin and sclerosis of the fingers (sclerodactyly). Variants of PSS include the CREST syndrome defined by calcinosis, Raynaud's phenomenon, esophageal hypomotility, sclerodactyly, and telangiectasias. In these patients, it is uncommon to have either kidney or other organ system involvement. Similarly, localized forms of scleroderma or limited cutaneous systemic sclerosis are not associated with renal disease.

Raynaud's phenomenon is found in > 90% of PSS patients. Whether Raynaud's phenomenon is associated with PSS or a limited and benign phenomenon can be tested at the bedside by careful examination of the periungual nail beds. The absence or drop-out of capillaries in the nail beds is typical of patients PSS but not in patients with benign Raynaud's phenomenon. Esophageal hypomotility or loss of esophageal sphincter tone is found in 75% of patients with PSS, resulting in gastroesophageal reflux. Small and large bowel hypomotility produces a plethora of symptoms, including malabsorption and bacterial overgrowth. Pulmonary fibrosis occurs in > 50% of patients.

The renal involvement tends to occur early in the course of the disease, usually within 2 – 5 years after the onset. It is possible that the disease process may occur more commonly in the fall and winter.

As many as 75% of all patients with PSS have evidence of renal damage, and 50% have clinically evident renal disease. Some patients have mild proteinuria (typically less than 3 g/day) and varying degrees of mild renal insufficiency and hypertension. Scleroderma renal crisis, characterized by the relatively sudden onset of hypertension and acute onset of renal disease in a patient with no prior evidence of renal injury, occurs in 10 – 15% of cases. In the series from Black et al. [10], severe sclerodermal renal disease occurred in approximately 12% of those patients who had diffuse cutaneous scleroderma, but only 1.6% of those with limited cutaneous scleroderma. The incidence was increased in blacks (21% compared to 7% in whites), and the concomitant use of high-dose corticosteroids and perhaps cyclosporine or tacrolimus (FK 506) accelerated the disease process. Considering the nonspecific nature of these predictive factors, prudence dictates close monitoring of patients with PSS with repetitive measurements of blood pressure, serum creatinine concentrations and urinalyses.

Treatment Recommendations

The pathogenesis of scleroderma renal crisis remains controversial. It is possible that the crisis is analogous to a Raynaud's phenomenon: severe and persistent vasospasm may lead to overelaboration of renin and angiotensin II, resulting in, or at least perpetu-

ating, vasoconstriction. ACE inhibitors are the agents of choice, resulting in improvement in hypertension in up to 90% of patients. While most treatment studies rely on captopril, it is likely that other ACE inhibitors have a similar affect. It is not known whether Ang II receptor antagonists are equally effective. With blood pressure control, there may be reversal of renal insufficiency, diminution of proteinuria, and amelioration of the extrarenal manifestations of systemic sclerosis, including improvement in Raynaud's phenomenon and even improvement of the sclerodermatous skin changes.

In a report reviewing the course of 108 patients with scleroderma renal crisis [108], the 1-year survival before the introduction of treatment with ACE inhibitors was 18%, improving to 76% with these agents. Nonetheless, long-term data indicate that renal failure or death still occurred in half of those patients treated with ACE inhibitors. A significant number of patients with scleroderma renal crisis require renal replacement therapy. These patients may pose substantial difficulties with respect to vascular access, perhaps as a consequence of the hardening of the skin overlying the vascular access and the vasoconstrictive propensity of larger arteries. Peritoneal dialysis may be complicated by fibrosis of the peritoneal membrane altering peritoneal clearance. There are very few reports PSS of transplantation in patients PSS.

Other Rheumatologic Diseases that Affect the Kidney

Patients with rheumatoid arthritis may have several forms of renal injury, including amyloidosis as a complication of long-standing, severe rheumatoid arthritis. These patients, as well as those with seronegative arthropathies, can have proliferative glomerulonephritides, either associated with pauci-immune glomerulonephritis or IgA nephropathy. Patients who are HLA-B27 positive with ankylosing spondylitis or Reiter's syndrome usually have an IgA nephropathy [62].

Relapsing polychondritis is an unusual condition associated with ANCA SVV and a pauci-immune necrotizing and crescentic glomerulonephritis, although other proliferative glomerular lesions have been described.

Patients with Sjögren's syndrome and sarcoidosis typically have a renal presentation of an interstitial nephritis associated with interstitial fibrosis. In both of these circumstances, corticosteroid therapy may have a salutary effect, especially in sarcoidosis where substantial response to glucocorticoids may occur.

Dysproteinemias

There are several dysproteinemias or paraproteinemias with deposition of abnormal proteins in the kidney. These include amyloidosis, light chain nephropathy, cast nephropathy, amyloid (AL and AA), fibrillary glomerulonephritis and immunotactoid glomerulonephropathy, and Waldenström's macroglobulinemia (Table 7). The dysproteinemias, especially light chain-related diseases that cause tubulointerstitial lesions including Fanconi's syndrome or tubular interstitial nephritis, are described in Chapter 8.

Pathology

Many dysproteinemias cause distortions of the glomerular architecture by deposition of the abnormal proteins in distinctive patterns

Table 7. Types of Glomerular Extracellular Fibrillar and Microtubular Structures

Disease	Approximate Diameter and Usual Range (nm)	Most Common Composition
AL or AA amyloidosis	10 (8 – 15)	Light chains or AA protein
Fibrillary glomerulonephritis	20 (15 – 30)	Oligoclonal immunoglobulin
Cryoglobulinemia	30 (25 – 35)	Cryoglobulins
Immunotactoid glomerulopathy	40 (20 – 50)	Monoclonal immunoglobulin

(Table 7). By light microscopy there often is an increase in acidophilic material in the glomeruli. Amyloid is characterized histologically by fluffy pale acidophilic deposits with specific staining properties by Congo red (i.e., apple-green birefringence when viewed with polarized light). These deposits appear as masses of thin nonbranching fibrils by electron microscopy. Amyloid deposits may also be found in small vessels, including arterioles and arteries, and along tubular basement membranes. Primary amyloid (AL) can be differentiated from secondary (AA) amyloid on the basis of immunofluorescent staining of the amyloid deposits with anti-AA protein antibody or antibodies to lambda or kappa light chains.

Light chain deposition disease is characterized histologically by nodular glomerulosclerosis that is identical to diabetic glomerulosclerosis. By electron microscopy, glomerular and tubular basement membranes are thickened by finely granular material, rather than by fibrils like those seen with amyloidosis. Unlike amyloid, the deposits of light chain deposition disease do not stain with Congo red stain. In renal biopsy specimens, approximately 80% of AL amyloid is composed of lambda light chains, whereas approximately 80% of light chain deposition disease is caused by kappa light chains.

Clinical Features, Course, and Therapy

Light chain deposition disease and primary amyloidosis may have similar clinical presentations. In amyloidosis, proteinuria and renal insufficiency are the major renal manifestations of disease. Proteinuria ranges from asymptomatic, non-nephrotic-range to severe, resulting in morbid edema, hypercholesterolemia, and marked hypoalbuminemia. Patients with amyloid frequently have disease in organs other than the kidney, especially the heart, liver, skin, gastrointestinal tract, and synovium. In most patients, multiorgan system involvement is present, with 50% of patients having renal disease and ≥ 40% having cardiac amyloid deposits. In an individual with carpal tunnel syndrome and nephrotic syndrome, the diagnosis of amyloid must be considered, since 25% of patients with primary amyloidosis have carpal tunnel syndrome.

The renal manifestation of light chain deposition disease is nephrotic syndrome and can appear very similar to AL amyloidosis. Both disorders affect the heart, liver, and nerves. AL amyloid more frequently affects the gastrointestinal tract and the lungs, while light chain deposition disease rarely affects those organs. Patients with light chain deposition

Table 8. Causes of Secondary Amyloidosis

Chronic infections
– Osteomyelitis
– Tuberculosis
– Leprosy
– Syphilis
– Xanthogranulomatous pyelonephritis
– Others

Chronic inflammatory disorders
– Rheumatoid arthritis
– Juvenile polyarthritis
– Inflammatory bowel disease
– Ankylosing spondylitis
– Sjögren's
– Bechet's syndrome
– Wipple's disease
– Others

Neoplastic disorders
– Multiple myeloma
– Hodgkin's
– Renal cell carcinoma
– Waldenström's macroglobulinemia
– Others

Inherited Disorders
– Glycogen storage disease
– Familial Mediterranean fever
– Others

disease have a higher plasma creatinine concentration at the time of biopsy and less proteinuria than those patients with primary amyloidosis. In our own studies [51], the plasma creatinine concentration was 2.4 mg/dL in the light chain deposition disease patients, whereas the patients with amyloidosis had a serum creatinine of 5.1 mg/dL. In contrast, patients with light chain deposition disease had a protein excretion rate of 3.7 g/24 hours, and patients with amyloidosis had 6.9 g/day.

The diagnosis of amyloidosis requires the presence of amyloid deposits in tissue. While kidney and liver biopsy are positive in 90 – 95% of cases, abdominal fat pad aspiration is positive in 60 – 90% of cases, bone marrow biopsy in up to 50% of cases, and rectal biopsy in 50 – 80% of patients. Most recently, an alternative to tissue biopsy has been suggested by the use of serum amyloid P component scintigraphy. This test is performed by the intravenous injection of technetium-labeled serum amyloid P component [101]. Scintigraphy has a sensitivity of nearly 100% with uptake in the spleen, kidney, and adrenal. Unfortunately, this test is not widely available, and substantial concern exists that the serum amyloid P protein obtained from numerous blood donors may be contaminated by infectious particles.

A clinical distinction between primary and secondary amyloidosis is based on the presence of systemic disease, especially inflammatory disease associated with secondary amyloidosis (Table 8).

Treatment Recommendations

Unfortunately, patients with primary amyloidosis have a dismal long-term prognosis with a five-year survival rate of <20%. Patients die either of malnutrition or congestive heart failure. While there are occasional responses to a combination of colchicine, prednisone, and melfalan, most patients do not appear to respond to these forms of therapy. In the largest study to date, 220 patients with biopsy-proven amyloidosis were randomly assigned to three different groups: colchicine alone, melfalan and prednisone, or melfalan, prednisone and colchicine. Patients were stratified according to whether they had renal disease, cardiac disease, or peripheral neuropathy. The median survival was only 8.5 months in the colchicine group, 18 months in those assigned to melfalan and prednisone, and 17 months in those assigned to melfalan, prednisone, and colchicine. In this important

study, the overall length of survival was 50 months among those who had a reduction in serum or urine monoclonal protein by 12-months, and 15% of patients survived for ≥ 5 years. This study concludes that treatment with melfalan and prednisone results in prolonged survival and a response to treatment as compared with colchicine alone, and forms the basis of current treatment recommendations. It is important to note that the use of melfalan is associated with melfalan-induced acute myelogenous leukemia (AML) and pancytopenia in about 6 – 20% of patients, depending on the duration of treatment and apparent response of the amyloid [66].

At the cutting edge of treatment, autologous bone marrow transplantation with stem cell rescue or stem cell rescue after ablative chemotherapy has recently been tried in a small number of patients. The relative success of this approach is not certain.

Therapy for secondary amyloidosis is aimed at the treatment of the underlying disorder except in familial Mediterranean fever, where colchicine is most useful in decreasing the severity of the attacks of serositis and arthritis [9]. Colchicine decreases, or at least slows, the accumulation of deposits in the kidney. The symptoms of familial Mediterranean fever are those of episodic attacks of serositis and fever. The use of colchicine in dosages of 1 – 3 mg/day has resulted in substantial diminution in the number of attacks in three-quarters of patients studied.

Other Paraproteinemias

There are several glomerular diseases due to nonamyloid fibrillar deposits. These lesions include fibrillary glomerulonephritis, immunotactoid nephropathy, and fibronectin glomerulopathy. Fibrillary glomerulonephritis is characterized on light microscopy by capillary wall thickening, mesangial matrix expansion, and varying degrees of hypercellularity and inflammation. The fibrils are larger than those of amyloid, but are smaller than those of immunotactoid glomerulonephropathy (Table 7). The deposits of fibrillary glomerulonephritis usually stain intensely for IgG (usually predominantly IgG4) and C3 [60].

Fibrillary glomerulonephrosis is found primarily in Caucasians, with a slightly increased female predominance. The clinical course of all of these forms of fibrillar deposition is largely that of nephrosis, although some patients have hematuria and hypertension as well. Half of all patients develop ESRD despite various forms of experimental therapy. Currently, it is not clear that any form of therapy is of benefit. In fact, most patients do not respond to either prednisone or cyclophosphamide. After 24 months of follow-up, there is only 48% renal survival [60].

Immunotactoid glomerulopathy is a different disorder in which the fibrils are larger and have a microtubular organization. Patients with immunotactoid glomerulopathy are more likely to have a circulating monoclonal immunoglobulin than patients with fibrillary glomerulonephritis. Immunotactoid deposits resemble those of cryoglobulinemia, which usually contain a monoclonal rheumatoid factor component.

The most recently described nonamyloid fibrillar deposition disease is fibronectin glomerulopathy. This extremely rare disease is characterized by massive amounts of fibronectin deposited in the mesangium. These deposits do not stain with Congo red. By electron microscopy, the fibrils are approximately 12 nm in diameter and are composed of fibronectin instead of immunoglobulin.

Paraneoplastic Nephropathies

The concept of paraneoplastic nephropathy is not new. The first report of a nephrotic syndrome associated with Hodgkin's disease dates back to 1939 [79]. In 1996, Lee et al. reported on a series of adults over the age of 40 with nephrotic syndrome [69]. In that cohort of patients, 11% developed neoplasms, all carcinomas. This corresponded to an incidence ten times greater than the age-matched actuarial rate. Interestingly, the renal disease antedated diagnosis of cancer in two-thirds of patients.

The prevalence of paraneoplastic nephropathy among patients with cancer is probably below 0.1% [3]. Conversely, the prevalence of cancers among older patients with glomerulonephritis may be quite high. For example, as many as 20% of patients 60 years and older with membranous nephropathy may have a concurrent cancer. Based on these findings, the search for occult malignancy is recommended in all elderly patients presenting with a glomerular disease.

The spectrum of glomerular diseases associated with concurrent cancers is wide. The most commonly reported nephropathies include membranous glomerulonephritis, minimal change disease, membranoproliferative glomerulonephritis, crescentic and necrotizing glomerulonephritis with or without a rapidly progressive glomerulonephritic syndrome, IgA nephropathy, and focal segmental glomerulosclerosis (FSGS).

Certain nephropathies tend to be associated with specific neoplasms. Membranous glomerulopathy accounts for about 30% of nephrotic syndrome in adults. Whereas it usually presents with proteinuria, as many as 40% of patients in this patient population may not have the nephrotic syndrome. There is a strong association of membranous nephropathy with epithelial cancers, especially those of bronchial or digestive tract origin. In fact, membranous nephropathy has been said to account for 60% to 70% of glomerular involvement in patients with these types of cancer. Conversely, the prevalence of membranous nephropathy among patients with nephrotic syndrome and hematologic cancers is only about 1%.

The characteristic histologic findings of classic or idiopathic membranous nephropathy is characterized by subepithelial immune complex deposits as seen by electron microscopy, however in cases of membranous nephropathy secondary to systemic disease such as SLE or neoplasms, one may find mesangial and/or subendothelial immune complex deposits in addition to the subepithelial deposits. These findings may be a clue for the presence of a secondary membranous nephropathy and should prompt the treating physician to search for an occult malignancy.

Minimal change disease (MCD) accounts for about 25% of nephrotic syndromes in the adult. In adult patients, especially the elderly, there is a higher incidence of hypertension and ARF than is seen in childhood disease. About 15 – 20% of adults may also present with microscopic hematuria. Minimal change disease is strongly associated with Hodgkin's lymphoma. Although the incidence of minimal change disease among patients with Hodgkin's is quite low, accounting for only 0.4% (7/1700 cases), MCD is, conversely, the most common finding in patients with Hodgkin's lymphoma and the nephrotic syndrome. The course of the nephrotic syndrome with MCD has been reported to parallel that of the lymphoma with treatment. The nephrotic syndrome and proteinuria may disappear when the Hodgkin's lymphoma goes into remission. There have also been reports of re-

current proteinuria heralding the recurrence of the lymphoma. MCD has also been reported with non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and carcinomas.

Membranoproliferative glomerulonephritis (MPGN) may present as the nephrotic syndrome but may also present as an acute nephritic syndrome with renal failure, microhematuria, and hypertension. It is usually associated with low levels of C3, circulating C3 nephritic factor and circulating immune complexes. It may be the most common cause of nephrotic syndrome in patients with chronic lymphocytic leukemia. MPGN is also pathogenetically associated with essential mixed cryoglobulinemia. Whereas greater than 90% of patients with essential mixed cryoglobulinemia have been reported to be infected with the hepatitis C virus, in those patients who are HCV negative, the cryoglobulins have been suggested to be the result of a monoclonal expansion of B cells producing them and IgM rheumatoid factor.

IgA nephropathy presents in patients between the ages of 10 and 30 years of age in 65% of cases, although it may occur in the elderly population. It usually presents with microscopic hematuria, but may also present with frank proteinuria, hypertension, renal failure and even macroscopic hematuria with tea-colored urine. In one series, 6/66 patients greater than 60 years old with IgA nephropathy were found to have a concomitant cancer, whereas 0/158 patients younger than 60 years old had a cancer. IgA nephropathy was also reported in association with bronchogenic, head and neck, and pancreatic carcinomas.

In a compendium of all glomerular diseases associated with non-Hodgkin's lymphoma, Harper and Adu found that the most common nephropathy associated with B cell non-Hodgkin's lymphoma was focal segmental necrotizing glomerulonephritis (FSNG) [50]. This diagnosis accounted for 12/23 patients with glomerulonephritis and non-Hodgkin's lymphoma. The second most common diagnosis, accounting for 7/23 patients, was MPGN. Interestingly, 6/12 patients with FSNG had no evidence of immune complex deposits by indirect immunofluorscence microscopy. Those reports make no mention of ANCA testing or ANCA positivity. The pauci-immune histology reported raises the possibility that this could be associated with the presence of circulating antineutrophil cytoplasmic autoantibodies. In our experience in a cohort of 206 patients with ANCA SVV and glomerulonephritis, 11 patients developed 12 cancers. Four patients had prostate cancer, 3 colon cancers, and one each stomach, lung, bladder, and skin cancer. One patient had an unknown primary cancer site. Of these 11 patients, 5 were diagnosed with cancer either at presentation with their ANCA SVV or within 3 months thereafter. In these patients, it is unlikely that the development or the rapid growth of the cancer would have been secondary to immunosuppression or the use of cytotoxic drugs. In fact, 2 of these patients never received any cytotoxic drugs, and one patient received cytotoxic drugs for less than 4 weeks.

Kidney Abnormalities Associated with Liver Disease

The kidney is affected in a number of ways once there is liver damage, including derangement of salt and water balance, acute azotemia (especially in the hepatorenal syndrome), and

in association with several glomerular diseases (Table 9). It is beyond the scope of this review to consider the alterations of salt and water disturbances in liver disease or the causes of acute renal insufficiency. Rather, this chapter will focus on the viral hepatitides and the association of IgA glomerulopathy in cirrhosis.

Table 9. The Kidney in Liver Disease

- Sodiumretention
- Water retention
- Acute renal insufficiency
  - Prerenal azotemia
  - Acute tubular necrosis
  - Hepatorenal syndrome
- Viral hepatitis (Hepatitis B, Hepatitis C)
- Cirrhosis
  - Sclerosing glomerulonephritis
  - IgA glomerulonephritis

Hepatitis B

Hepatitis B causes several glomerular syndromes including serum sickness, membranous nephropathy, MPGN, and polyarteritis nodosa. Serum sickness is found in up to 25% of patients with hepatitis B, with associated arthralgias and arthritis, purpura, fever, and transient renal disease.

Membranous nephropathy has long been associated with hepatitis B, especially in Asia and Australia, where the majority of children with membranous nephropathy have hepatitis B. The proof that viral infection has a pathogenetic role in glomerular disease has been demonstrated in a number of ways. The most specific evidence is the immune complex deposits in membranous nephropathy containing hepatitis B antigen and especially the Hbe antigen [63]. In addition, both hepatitis B viral DNA and RNA have been observed in glomerular and tubular cells in patients with renal disease. Fortunately, in children with hepatitis B, spontaneous remission almost always accompanies the disappearance of hepatitis Be antigenemia and conversion to a positive hepatitis Be antibody state, contraindicating treatment with immunosuppressive drugs so as not to either stimulate viral replication or alter the development of an antibody state.

Whether there is a role for alpha-interferon therapy in hepatitis B and other types of glomerular injury is controversial. Conjeevaram et al. treated 15 chronic hepatitis B glomerulonephritis patients with alpha-interferon [23]. Of these individuals, half had a long-term serological response with loss of the serum hepatitis B antigen and hepatitis B viral DNA. Seven of 8 patients had a gradual improvement in proteinuria, although their liver disease improved more quickly. All 8 had membranous glomerulonephritis. Interestingly, of the other 7 patients, 4 had MPGN. This study suggests that the interferon-α may have an ameliorative role in the treatment of hepatitis B-associated membranous nephropathy in adults.

Polyarteritis nodosa has been associated with hepatitis B [47]. The symptoms of the disease may vary from subtle weight loss and malaise to sudden perforation of the abdominal viscus and renal infarction. The spectrum of injury includes mononeuritis multiplex, abdominal pain from ischemic injury to the bowel wall, central nervous system infarctions including central retinal arteritis, coronary arteritis resulting in myocardial infarctions, deep nodular lesions in the skin, and arterial damage in other vascular beds with

associated tissue destruction [47]. The treatment of hepatitis B-related polyarteritis nodosa is best described in a recent study by Guillevin. Of 41 patients with hepatitis B-associated polyarteritis nodosa, 35 were treated with the antiviral agent vidarabine, and 6 patients were treated with interferon α and plasma exchange. Fifty two percent of patients converted to hepatitis B antibody and 24% also seroconverted to anti-hepatitis B surface antibody. In fact, half of the patients no longer had serologic evidence of hepatitis B viral disease at all. Eight patients died.

The treatment strategy at present is short-term steroid therapy, antiviral agents, and plasma exchange. The use of corticosteroids and cyclophosphamide, which may or may not facilitate viral replication, is not indicated.

Hepatitis C (HCV) -related Glomerulonephritis

Cryoglobulins are composed of different types of immunoglobulins, which may be separated into 3 types. Whereas type I cryoglobulins are characterized by the presence of monoclonal antibodies, usually IgM, type II and type III are mixtures of monoclonal and polyclonal, or polyclonal with polyclonal immunoglobulins, respectively. In type II mixed cryoglobulins, the monoclonal component is usually an IgM with a kappa light chain. The polyclonal component is usually an IgG, with either type of light chains [2]. A growing number of reports have linked HCD infection and type II cryoglobulin [16, 33, 81].

Cryoglobulins are detectable in up to 30% of patients with HCV, but the clinical syndrome of mixed cryoglobulinemia occurs only in 1 – 2% of patients with HCV infection. Misiani et al. studied the association between HCV infection and cryoglobulinemia in 51 patients, using as controls 45 patients with non-cryoglobulinemic glomerulonephritis [74]. The authors looked for the presence of HCV by a number of different techniques, including a c100 ELISA and a c22/c200 ELISA, a recombinant immunoblot assay (4 RIBA), and a serum HCV RNA by PCR. Depending on the assay used, up to 98% of patients with type II cryoglobulinemia had evidence of HCV infection compared to only 2% in the control group. In addition, the study of the cryoglobulin precipitate revealed detectable anti-HCV activity in the cryoglobulin precipitate from 94% of patients after the use of dithiothreitol, a substance that destroys the IgM antibodies with rheumatoid factor activity. Similarly, Agnello et al. demonstrated that the concentrations of HCV, RNA, and anti-HCV antibody, but not antibodies to EBV or rubella, were much higher in the cryoglobulin precipitate than in the corresponding serum [1].The high prevalence of HCV infection and type II cryoglobulinemia, as well as the demonstration of anti-HCV antibodies and HCV RNA in the cryoglobulin precipitate, provides compelling evidence of an association between HCV infection and the development of type II cryoglobulinemia.

The mechanism by which HCV infection might lead to the development of type II cryoglobulinemia is unclear. The recent finding that peripheral blood leukocytes, especially B cells, can be the site of extrahepatic HCV replication has led to the postulation that direct active viral replication in B cells induces type III mixed cryoglobulins by triggering the activation of B cells to hyperproduce polyclonal IgM rheumatoid factors in a subgroup of patients with chronic infection. Some other uncharacterized event might induce the abnormal proliferation of a single clone, leading to the production of a monoclonal IgM rheumatoid factor and type II mixed cryoglobulinemia.

Pathology

The most common renal lesion in patients with type II mixed cryoglobulinemia is type I MPGN. Pathologic characteristics include endocapillary hypercellularity due to proliferation of mesangial and endothelial cells, and infiltration of monocytes and T lymphocytes. There are typically large amorphous eosinophilic, PAS-positive, Congo red-negative deposits that may fill the capillary lumina ("hyaline thrombi"). The basement membrane is typically thickened with a "double contour" appearance. A few patients have fibrinoid necrosis of the walls of arterioles and venules. Electron microscopy may reveal subendothelial electron dense deposits consisting of a microtubular structure of hollow fibers, 100 to 1000 nm long. By immunofluorescence microscopy, there is granular-to band-like staining of the vessel walls for IgM, IgG, and complement C3 (144). Some patients exhibit intense staining of large deposits that fill the capillary lumen.

Clinical Manifestations

Type II mixed cryoglobulinemia is most often diagnosed in the fifth and sixth decade of life, often many years after the first symptoms appear. Cryoglobulinemic vasculitis is often characterized by purpura, weakness, arthralgias, arthritic vasculitis, neuropathy and proliferative glomerulonephritis. Renal involvement occurs in 8 – 58% of patients and is more common in women with mixed cryoglobulinemia. Manifestations of renal involvement typically appear many years after the first symptoms of cryoglobulinemic vasculitis develop. The renal disease may occasionally appear concomitantly with the extrarenal manifestations, but rarely before. The most frequent renal findings are isolated proteinuria and microscopic hematuria with moderate chronic renal insufficiency. Twenty to 30% of patients may present with an acute nephritic syndrome with ARF, severe proteinuria, hematuria and hypertension. Twenty percent of patients may present with a nephrotic syndrome.

Clinical Course and Prognosis

The clinical course of type I MPGN associated with HCV varies. Ten to 15% of patients attain complete remission, even when presenting with an acute nephritis, while 30% of patients follow an indolent course that does not progress to ESRD despite the persistence of abnormal urinary sediment and chronic renal insufficiency and 20% of patients may have recurrent episodes of acute nephritis that may go into remission either spontaneously or in response to high-dose corticosteroids and/or plasmapheresis. The latter course usually leads to chronic renal insufficiency. According to the data of D'Amico et al., only about 15% of patients progress to ESRD over a mean period of 10 years [41]. These authors, however, report a high mortality rate over the same period of time secondary to extrarenal disease. Based on a cohort of 105 patients diagnosed over 25 years [98] and followed up for a median of 72 months post-biopsy, the 10-year probability of survival without ESRD was 49%. The major causes of death in that group were due to cardiovascular disease, infection, liver failure, and neoplasia. The main risk factors were age > 50, vascular purpura, splenomegaly, cryocrit level > 10% and C3 plasma levels < 54 mg/dL. As with other glomerulonephritides, a serum creatinine > 1.5 mg/dL was an important risk factor for chronic renal failure or death (relative risk of 1.25, 95% confidence interval of 1.11).

Treatment Recommendations

The recognition of an association between HCV infection and type I MGPN has led to great interest in the treatment of this glomerular disease with antiviral agents. While a large body of data has accumulated over the last several years concerning the treatment of HCV infection, most knowledge is derived from the treatment of hepatic disease. Several subtypes of interferon alpha have been employed. One of the first reports, by Misiani et al., was a randomized study of the use of interferon alpha in the treatment of patients with HCV-related mixed cryoglobulinemia [75]. Patients were treated thrice weekly for 24 weeks versus symptomatic therapy in the control group. Treatment with interferon p–α resulted in improvement in cutaneous vasculitis, cryocrit, and serum creatinine, and a decrease in HCV RNA. However, the viremia and cryoglobulinemia recurred in all patients after discontinuation of interferon alpha. Carithers et al. performed a meta-analysis of interferon alpha 2b trials [19]. The results are expressed as biochemical response (correction of alanine amino-transferase, ALT) or serologic response (decrease in or disappearance of HCV virus titers). Response is defined as either "end of treatment response" or "sustained response", referring to the result six months after discontinuation of treatment. The authors report a biochemical end of treatment response of 47% and 29% for virologic response. The sustained response dramatically drops to 23% and 8%, respectively. Treatment for prolonged periods (12 to 24 months versus 6 months) or with high-dose interferon alpha might lead to a very modest improvement in these results. Most patients experienced mild to severe influenza-like symptoms.

The results of the use of interferon alpha alone led to the evaluation of combination therapy including interferon alpha and the nucleoside analog ribavirin [87]. Three randomized placebo-controlled studies comprising more than 150 patients have shown that therapy with Ribavirin alone for 24 – 48 weeks resulted in an improvement ALT levels, but no substantial reduction in HCV RNA levels. ALT levels increased to pretreatment values when therapy was discontinued. However, ribavirin in standard doses combined with interferon alpha in doses of 3 million units, 3 times weekly for 6 months, was found to significantly improve the sustained biochemical and virological response rates compared to interferon alpha alone. No study has yet been reported as to the use of this combination therapy in the treatment of HCV-related mixed cryoglobulinemia or MPGN.

There are currently 2 non-randomized case series on the use of plasmapheresis with or without small doses of corticosteroids in the treatment of acute exacerbation of cryoglobulinemic MPGN [12, 39]. These case series report a beneficial effect of plasmapheresis in the treatment of acute exacerbation of vasculitis. Patients with acute deterioration of renal function seemed to benefit the most, whereas patients with chronic stable renal insufficiency had a less marked benefit from the treatment. Of note is that in 5/9 patients [39] plasma exchange led to sustained remission without clinical relapse when the procedures were reduced in frequency or discontinued.

Cirrhosis

Cirrhosis of the liver is associated with two syndromes. First, in many cirrhotic patients, there is an associated diffuse glomerular sclerotic process that has been called "cirrhotic glomerulosclerosis". By immunofluorescence microscopy, some of these samples

have IgA or IgM deposition. The second, and most common histologic finding is a process indistinguishable from idiopathic IgA nephropathy. In fact, IgA deposition with variable degrees of MPGN is found in 50% of autopsy subjects who have died with alcoholic liver disease. The IgA deposition in this circumstance (clinical course of IgA nephropathy) is reviewed in the previous chapter.

Kidney in Infectious Disease

Acute Post-streptococcal Glomerulonephritis (APSGN)

APSGN is the prototype disease of an acute glomerulonephritis associated with an infectious etiology. The first description linking an acute glomerulonephritis to an infectious etiology dates back to the early 18th century after scarlet fever epidemics in Florence and Vienna. The association was also described in 1838 by Bright, again in association with scarlet fever [109]. Rammelkamp et al. further refined the association of post-streptococcal glomerulonephritis with specific serotypes of Streptococci [85].

APSGN is a disease that affects primarily children, with a peak incidence between ages 2 and 6 years. Children younger than age 2 and adults older than age 40 account for only about 10 – 15% of patients affected with APSGN. The disease is often subclinical and the incidence of subclinical nephritis outnumber that of overt nephritis by a ratio of 4 – 10:1. Males are more likely to have overt nephritis than females.

APSGN may occur as part of an epidemic or as sporadic disease. The clinical syndrome preceding APSGN may be either pharyngitis or a skin infection. In temperate countries, the pharyngitis is more common, whereas impetigo and pyoderma predominate, in the tropics.

Pathology

On light microscopy, APSGN is marked by an acute diffuse proliferative glomerulonephritis. The hypercellularity results both from endogenous mesangial and endothelial cell proliferation, and infiltration of the glomerular tuft by inflammatory cells, especially neutrophils. The early “exudative phase” of disease is characterized by the infiltration of the capillary tuft by neutrophils, eosinophils, lymphocytes, and monocytes. These cells may be present both in the capillary lumen and the mesangium. After 4 – 6 weeks, polymorphonuclear neutrophils (PMN) are usually no longer present and the hypercellularity is mostly residual mesangial hypercellularity.

During the exudative phase and acute disease, there is often occlusion of the capillary lumina. During that time, the capillary walls are thickened by the deposition of large subepithelial immune complexes. In severe cases, crescent formation occurs.

By immunofluorescence microscopy, APSGN is characterized by granular deposits of IgG and C3 distributed in a diffuse granular pattern within the mesangium and along the capillary walls. The IgG usually disappears within a few weeks, leaving a C3-dominant staining that may persist for several months.

By electron microscopy, APSGN is characterized by the deposition of dome-shaped electron-dense deposits (humps) in the

subepithelial zone. These electron-dense deposits are typically seen early in the course of disease, and tend to disappear within two months as the acute glomerulonephritis resolves. Subendothelial, mesangial, and intramembranous deposits also occur in variable amounts and usually persist longer than the subepithelial deposits.

Clinical Manifestations

The glomerulonephritis associated with post-streptococcal disease is typically abrupt in onset. There is a latent period of 7– 14 days after an upper respiratory tract infection, or 14 – 28 days after a pyodermal infection. The most common clinical manifestations of APSGN include symptoms of nephritis, hematuria, hypertension, edema, and oliguria. Anuria and renal insufficiency are uncommon. Patients typically present with mild to moderate hypertension. The hypertension is the most likely cause of headaches that are typically of mild to moderate intensity. However, severe neurological manifestations have been described, including hypertensive encephalopathy with headaches, ocular disturbances, and even stupor, coma, and seizure activity. Excessive intravascular fluid results in pulmonary vascular congestion that may lead to clinical symptoms of dyspnea, orthopnea, and – even in these young individuals – evidence of congestive heart failure (CHF) with pulmonary edema, pleural effusions, and a gallop rhythm. Children typically have systemic symptoms including nausea, vomiting, and abdominal pain with mild fever.

The clinical course in APSGN is usually a self-limited one; resolution of the disease is marked by the institution of a diuretic phase within 1 – 2 weeks after the onset of illness. Associated with the diuresis is amelioration of hypertension and vascular congestion. Interestingly, the hematuria and proteinuria disappear in the vast majority of children within 6 months; in adults, proteinuria may be present in half of patients for more than a year, and one-third may have proteinuria over a longer term. Thus, the long-term prognosis in children is relatively benign, exept in some children with severe crescentic disease, in whom it is likely that evidence of chronic glomerulonephritis persists indefinitely. Some long-term studies of adult patients suggest that complete recovery may take as much as a decade, while some patients may progress to ESRD [17]. Importantly, the episodes of ASPGN that occur in epidemics respond more favorably than do those that occur as sporadic infections.

Treatment Recommendations

No specific treatment is indicated in the care of patients with APSGN. Treatment of hypertension is usually responsive to diuretics as well as other antihypertensive medications, namely calcium channel blockers, or ACE inhibitors. Treatment of acute uremia and advanced renal failure may be indicated, requiring the transient institution of dialysis. No immunosuppressive regimens have been studied and evaluated in the treatment of APSGN. Kobrin and Madaio [65] suggest the use of high-dose corticosteroids for 3 – 5 days only in patients with an rapidly progressive glomerulonephritis (RPGN) and the findings of crescents in > 30% of glomeruli on renal biopsy. These recommendations are not based on clinical trial data. Specific treatment of the streptococcal infection is essential. Both the patient and exposed family members should be treated with penicilline G or erythromycin. It is unclear as to whether treatment of the streptococcal infection prevents the occurrence of nephritis.

Infective Endocarditis, Shunt Nephritis, and Visceral Sepsis

Infective endocarditis, shunt nephritis and visceral sepsis-induced glomerulonephritis are examples of immune-mediated glomerulonephritis. The pathology of each of these syndromes includes a spectrum of proliferative lesions that range from focal proliferative glomerulonephritis, to acute diffuse proliferative glomerulonephritis, to membranoproliferative glomerulonephritis. Evidence of immune deposition is found both by immunofluorescence microscopy and electron microscopy. Granular deposition of immunoglobulins and complement forms along the glomerular capillary wall and in the mesangium. Immunostaining for IgM often is more intense than staining for IgG.

The responsible pathogen in infective endocarditis, shunt nephritis, and visceral sepsis may be different for each condition. Previously, infective endocarditis was largely due to staphylococcal and streptococcal disease, but now includes gram-negative organisms and opportunistic organisms as well, primarily in immunocompromised hosts and those who use intravenous drugs [76]. The same is true for visceral sepsis. Shunt nephritis is associated predominantly with *Staphylococcus sp.*, but also with other organisms, both gram-positive and gram-negative. Interestingly, ventriculoperitoneal shunts are more resistant to infections than are ventriculo atrial shunts.

The clinical manifestations of all of these diseases are very similar, resulting in either microscopic or gross hematuria and proteinuria. While glomerulonephritis is the predominant manifestation, some individuals (up to 25%) present with nephrotic syndrome. Fever, chills, rigors, and leukocytosis are clues to early detection and institution of appropriate antimicrobial agent therapy. The total complement (CH50) and C3 levels are frequently decreased. Cryoglobulins and circulating immune complexes are detected in some individuals. Among patients with visceral sepsis and infective endocarditis, as many as one-third will have dermal manifestations of injury as well, including peripheral emboli in infective endocarditis and purpura.

The treatment of these conditions depends on identification and eradication of the pathogenetic microorganism. In the case of shunt nephritis oraprosthetic heart valve, removal of the foreign body may be required.

Protozoal and Other Parasitic Infections

Nephrotic syndrome is a common consequence of protozoal and parasitic infections. In areas of Africa, especially Uganda, as many as one third of nephrotic children have quartan malaria. Nephrotic syndrome also occurs in other parasitic and protozoal infections, predominantly those associated with Schistosoma mansoni, as noted in Table 1. In patients with typical nephrotic syndrome, glomerular lesions are variable, including membranous glomerulopathy, focal glomerular sclerosis and minimal change glomerulopathy. Fully one third of patients have focal or diffuse proliferative glomerulonephritis, often with a membranoproliferative pattern. A distinctive entity associated with quartan malarial infection is a pattern of glomerular sclerosis with formation of new matrix material in the subendothelial zone, resulting in basement membrane replication and thickening.

Unfortunately, the long-term prognosis of these conditions is poor; there does not appear to be spontaneous remission when nephrotic syndrome is attributable to malaria. Antimalarial drugs do not help, and the effects of

anti-inflammatory and immunosuppressive drugs are unknown. *Schistosoma mansoni* may respond to antiparasitic medications in combination with a variety of anti-inflammatory and immunusuppressive drugs.

Human Immunedeficiency Virus Associated Nephropathy (HIV-AN)

The occurrence of kidney disease in the setting of HIV infection is common and the spectrum of renal disease is very broad. In a retrospective review of 449 patients with acquired immune deficiency syndrome (AIDS) admitted to Bellevue Hospital in New York [103], almost 20% suffered an acute episode of renal insufficiency. In 5% of patients this led to ARF, with a rise in serum creatinines to > 6 mg/dL. In the subset of patients with severe renal failure, the mortality rate was over 50%. In survivors, recovery of renal function was almost complete, except when nephrotoxic antimicrobial drugs were the cause of renal failure.

The etiology underlying ARF in patients with HIV infection or acquired immunodeficiency syndrome (AIDS) is related, directly or indirectly, to sepsis in up to 75% of the cases [88]. Other important causes of ARF are volume depletion with hypotension and acute tubular necrosis precipitated by nephrotoxic drugs, e.g. aminoglycosides, pentamidine, trimethoprim-sulfamethoxazole and NSAIDs. Pathological changes include acute tubular necrosis (ATN), acute interstitial nephritis, and other findings such as nephrocalcinosis, carcinoma, streptococcal abscesses and various glomerular lesions.

HIV-associated nephropathy refers to a specific glomerulonephritis seen in the setting of HIV infection. Its presenting features are those of nephrotic-range proteinuria and renal insufficiency. Most patients present with a full nephrotic syndrome, including edema, hypoalbuminemia and hyperlipidemia. Some patients, however, present with sub-nephrotic-range proteinuria as well as with microscopic hematuria and sterile pyuria.

The course of HIV nephropathy usually progresses rapidly to renal failure. Initially, Rao and Carbone reported a progression to ESRD within a period of about 3 – 4 months among patients with HIV-AN [18, 87]. In the study by Carbone et al., the median length of survival from diagnosis of renal disease to death was determined by the stage of the underlying HIV infection. The longest median survival period (9.7 months) was among asymptomatic patients, as compared to that of patients with AIDS-related complex (ARC) or clinical AIDS, who had median survival periods of 3.6 and 1.9 months, respectively. (It is important to note that these data were derived from the "pre-zidovudine (AZT)" era.) HIV-AN may occur at any stage in the HIV infection, possibly most commonly in asymptomatic HIV-infected patients [18].

From the earliest reports of HIV nephropathy, a geographic discrepancy in the incidence of HIV-AN was noted with a predominance of cases reported from East Coast centers, and a very low prevalence of the disease in San Francisco. This geographic difference in prevalence suggested possible associations with the mode of transmission of the infection, with IV drug use, or with racial differences. It is now apparent that there is a strong racial predominance of African-Americans in HIV-AN that is independent of concomitant intravenous drug use. A study by Bourgoignie et al. also describes a much more severe form of the disease among the black population, with blacks being more likely to have nephrotic-range proteinuria and renal insufficiency [14]. This racial difference is also seen in other glomerular diseases such as idiopathic focal segmental glomerulosclerosis,

hypertension and diabetes. The basis for this predilection of HIV-AN among African-Americans is currently unknown.

The incidence of HIV-AN in autopsy and biopsy-based series has varied, depending on geographic location, criteria for diagnosis and indications for biopsy. Overall the incidence appears to be somewhere between 1 – 10%. In the study by Bourgoignie, no relationship was found between the development of nephropathy and patient age, duration of HIV infection or types of opportunistic infections [14].

Pathology

Pathologically, HIV-AN has features of a collapsing form of FSGS, characterized by focal to global wrinkling, thickening and retraction of the GBM, and expanded mesangial matrix, resulting in obliteration of capillary lumens. There is no associated increase in mesangial cellularity. A characteristic feature of collapsing FSGS associated with HIV-AN is hypertrophy and hyperplasia of the visceral epithelial cells overlying the glomerular tuft. These visceral epithelial cells may also show numerous intracytoplasmic protein resorption droplets. There is interstitial edema, fibrosis, and inflammation with variable degrees of tubular atrophy. There often is focal microcystic dilatation of tubules containing proteinaceous casts.

By indirect immunofluorescence microscopy, some degree of staining for IgM, and C3 (and, less commonly, C1q) is seen in the mesangium and in areas of glomerular sclerosis. There may be staining for IgG, IgA, and albumin within the visceral epithelial cell resorption droplets.

By electron microscopy, one can see collapse of the glomerular tufts with wrinkling and retraction of segments of the GBM. There is extensive foot process effacement of podocytes, as well as microvillus transformation. Over 90% of HIV-AN biopsies reveal numerous tubuloreticular inclusions within endothelial cells. These inclusions consist of 24 nm tubular structures located within the endoplasmic reticulum. These structures (also seen in SLE) are thought to be the result of interferon α activation.

There is some controversy as to whether one aspect of HIV-AN consists of diffuse mesangial hypercellularity. A milder mesangial lesion appears to be more common in children and caucasian patients, and is associated with less severe proteinuria.

Treatment Recommendations

No specific treatment for HIV-AN is currently available. The care of patients with HIV-AN consists of 3 goals: (1) the reduction in proteinuria in an attempt to minimize the nephrotic syndrome, (2) the delay of progression to ESRD, and (3) the provision of renal replacement therapy when ESRD is reached.

– *Minimizing proteinuria.* To date, 3 studies involving small numbers of patients with nephrotic syndrome and HIV infection have documented a reduction in proteinuria resulting from treatment with an ACE inhibitor. This benefit appears to be associated with stabilization in renal function. Overall, the use of ACE inhibitors in HIV-AN seems to be of benefit. However, this intervention is sometimes limited by the development of hyperkalemia, especially in patients concomitantly receiving trimethoprim-sulfamethoxazole.
– *Delay of progression to ESRD.* Two lines of intervention currently available are (a) treatment with antiretroviral drugs, and (b) immunosuppression with high-dose corticosteroids. Several reports involving

series of patients with HIV and the nephrotic syndrome suggest that treatment with AZT decreases the degree of proteinuria and delays the progression of HIV-AN to ESRD.

Some of these studies are case controlled, others are prospective studies compared with historic control subjects [59], and other studies are uncontrolled [67, 73]. It is likely that the effect of AZT may depend, in part, on the stage of histologic progression and the degree of azotemia attained at the time treatment is instituted. It is noteworthy that these were derived in the early days of HIV treatment; at the time when treatment of HIV was almost entirely dependent on the institution of AZT. No new data are currently available on the effect of combination therapy with reverse transcriptase inhibitors or protease inhibitors. Likewise, there are no data concerning the effect of combination therapy on the incidence of HIV nephropathy.

The other line of treatment to delay progression of azotemia to ESRD has been based on immunosuppression, with reports of improvement in renal function and proteinuria in response to high-dose corticosteroids. Most reports are single cases, although a few case series that have included HIV-infected children and adults. Whereas the use of high-dose corticosteroids seems to improve proteinuria and delay the decline of renal function, this treatment appears to be associated with a high incidence of life-threatening infections. Based on these results, it is difficult to recommend the use of high-dose corticosteroids to all patients with HIV-AN.

Renal Replacement Therapy

The issues of renal replacement therapy in HIV-infected patients pertain to (1) long-term survival after reaching ESRD, and (2) the choice of renal replacement therapy modality.

Long-term Survival

Early reports of dismal survival prospects for patients with ESRD has led to reluctance to start replacement therapy in these patients. More recent studies, however, have documented a stratification of the survival rate of patients with HIV infection and ESRD that depends on the stage of their HIV infection. It now appears that patients with HIV infection and ESRD have a survival rate similar to that of stage-matched patients without ESRD. However, the survival of patients on dialysis with AIDS remains poor, with a mean survival of about 3 months, as opposed to about 16 months for patients with ESRD and asymptomatic HIV infection. A recent cross-sectional study [58] assessed the survival of HIV-infected patients requiring dialysis. Of 34 subjects, 29 patients had clinical AIDS. Surprisingly, only 6 patients were receiving an antiretroviral medication (AZT = 5; dideoxyinosine (DDI) = 1). In 68% of cases, AIDS was diagnosed before ESRD; the remaining patients were diagnosed with HIV infection only after initiation of maintenance hemodialysis. In this cohort, the mean duration of ESRD was 57 months, with a range of 4 to 196 months. The mean survival is remarkably improved over the initial reports by Rao [88] and others [57, 80], when the mean survival of AIDS patients on hemodialysis was about 3 months. The authors suggest that the improved survival may be attributed to several factors, including more aggressive institution of dialysis, more aggressive dialysis, improved treatment of opportunistic infection, improved management of uremia including the use of erythropoietin, and perhaps the improvement in anti-retroviral medication. The latter point is not directly supported by

this study, in which only 17% of patients received anti-retroviral medication.

Choice of Modality of Renal Replacement Therapy

There was considerable fear of transmission of HIV infection from patients to staff or other patients in the setting of the use of hemodialysis. This fear has not been substantiated by any reports of patient-to-patient or patient-to-staff transmission of the disease in hemodialysis units in the United States. To date, the cases of patient-to-patient spread of the infection in a dialysis unit in Columbia, South American can be attributed to the reuse of access needles in that country. The same measures taken to prevent spread of the Hepatitis B virus are sufficient to minimize the risk of HIV transmission.

The early interest in the use of peritoneal dialysis in patients infected with the HIV virus stems from the concern to minimize risk of disease transmission to staff and other patients. Whether the rates of peritonitis in this patient population is higher than in control populations remains to be confirmed, as current reports are conflicting. There is no comparison of survival among patients treated with peritoneal dialysis versus hemodialysis.

Emerging Infections

Two viruses of note have emerged that may prove to be important causes of glomerular and tubular interstitial injury. The Hanta virus infection, known to cause hemorrhagic fever with renal involvement, was of substantial consequence during the Korean War. Recently, cases have been described in the United States, primarily causing respiratory distress. The renal lesions in these patients was confined to slight mesangial alterations with tubulointerstitial inflammation and ARF.

The parvovirus B19 has been recently associated with FSGS and especially the collapsing variant of FSS. Whether this association leads to improved understanding of the pathogenesis of this condition remains uncertain.

References

[1] *Agnello V, Chunt RT, Kaplan LM* 1992 A role for hepatitis C virus infection in type II cryoglobulinemia. *327:* 1490-1495

[2] *Agnello V* 1997 The etiology and pathophysiology of mixed cryoglobulinemia secondary to hepatitis C virus infection. Springer Seminars in Immunopathology *19:* 111-129

[3] *Alpers CE, Cotran RS* 1986 Neoplasia and glomerular injury [review]. Kidney Int *30:* 465-473

[4] *Appel GB, Cohen DJ, Pirani CL et al* 1987 Long-term follow-up of lupus nephritis: A study based on the WHO classification. Am J Med *83:* 877

[5] *Appel GB* 1997 Cyclophosphamide therapy of severe lupus nephritis (Journal Club). Am J Kidney Dis *30:* 872

[6] *Austin HA III, Muenz LR, Joyce KM et al* 1984 Diffuse proliferative lupus nephritis: Identification of specific pathologic features affecting renal outcome. Kidney Int *25:* 689

[7] *Barada FA Jr, Andrews BS, Davis JS 4th, Taylor RP* 1981 Antibodies to Sm in patients with systemic lupus erythematosus. Correlation of Sm antibody titers with disease activity and other laboratory parameters. Arthritis Rheum *24:* 1235-1244

[8] *Beaufils M, Kouki F, Mignan F, Camus JP, Morel-Maroger L, Richet G* 1983 Clinical significance of anti-SM antibodies in systemic lupus erythematosus. Am J Med *74:* 201-205

[9] *Ben-Chetrit E, Levy M* 1991 Colchicine prophylaxis in familial Mediterranean fever: reappraisal after fifteen years. Seminars in Arthritis and Rheumatism *20:* 241-246

[10] *Black CM* 1992 Scleroderma. In: Oxford Textbook of Clinical Nephrology. Oxford University Press, Oxford

[11] *Blanco R, Martiniz-Taboada VM, Rodriguez-Valverde V et al* 1997 Henoch-Schönlein purpura in adulthood and childhood: Two different expressions of the same syndrome. Arthritis Rheum *40:* 859-864

[12] *Bombardieri S, Ferri C, Paleologo G, Bibolotti E, Camici M, Fosella PV, Pasero G, Moriconi L* 1983 Prolonged plasma exchange in the treatment of renal involvement in essential mixed cryoglobulinemia. Int J Artifi Org *6 Suppl 1:* 47-50

[13] *Boumpass DT, Austin HA, Vaughn EM, Klippel JH, Steinberg AD, Yarboro CH, Balow JE* 1992 Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. Lancet *340:* 741-745

[14] *Bourgoignie JJ* 1990 Renal complications of human immunodeficiency virus type 1. Kidney Int *37:* 1571-1584

[15] *Burns GC, Paul SK, Toth IR, Sivak SL* 1997 Effect of angiotensin-converting enzyme inhibition in HIV-associated nephropathy. J Am Soc Nephrol *8:* 1140-1146

[16] *Burstein DM, Rodby RA* 1993 Membranous glomerulonephritis associated with Hepatitis C virus infection. J Am Soc Nephrol *4:* 1288-1293

[17] *Buzio C, Allegri L, Mutti A, Perazzoli F, Bergamaschi E* 1994 Significance of albuminuria in the follow-up of acute poststreptococcal glomerulonephritis. Clin Nephrol *41:* 259-264

[18] *Carbone L, D'Agati V, Chent JT, Appel GB* 1989 Course and prognosis of human immunodeficiency virus-associated nephropathy. Am J Med *87:* 389-395

[19] *Carithers RL Jr, Emerson SS* 1997 Therapy of hepatitis C: meta-analysis of interferon alfa-2b trials. Hepatology. *26 Suppl 1:* 83S-88S

[20] *Clements PJ, Furst DE* 1997 Choosing appropriate patients with systemic sclerosis for treatment for autologous stem cell transplantation. Rheumatol Suppl *48:* 85-88

[21] *Clements PJ, Lachenbruch PA, Furst DE, Maxwell M, Denovitch G, Paulus HE* 1994 Abnormalities of renal physiology in systemic sclerosis. A prospective study with 10-year followup. Arthritis Rheum *37:* 67-74

[22] *Clements PJ, Lachenbruch PA, Sterz M, Danovitch G, Gawkins R, Ippolita A, Paulus HE* 1993 Cyclosporine in systemic sclerosis. Results of a forty-eight week open safety study in ten patients. Arthritis Rheum *36:* 75-83

[23] *Conjeevaram HS, Hoofnagle JH, Austin HA, Park Y, Fried MW, Di Bisceglie AM* 1995 Long-term outcome of hepatitis B virus-related glomerulonephritis after therapy with interferon alpha. Gastroenterology *109:* 540

[24] *D'Cruz D, Chesser AM, Lightowler C et al* 1995 Antineutrophil cytoplasmic antibody-positive crescentic glomerulonephritis associated with antithyroid drug treatment. Br J Rheumatol *34:* 1090-1091

[25] *D'Agati V, Appel GB* 1997 HIV infection and the kidney. J Am Soc of Nephrol. *8:* 138-52

[26] *D'Amico G, Fornasieri A* 1995 Cryoglobulinemic glomerulonephritis: a membranoproliferative glomerulonephritis induced by hepatitis C virus. Am J Kidney Dis *25:* 361-369

[27] *Davies DJ, Moran JE, Niall JF, Ryan GB* 1982 Segmental necrotising glomerulonephritis with antineutrophil antibody: possible arbovirus aetiology? Br Med J *285:* 606

[28] *de Groot K, Reinhold-Keller E, Tatsis E et al* 1996 Therapy for maintenance of remission in sixty-five patients with generalized Wegener's granulomatosis: methotrexate versus trimethoprim/sulfamethoxazole. Arthritis Rheum *39:* 2052-2061

[29] *Dolcher MP, Marchini B, Sabbatini A, Longombardo G, Ferri C, Riente L, Bombardieri S, Migliorini P* 1994 Autoantibodies from mixed cryoglobulinaemia patients bind glomerular antigens. Clin Exp Immunol *96:* 317-322

[30] *Dolman KM, Gans ROB, Vervaat TJ et al* 1993 Vasculitis and antineutrophil cytoplasmic autoantibodies associated with propylthiouracil therapy. Lancet *342:* 651-652

[31] *Donohoe JF* 1992 Scleroderma and the kidney. Kidney Int *41:* 462.

[32] *Dooley MA, Hogan S, Jennette C, Falk R* 1997 Cyclophosphamide therapy for lupus nephritis: Poor renal survival in black Americans. Kidney Int *51:* 1188

[33] *Durand JM, Lefevre P, Harle JR, Boucrat J, Vitviski L, Soubeyrand J* 1991 Cutaneous vasculitis and cryoglobulinemia type II associated with hepatitis C virus infection. Lancet *337:* 499-500

[34] *Euler HH, Schroeder JO, Harten P, Zeuner RA, Gutschmidt HJ* 1994 Treatment-free remission in severe systemic lupus erythematosus following synchronization of plasmapheresis with subsequent pulse cyclophosphamide. Arthritis and Rheum *37:* 1784-1794

[35] *Falk RJ, Hogan S, Carey TS, Jennette JC* 1990 Clinical course of anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and systemic vasculitis: The Glomerular Disease Collaborative Network. Ann Int Med *113:* 656-663

[36] *Falk RJ, Jennette JC* 1997 ANCA Small-Vessel Vasculitis. J Am Soc Nephrol *8:* 314-322

[37] *Falk RJ, Jennette JC* 1988 Anti-neutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. N Engl J Med *318:* 1651-1657

[38] *Farrugia E, Torres VE, Gastineau D et al* 1992 Lupus anticoagulant in systemic lupus erythematosus: A clinical and renal pathological study. Am J Kidney Dis *20:* 463

[39] *Ferri C, Moriconi L, Gremignai G, Migliorini P, Paleologo G, Fosella PV, Bombardieri S* 1986 Treatment of the renal involvement in mixed cryoglobulinemia with prolonged plasma exchange. Nephron *43:* 246-253

[40] *Fornasieri A, Armelloni S, Bernasconi P, Li M, de Septis CP, Sinico RA, D'Amico G* 1996 High binding of immunoglobulin M kappa rheumatoid factor from type II cryoglobulins to cellular fibronectin: a mechanism for induction of in situ immune complex glomerulonephritis? Am J Kidney Dis *27:* 476-483

[41] *Fornasieri A, D'Amico G* 1996 Type II mixed cryoglobulinaemia, hepatitis C virus infection, and glomerulonephritis. Nephrol Dial Transplant *11 (Suppl 4):* 25-30

[42] *Fornasieri A, Li M, Armelloni S, de Septis CP, Schiaffino E, Sinico RA, Schmid C, D'Amico G* 1993 Glomerulonephritis induced by human IgMK-IgG cryoglobulins in mice. Lab Invest *69:* 531-540

[43] *Frampton G, Hicks J, Cameron JS* 1991 Significance of anti-phospholipid antibodies in patients with lupus nephritis. Kidney Int *39:* 1225

[44] *Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, Bacon P, Bombardieri S, Hanly J, Hay E, Isenberg D, Jones J, Kalunian K, Maddison P, Nived O, Petri M, Richter M, Sanchez-Guerrero J, Snaith M, Sturfelt G, Symmons D, Zoma A* 1996 The development of an initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arth Rheum *39:* 363-369

[45] *Goldstein AR, White RHR, Akuser R, Schantler C* 1992 Long-term follow up of childhood Henoch Schönlein nephritis. Lancet *339:* 280

[46] *Guillevin L, Lhote F, Amouroux J, Gherardi R, Callard P, Casassus P* 1996 Antineutrophil cytoplasmic antibodies, abnormal angiograms and pathological findings in polyarteritis nodosa and Churg-Strauss syndrome: indications for the classification of vasculitides of the polyarteritis nodosa group. Br J Rheumatol *35:* 958-64

[47] *Guillevin L, Lhote F, Cohen P, Sauvaget F, Jarrousse B, Lortholary O, Noel LH, Trepo C* 1995 Polyarteritis nodosa related to Hepatitis B virus. A prospective study with long-term observation of 41 patients. Medicine *75:* 238-253

[48] *Hagan EC, Ballieux Be, van Es LA, Daha MR, van der Woude FJ* 1993 Antineutrophil cytoplasmic autoantibodies: A review of the antigens involved, the assays, and the clinical and possible pathogenetic consequences. Blood *91:* 1996-2002

[49] *Hammoud H, Haem J, Laurent B, Alamartine E, Diab N, Defilippis JP, Berthoux P, Berthoux F* 1996 Glomerular disease during HCV infection in renal transplantation. Nephrol Dial Transplant. *11 (Suppl 4):* 54-55

[50] *Harper L, Adu D* 1997 Glomerulonephritis and non-Hodgkin's lymphoma. Nephrol, Dial, Transplant 12: 1520-1525

[51] *Harris AA, Wilkman AS, Hogan SL, Falk RJ, Jennette JC* 1997 Amyloidosis and light chain deposition disease (LCDD) in renal biopsy specimens: pathology, laboratory data, demographics, and frequency. J Am Soc Nephrol *8:* 537A

[52] *Hebert LA, Cosio FG, Bay WH et al* 1997 Mycophenolate mofetil (CellCept, MMF) therapy of systemic lupus erythematosus (SLE) and ANCA vasculitis (V). J Am Soc Nephrol *8:* 86A

[53] *Hebert LA, Cosio FG, Neff JC* 1991 Diagnostic significance of hypocomplementemia. Kidney Int *39:* 811-821

[54] *Hogan SL, Nachman PH, Wilkman AS, Jennette JC, Falk RJ, Glomerular Disease Collaborative Network* 1996 Prognostic markers in patients with antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. J Am Soc Nephrol *7:* 23-32

[55] *Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis ED, Rottem M, Fauci AS* 1992 Wegener's granulomatosis: an analysis of 158 patients. Ann Intern Med *116:* 488-498

[56] *Holm SE* 1988 The pathogenesis of acute poststreptococcal glomerulonephritis in new lights. APMIS *96:* 189-193

[57] *Humphreys MH* 1995 Human immunodeficiency virus-associated glomerulosclerosis. Kidney Int *48:* 311-320

[58] *Ifudu O, Mayers JD, Matthew JJ, Macey LJ, Brezsnyak W, Reydel C, McClendon E, Surgrue T, Rao TK, Friedman EA* 1997 Uremia therapy in patients with end-stage renal disease and human immunodeficiency virus infection: has the outcome changed in the 1990s? Am J Kidney Dis *29:* 549-552

[59] *Ifudu O, Rao TK, Tan CC, Fleischman H, Chirgwin K, Friedman EA* 1995 Zidovudine is beneficial in human immunodeficiency virus associated nephropathy. Am J Nephrol *15:* 217-221

[60] *Iskandar SS, Falk RJ, Jennette JC* 1992 Clinical and pathological features of fibrillary glomerulonephritis. Kidney Int *42:* 1401-1407

[61] *Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, Hagen C, Hoffman GS, Hunder GG, Kallenberg CGM, McCluskey RT, Sinico RA, Rees AJ, van Es LA, Waldherr R and Wiik A* 1994 Nomenclature of systemic vasculitides: proposal of an International Consensus Conference. Arth and Rheum *37:* 187-192

[62] *Jennette JC, Iskandar SS, Dalldorf FG* 1983 Pathologic differentiation between lupus and nonlupus membranous glomerulopathy. Kidney Int *24:* 377

[63] *Johnson RL, Couser WG* 1990 Hepatitis B infection in renal disease: clinical, immunopathogenic, and therapeutic considerations. Kidney Int *37:* 663

[64] *Kallenberg CGM, Brouwer E, Weening JJ, Cohen Tervaert JW* 1994 Anti-neutrophil cytoplasmic antibodies: current diagnostic and pathophysiologic potential. Kidney Int *46:* 1-15

[65] *Kobrin S, Madaio MP* 1997 Acute Poststreptococcal glomerulonephritis and other bacterial infection-related glomerulonephritides. In: Schrier RW, Gottschalk CW (eds.): Diseases of the Kidney, 6th edition. Little Brown and Company, Boston 1579-1593

[66] *Kyle RA, Gertz MA, Greipp PR, Whitzig TE, Lust JA, Lacey MQ, Therneau TM* 1997 A trial of three regimens for primary amyloidosis: Colchicine alone, melfalen and prednisone, and melfalen, prednisone and Colchicine. N Engl J Med *336:* 1202-1207

[67] *Lam M, Park MC* 1990 HIV-associated nephropathy: beneficial effect of zidovudine therapy [letter]. N Engl J Med *323:* 1775-1776

[68] *Layrisse Z, Rodriguez-Iturbe B, Garcia-Ramirez R, Rodriguez A, Tiwari J* 1983 Family studies of the HLA system in acute post-streptococcal glomerulonephritis. Human Immunol *7:* 177-185

[69] *Lee JR, Yamauchi H, Hopper J Jr* 1966 The association of cancer and nephrotic syndrome. Ann Int Med *64:* 41-55

[70] *Lewis EJ, Hunsicker LG, Lan SP, Rohde RD, Lachin JM* 1992 A controlled trial of plasmapheresis therapy in severe lupus nephritis. The Lupus Nephritis Collaboratory Study Group. N Engl J Med *326:* 1373-1379

[71] *Lopez-Overjero JA, Sall SD, D'Angelo WA et al* 1979 Reversal of vascular and renal crises of scleroderma by oral angiotensin converting enzyme blockade. N Engl J Med *300:* 1417

[72] *McDermott EM, Powell RJ* 1996 Incidence of ovarian failure in systemic lupus erythematosus after treatment with pulse cyclophosphamide. Ann Rheum Dis *55:* 224-229

[73] *Michel C, Dosquet P, Ronco P, Mougenot B, Viron B, Mignon F* 1992 Nephropathy associated with infection by human immunodeficiency virus: a report on 11 cases including 6 treated with zidovudine. Nephron *62:* 434-440

[74] *Misiani R, Bellavita P, Fenili D, Borelli G, Marchesi D, Massazza M, Vendramin G, Comotti B, Tanzi E, Scudeller G et al* 1992 Hepatitis C virus infection in patients with essential mixed cryoglobulinemia. Ann Int Med *117:* 573-577

[75] *Misiani R, Bellavita P, Fenili D, Vicari O, Marchesi D, Sironi PL, Zilio P, Vernocchi A, Massazza M, Vendramin G et al* 1994 Interferon alpha-2a therapy in cryoglobulinemia associated with hepatitis C virus. N Engl J Med *330:* 751-756

[76] *Montseny JJ, Meyrier A, Kleinknecht D* 1995 The current spectrum of infectious glomerulonephritis. Experience with 76 patients and review of the literature. Medicine *74:* 63-73

[77] *Nachman PH, Dooley MA, Hogan SL et al* 1997 Mycophenolate mofetil therapy in patients with cyclophosphamide-(CyP) resistant or relapsing diffuse proliferative lupus nephritis (SLE-DPGN) (abstract). J Am Soc Nephrol *8:* 94A

[78] *Nachman PH, Hogan SL, Jennette JC, Falk RJ* 1996 Treatment response and relapse in antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. J Am Soc Nephrol *7:* 33-39

[79] *Norris SH* 1993 Paraneoplastic glomerulopathies. Seminars in Nephrology *13:* 258-272

[80] *Ortiz C, Meneses R, Jaffe D, Fernandez JA, Perez G, Bourgoignie JJ* 1988 Outcome of patients with human immunodeficiency virus on maintenance hemodialysis. Kidney Int *34:* 248-253

[81] *Pascual M, Perrin L, Giostra E, Schifferli JA* 1990 Hepatitis C virus in patients with cryoglobulinemia type II. J Infect Dis *162:* 56-567

[82] *Pasquali S, Banfi G, Zucchelli A, Moroni G, Ponticelli C, Zucchelli P* 1993 Lupus membranous nephropathy: long-term outcome. Clin Nephrol *39:* 175-182

[83] *Ponticelli C, D'Amico G* 1997 Mixed cryoglobulinemia. In: Schrier RW, Gottschalk CW (eds.): Diseases of the Kidney, 6th edition. Little Brown and Company, Boston 1879-1891

[84] *Pusey CD, Rees AJ, Evans DJ, Peters CK, Lockwood CM* 1991 Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. Kidney Int *40:* 757-763

[85] *Rammelkamp CH Jr et al* 1952 Transcripts of Association of American Physicians *65:* 168-175

[86] *Rammelkamp CH Jr, Weaver RS* 1953 Acute glomerulonephritis: the significance of variations in the incidence of disease. J Clin Invest *32:* 345-358

[87] *Rao TKS, Fillippone EJ, Nicastri AD, Landesman SH, Frank E, Chen CK, Friedman EA* 1984 Associated focal and segmental glomerulosclerosis in the acquired immunodeficiency syndrome. N Engl J Med *310:* 669-673

[88] *Rao TKS, Friedman EA* 1995 Outcome of severe renal failure in patients with acquired immunodeficiency syndrome. Am J Kidney Dis *25:* 390-398

[89] *Reichard O, Schvarcz R, Weiland O* 1997 Therapy of hepatitis C: alpha interferon and ribavirin. Hepatology *26 Suppl 1:* 108S-111S

[90] *Savage COS, Harper L, Adu D* 1997 Primary systemic vasculitis. Lancet *349:* 553-558

[91] *Savage COS, Winearls CG, Evans DJ, Rees AJ, Lockwood CM* 1985 Microscopic polyarteritis: presentation, pathology, and prognosis. Q J Med *220:* 467-83

[92] *Sloan RP, Schwartz MM, Korbet SM, Borok RZ* 1996 Long-term outcome in systemic lupus erythematosus membranous glomerulonephritis. Lupus Nephritis Collaborative Study Group. J Am Soc Nephrol *7:* 299-305

[93] *Sneller MC, Hoffman GS, Talar-Williams C, Kerr GS, Hallahan CW, Fauci AS* 1995 An analysis of forty-two Wegener's granulomatosis patients treated with methotrexate and prednisone. Arthritis Rheum *38:* 608-613

[94] *Steen VD, Medsger TA, Osial TA et al* 1984 Factors predicting development of renal involvement in progressive systemic sclerosis. Am J Med *76:* 779

[95] *Stegeman CA, Cohen Tervaert JW, de Jong PE, Kallenberg CG* 1996 Trimethoprin-sulfamethoxazole (co-trimaxazole) for the prevention of relapses of Wegener's granulomatosis. N Engl J Med *335:* 16-20

[96] *Stegeman CA, Cohen Tervaert JW, Sluiter WJ, Manson WL, de Jong PE, Kallenberg CG* 1994 Association of chronic nasal carriage of Staphylococcus aureus and high relapse rates in Wegener's granulomatosis. Ann Intern Med *120:* 12-17

[97] *Tan EM, Cohen AS, Fries JF* 1982 The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum *25:* 1271-1277

[98] *Tarantino A, Campise M, Banfi G, Confalonieri R, Bucci A, Montoli A, Colasanti G, Damilano I, D'Amico G, Minetti L et al* 1995 Long-term predictors of survival in essential mixed cryoglobulinemic glomerulonephritis. Kidney Int *47:* 618-623

[99] *Tarantino A, Moroni G, Banfi G, Manzoni C, Segagni S, Ponticelli C* 1994 Renal replacement therapy in cryoglobulinaemic nephritis. Nephrol Dial Transplant *9:* 1426-30

[100] *Tarlar-Williams C, Hijazi YU, Walther MM et al* 1996 Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener's granulomatosis. Ann Intern Med *124:* 477-484

[101] *Ten SY, Pepys MB, Hawkins PN* 1995 Treatment of amyloidosis. Am J Kidney Dis *26:* 267-285

[102] *Traub YM, Shapiro AP, Rodnan GP et al* 1983 Hypertension and renal failure (scleroderma renal crisis) in progressive systemic sclerosis. Review of a 25-year experience with 68 cases. Medicine *62:* 335

[103] *Valeri A, Neusy AJ* 1991 Acute and chronic renal disease in hospitalized AIDS patients. Clin Nephrol *35:* 110-118

[104] *Valeri A, Radhakrishnan J, Estes D et al* 1994 Intravenous pulse cyclophosphamide treatment of severe lupus nephritis: A prospective five-year study. Clin Nephrol *42:* 71

[105] *Ward MM, Pyun E, Studenski S* 1995 Causes of death in systemic lupus erythematosus. Long-term follow up of an inception cohort. Arthritis Rheum *38:* 1492-1499

[106] *Jennette JC, Falk RJ* 1997 Small vessel vasculitis. N Engl J Med *337:* 1512-1523

[107] *DeRemee RA* 1988 The treatment of Wegener's granulomatosis with trimethoprim/sulfamethoxazole: illusion or vision? Arthritis Reum *31:* 1068-1074

[108] *Steen VD, Costatino JP, Shapiro AP, Medsger TA jr* 1990 Outcome of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme (ACE) inhibitors. Ann Intern Med *113:* 352-357

[109] *Bright R* 1836 Cases and observations, illustrations of renal disease accompanied with secretion of albuminous urine. Guy's Hop Rep *1:* 338