

18. Immune-mediated renal disease

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Immune-mediated renal diseases can be classified by the clinical syndromes they produce, by the attendant renal pathology, or by the dominant immune effector mechanism of renal injury. The major clinical syndromes produced by immune-mediated renal injury include the nephrotic syndrome, the nephritic syndrome, rapidly progressive glomerulonephritis, and acute renal failure. The notion of clinical syndromes facilitates diagnosis and treatment, but does not accurately define disease pathogenesis. In this summary, we discuss pathologically defined immune-mediated renal diseases under the clinical syndrome with which they are most frequently associated. There is overlap between the clinical syndromes, but the syndromes provide a useful framework. Relevant information regarding the proposed pathogenesis of disease entities is included under specific disease entities. (*J Allergy Clin Immunol* 2003;111:S637-44.)

Key words: *Glomerulonephritis, nephrotic syndrome, interstitial nephritis, rapidly progressive renal failure, immunosuppression*

The nephrotic syndrome is characterized by greater than 3.5 g/day of proteinuria, edema, hyperlipidemia, and hypoalbuminemia. In contrast, patients with the nephritic syndrome present with an active urinary sediment, including red blood cell casts, hematuria, variable proteinuria, hypertension, and renal insufficiency. Rapidly progressive glomerulonephritis (RPGN) is defined as acute glomerulonephritis (GN) in association with a decrease in glomerular filtration rate (GFR) of 50% or more within a 3-month period or less. Renal biopsies from such patients with the clinical syndrome of RPGN usually have evidence of glomerular crescents that are formed in conjunction with disruption of the glomerular basement membrane (GBM). This disruption leads to the influx of leukocytes and lymphocytes and release of inflammatory mediators, which drive epithelial cell proliferation. Atheroembolic disease, acute tubular necrosis, scleroderma renal crisis, and acute interstitial nephritis (AIN) can also cause rapid reductions in renal function.

IMMUNE-MEDIATED RENAL INJURY ASSOCIATED WITH NEPHROTIC SYNDROME

The following pathologic entities typically present clinically with nephrotic syndrome associated with a bland urine sediment.

Abbreviations used

ACE:	Angiotensin-converting enzyme
AIN:	Acute interstitial nephritis
ANCA:	Antineutrophil cytoplasmic antibodies
CSS:	Churg-Strauss syndrome
EM:	Electron microscopy
ESRD:	End-stage renal disease
FSGS:	Focal segmental glomerulosclerosis
GBM:	Glomerular basement membrane
GFR:	Glomerular filtration rate
GN:	Glomerulonephritis
HSP:	Henoch-Schönlein purpura
IC:	Immune complex
MCNS:	Minimal change nephrotic syndrome
MN:	Membranous nephropathy
MPA:	Microscopic polyangiitis
MPGN:	Membranoproliferative glomerulonephritis
NP:	Nephropathy
NSAID:	Nonsteroidal anti-inflammatory agent
PSGN:	Poststreptococcal glomerulonephritis
RA:	Rheumatoid arthritis
RPGN:	Rapidly progressive glomerulonephritis
SLE:	Systemic lupus erythematosus
svv:	Small-vessel vasculitis
WG:	Wegener's granulomatosis

Minimal change nephrotic syndrome

Minimal change nephrotic syndrome (MCNS) is the most common diagnosis associated with nephrotic syndrome in children and accounts for 10% to 15% of nephroses in adults.^{1,2} Patients present with nephrotic range proteinuria, hypoalbuminemia, hyperlipidemia, and edema, usually with preserved renal function. By definition, MCNS has no abnormalities on light microscopy of renal biopsies and humoral components of the immune system, such as immunoglobulin, and complement are absent on immunofluorescence studies. The sole abnormality seen in the kidney is effacement of the visceral epithelial foot processes identified by electron microscopy (EM). Pathogenesis is uncertain but may relate to abnormal T-cell function.³ MCNS can be associated with infections, medications (gold, nonsteroidal anti-inflammatory agent [NSAID], lithium, interferon, ampicillin), malignancies, and allergies (bee stings, food). As with other primary nephritides, it is crucial to rule out secondary causes, as the nephropathy (NP) often abates when the condition is cured or medication is withdrawn. Children presenting with the classic nephrotic syndrome are empirically treated with prednisone (60 mg/m²/d). Proteinuria remits in over 90% of patients in the first 4 to 6 weeks. In adults who present with nephrotic syndrome, preemptive biopsy is recommended. Adults with MCNS are treated with 1 mg/kg/day of prednisone

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TABLE. Supportive therapies for renal dysfunction

Sodium and water prescriptions
Blood pressure control with ACE inhibitors, angiotensin receptor blockers
Avoidance of nephrotoxins, such as NSAIDs, contrast agents
Smoking avoidance, low-protein diet (benefit controversial, but not harmful)

(maximum 80 mg/d) and often require longer than 4 to 6 weeks to attain remission. Cyclophosphamide and chlorambucil can be used in relapses or in steroid-resistant cases. Cyclosporine is quite effective in inducing remission; however, as in other nephroses, disease can recur after cessation of therapy. Progression to end-stage renal disease (ESRD) in MCNS is rare. Complications include those related to prolonged nephrotic syndrome, and the side effects of therapy.

Membranous nephropathy

Idiopathic membranous NP (MN) is the most common cause of nephrotic syndrome in adults. MN can also occur secondary to hepatitis B, malaria, syphilis, neoplasms, drugs, systemic lupus erythematosus (SLE), and environmental toxins. The clinical presentation is variable; however, most patients present with the classic nephrotic syndrome, bland urinalysis, and preserved renal function. Both humoral and cellular immunity, as well as an activated complement cascade, have been implicated as effector mechanisms of this disease.⁴

Renal biopsy specimens demonstrate diffuse thickening of the GBM. Immunofluorescence reveals prominent granular staining of IgG and C3 along the GBM. EM studies are characterized by epithelial foot process effacement with electron-dense (immune complex [IC]) deposits distributed above the GBM in subepithelial or intramembranous positions. Predictors of clinical progression to ESRD include high levels of proteinuria or renal insufficiency at presentation, older age, male gender, and histologic findings of glomerulosclerosis and tubulointerstitial inflammation.

The appropriate therapy of idiopathic MN has long been, and continues to be, a controversial topic for nephrologists. In idiopathic MN, one-quarter to one-third of patients spontaneously remit, one-third remain unchanged, and one-third progress to ESRD.⁵ Once supportive therapy is initiated (Table) and secondary causes are ruled out, one reasonable approach is to monitor patients for 6 months prior to utilizing immunosuppressive therapy. After 6 months, if patients with a moderate risk of progression (4-8 g/d of proteinuria) develop worsening renal function, then they are treated with the Italian (Ponticelli) regimen that involves monthly cycling of prednisone alternating with chlorambucil (0.2 mg/kg/d) or cyclophosphamide.⁶ In high-risk patients (>8 g/d of proteinuria) either the Ponticelli regimen, oral cyclophosphamide, or cyclosporine is recommended.⁷ High-risk patients are at risk for thromboembolic complications. It remains controversial whether to empirically treat with anticoagulants.

Focal segmental glomerulosclerosis

Focal segmental glomerulosclerosis (FSGS) is considered the final common pathway of many forms of glomerular injury. FSGS can present as a primary process or secondary to a wide variety of diseases, including HIV infection, hypertension, vesicoureteral reflux, obesity, sickle cell disease, or heroin abuse. Patients commonly present with the nephrotic syndrome with associated microscopic hematuria, hypertension, and progressive renal failure. Pathologically, there is segmental (part of the glomerulus) glomerular collapse, and some, but not all glomeruli (focal), are involved. With clinical progression there is interstitial disease, glomerulosclerosis, and adhesions of the sclerotic glomeruli to Bowman's capsule. FSGS is thought to be associated with direct damage to the glomerular epithelial cell.⁸ Whether this damage is secondary to immune mechanisms is unresolved. Prognosis is dictated by the degree of proteinuria and serum creatinine at presentation and the extent of interstitial fibrosis on biopsy. Greater than 50% of patients who present with nephrotic range proteinuria will reach ESRD in 6 to 8 years. Spontaneous remissions are rare, and patients who attain remission have a much improved prognosis. Treatment is generally recommended for nephrotic patients.⁹ Current protocols recommend treating with prednisone 1 mg/kg/d for 3 to 4 months. In the elderly, an alternate day regimen can be employed. As with other nephroses, angiotensin-converting enzyme (ACE) inhibitors reduce proteinuria and are renoprotective. Primary FSGS can recur early in the posttransplant period. In these patients, a circulating permeability factor has been identified, and these patients have been successfully treated with protein adsorption or plasmapheresis.¹⁰

Amyloidosis

Amyloidosis describes a group of disorders associated with the deposition of proteins in various organs. AL amyloidosis (primary amyloidosis) is the most common form and involves deposition of immunoglobulin light chains. AA (secondary amyloidosis) occurs in patients with chronic inflammatory or infectious conditions and involves the deposition of the acute phase reactant, serum amyloid A protein in tissues. Patients tend to be 60 years of age or older and commonly present with nonspecific symptoms, such as fatigue and weight loss. Renal manifestations include proteinuria, variable degrees of azotemia, and hypertension. Orthostatic hypotension due to peripheral nerve involvement can also complicate the disease. Diagnostic evaluation of every nephrotic patient should include immunofixation of the serum and urine, as protein electrophoresis may not be sufficiently sensitive to detect all patients with AL. Definitive diagnosis is obtained by the finding of Congo red-positive deposits in tissues.¹¹ The prognosis of patients with amyloidosis is poor and therapy with melphalan and prednisone are recommended. Despite the high morbidity and mortality, younger patients with minimal cardiac involvement do derive benefit from stem cell transplantation. In patients

with AA amyloidosis, treatment should be focused on resolving the chronic inflammatory state. Colchicine has been effective in treating amyloidosis, in particular, in familial Mediterranean fever.¹²

IMMUNE-MEDIATED RENAL DISEASE ASSOCIATED WITH NEPHROTIC SYNDROME

The following entities typically present with prominent features of the nephritic syndrome.

Postinfectious glomerulonephritis

The prototype form of postinfectious GN is poststreptococcal GN (PSGN). Other infections can lead to GN, as can the presence of deep visceral abscesses. PSGN, generally a disease of childhood, characteristically occurs 10 to 14 days after streptococcal pharyngitis or impetigo. Antigen-antibody complexes form in the circulation and are deposited in the glomeruli, leading to complement activation and recruitment of neutrophils and monocyte/macrophages.¹³ Symptoms include hematuria, edema, and hypertension. Oliguria and azotemia are less common. Depressed levels of C3 with evidence of circulating ICs and cryoglobulins, rheumatoid factor, and elevated IgG are typical serologic findings. Diagnosis is based on the combination of evidence of an antecedent streptococcal infection: a positive antistreptolysin O or anti-Dnase B titers. Biopsy is only recommended in cases when the diagnosis is in question. Classically, light microscopic findings reveal diffuse proliferative GN with neutrophils in the glomeruli. EM studies are distinguished by subepithelial electron-dense deposits "humps."¹⁴

In most children PSGN is self-limited. However, in some adults the disease can be more chronic. Antibiotics and supportive therapy are recommended. Increasingly other bacteria, such as staphylococci and gram-negative rods, are implicated in causing postinfectious GN. The pathogenesis is presumed to also be secondary to ICs. Alcoholics, diabetics, and intravenous drug users are most commonly affected.¹⁵

IgA nephropathy

IgA NP, the most common GN in the world, is considered to be a renal-limited form of Henoch-Schönlein purpura (HSP). A number of diverse diseases can be associated with IgA NP, including ankylosing spondylitis, Reiter's syndrome, rheumatoid arthritis (RA), celiac disease, chronic liver disease, HIV, hepatitis B, and some neoplasias, such as mycosis fungoides. Most patients present with asymptomatic microscopic or synpharyngitic macroscopic hematuria. The nephrotic syndrome and acute renal failure are uncommon. IgA NP is related to aberrant galactosylation of IgA molecules and abnormal hepatic and mesangial clearance of IgA that leads to mesangial IgA deposition.¹⁶ Renal biopsies are usually only recommended for patients with progressive renal insufficiency or greater than 1 g/d of proteinuria. Mesangial IgA staining is seen on immunofluorescence of renal biopsies. There is evidence of elevated circulating poly-

meric IgA₁ and IgA-containing complexes in the serum. These have not proven to be of diagnostic use.

ESRD occurs in 20% to 30% of patients with IgA NP after 20 years. Predictors of poor outcome include male gender, hypertension, early age of onset, and the extent of proteinuria and renal insufficiency at diagnosis. Therapy is generally limited to patients with abnormal renal function. Patients with mild disease should be closely monitored and blood pressure aggressively controlled with an ACE inhibitor. Corticosteroids may slightly benefit patients with preserved renal function, and greater than 1 g/d of proteinuria. Traditionally immunosuppressive agents have conferred no benefit in patients, except in those with IgA-associated RPGN. However, a recent study reports benefits with long-term cytotoxic therapy and prednisone in patients with moderately progressive renal failure.¹⁷ Fish oil may be of benefit.¹⁸

Henoch-Schönlein purpura

HSP is a multisystem disorder characterized by the deposition of IgA ICs in affected organs. The renal histopathologic findings are indistinguishable from IgA NP, however, there may be more frequent staining for IgA in capillary walls. Necrotizing glomerular lesions, endocapillary proliferation, and fibrin deposition are more commonly seen in HSP.¹⁹ HSP typically affects children less than 10 years of age with a male predominance. It often follows an upper respiratory tract infection, and manifestations include abdominal pain, arthralgias, purpuric lower-extremity rash, and hematuria. Associations with drug hypersensitivities have been reported. The renal manifestations are generally self-limited; however, progressive renal failure can ensue. Although there are no systematized studies to support its use, corticosteroids may be of benefit in patients with severe nephritis. Treatment protocols designed for IC RPGN should be employed in patients with crescentic changes and renal failure. Intravenous immunoglobulin has also been used.²⁰

Systemic lupus erythematosus

Rheumatologists and nephrologists frequently share the care of patients with SLE. A wide range of histologic patterns of renal injury can be seen in patients with SLE. The pathogenesis, classification, and treatment of these various forms of renal injury are complex and cannot be thoroughly discussed in this brief compendium. The reader is referred to more detailed reviews of this topic.²¹⁻²⁸

Renal abnormalities eventually develop in the majority of patients with SLE. The most common renal abnormality is proteinuria seen in 75% of patients. Hematuria and elevated serum creatinine are seen in roughly 40% and 30% of patients, respectively. Given the prevalence of SLE in young women, it is important to emphasize that serum creatinine is an indicator of both GFR and muscle mass. In individuals with low muscle mass, significant deterioration in GFR can coexist with serum creatinine concentrations within the "normal" range.

Renal biopsies in SLE patients with urinary abnormalities are typically characterized on the basis of glomerular abnormalities visualized by light microscopy and EM, as well as immunofluorescence staining for immunoglobulins. Mesangial lupus nephritis is a mild form of renal injury, with mild proliferation of glomerular mesangial cells and mesangial immune deposits. Patients typically demonstrate macroscopic hematuria without significant decrements in GFR or nephrotic range proteinuria. This form of injury is seen in 10% to 20% of patients with lupus nephritis.

Focal proliferative lupus nephritis is also seen in 10% to 20% of lupus nephritis patients. Microscopic findings of renal biopsies demonstrate involvement of <50% of glomeruli by segmental areas of proliferation. EM and immunofluorescent analyses demonstrate subendothelial and mesangial immune deposits. These patients typically have hematuria, significant proteinuria, and can have hypertension and azotemia.

Diffuse proliferative lupus nephritis is the most severe and common form of lupus nephritis. Patients typically present with hematuria, proteinuria, hypertension, and renal insufficiency. Hypocomplementemia and elevated anti-DNA antibodies are uniformly present. Renal biopsy findings are similar to those in focal proliferative disease but more severe and extensive. Glomeruli can exhibit proliferative, necrotic, and crescentic changes, typically in greater than 50% of sampled glomeruli. Significant immunoglobulin and complement deposition is seen by EM. The interstitium is frequently abnormal, with mononuclear cell infiltrates.

MN is seen in 10% to 20% of patients. Clinical presentation is typically nephrotic syndrome, and can have associated hypertension. Biopsies reveal basement membrane thickening and subepithelial immune deposits by immunofluorescence and EM. This syndrome can present in lupus without other serologic or clinical manifestations of lupus. Biopsy findings suggestive of lupus MN, rather than idiopathic MN, include the presence of immune deposits in other glomerular, vascular, and tubular locations. The clinical spectrum of MN in SLE is broad, from nonnephrotic range proteinuria with normal renal function to severe disabling nephrosis and progressive renal failure.

Indications for a renal biopsy in SLE patients with urinary abnormalities are controversial, and beyond the scope of this review. The important issue is how biopsy findings will alter patient management. While the patient with significant azotemia, hypertension, and significant proteinuria and hematuria typically will have diffuse proliferative disease, the prediction of histology with less severe clinical presentations is poor. Histologic findings do influence treatment of lupus nephritis. Typically, patients with mesangial disease alone do not require specific therapy for their renal disease. Focal and diffuse proliferative GN form a spectrum of disease. There is general agreement that diffuse proliferative GN should be treated aggressively, meaning dual treatment with corticosteroids and a cytotoxic agent. Those patients who enter clinical remission on such therapy have an excel-

lent long-term prognosis.²⁹ Milder forms of focal proliferative disease may not require such aggressive treatment. Those forms of focal proliferative disease demonstrating more widespread renal involvement should probably be aggressively treated like diffuse proliferative disease. Prediction of which patients with mild focal proliferative disease will "progress" remains difficult, warranting close follow-up of such patients. Optimal treatment of MN in lupus again depends on the severity of disease. Those with renal insufficiency or severe disabling nephrosis should likely be treated as diffuse proliferative disease, while milder disease can frequently be controlled with prednisone alone.

Membranoproliferative GN

The term membranoproliferative GN (MPGN) describes a light microscopic appearance of glomeruli, demonstrating endocapillary proliferation and glomerular capillary wall thickening. This light microscopic appearance can occur in conjunction with many diseases or can be a renal-limited, idiopathic disease. The latter form is separated into 3 forms, Types I, II, and III, that are distinguished by the location of electron-dense deposits by EM. There are many clinical similarities between these 3 types. Most patients present with variable amounts of microscopic hematuria, proteinuria, hypertension, and renal insufficiency.³⁰ The Type II form of idiopathic MPGN most commonly presents like an acute GN. Approximately 50% of patients will progress to ESRD within 10 years of diagnosis. The presence of hypertension and nephrotic syndrome are risk factors for progression. Glucocorticoids are more efficacious in children than adults.³¹ Long-term treatment with antiplatelet agents may slow progression of the disease in adults.³²

The most common disorder causing "secondary" MPGN is essential mixed cryoglobulinemia, now known to be associated with hepatitis C infection in the majority of cases.^{33,34} In this disorder, monoclonal IgM, possessing rheumatoid factor activity, is a cryoglobulin. The pathogenesis of the renal diseases is either related to deposition of circulating ICs with attendant complement activation, or the monoclonal IgM may additionally recognize endogenous glomerular proteins. The pathology shares features with idiopathic MPGN, but additionally demonstrates significant monocyte infiltration and thrombi within the glomerular capillary lumens. The disease is a systemic vasculitis, with the renal involvement typically demonstrating proteinuria, hematuria, renal insufficiency, and hypertension. The efficacy of interferon- α and ribavirin for hepatitis C-related renal disease has yet to be defined, but it is being used. Ribavirin should not be used with creatinine clearance less than 50 mL/min.

IMMUNE-MEDIATED RENAL DISEASES FREQUENTLY PRESENTING AS RPGN

Traditionally, RPGNs have been divided into antibody-mediated (anti-GBM) disease, pauci-immune GN (eg, Wegener's granulomatosis [WG]), and IC-mediated dis-

eases. As these diseases are more rigorously studied, their traditional immunologic classification is being challenged.

Anti-GBM disease

Anti-GBM disease can present as a disease limited to RPGN or as the classic pulmonary-renal vasculitic syndrome known as Goodpasture's syndrome. Anti-GBM disease has a bimodal incidence, and the first peak preferentially affects young males who smoke. These patients often present with classic Goodpasture's syndrome, characterized by proliferative GN in association with pulmonary hemorrhage. The second peak of incidence generally affects women in their sixth to seventh decades and is characterized by renal-limited disease.

Patients with anti-GBM disease typically present with the abrupt onset of oliguria or anuria, hematuria, and anemia.³⁵ Most renal biopsy light microscopic samples are distinguished by the presence of crescents in greater than 50% of the glomeruli, with associated fibrinoid necrosis of adjacent glomerular structures. Immunofluorescent studies of diseased glomeruli reveal linear staining of IgG along the GBM. Diagnosis is confirmed by the detection of circulating antibodies directed against the $\alpha 3$ chain of type IV collagen. Both antibody and antigen-specific T cells likely serve as effector mechanisms of renal injury.

Immediate treatment with prednisone and cyclophosphamide with plasmapheresis is essential.³⁶ Daily plasmapheresis is continued until antibodies become undetectable, and after 6 months cyclophosphamide can be transitioned to azathioprine. With early treatment, patient survival approaches 85% and renal survival, 60%. If patients present with oliguria and serum creatinines (Scr) > 6 mg/dL, their likelihood of renal recovery is poor, and risks of immunosuppression must be weighted against this prognosis.³⁷ Patients uniformly do well with transplantation, but anti-GBM antibody should be undetectable for over 6 months prior to transplantation.

Up to one-third of patients with anti-GBM disease also have evidence of circulating antineutrophil cytoplasmic antibodies (ANCA) (both p-ANCA and c-ANCA).³⁸ Patients with both circulating antibodies have a milder course of disease than individuals with anti-GBM disease alone, and immunosuppression should not be withheld even in the patients who require dialysis at the time of presentation.

Pauci-immune crescentic GN

Pauci-immune GN, the most common cause of RPGN in adults, is characterized by crescentic GN associated with focal necrotizing lesions in the glomeruli and small vessels. The designation of pauci-immune GN is related to the lack binding of antibody or complement to the affected glomeruli.³⁹ Approximately 85% to 90% of patients with pauci-immune GN present with ANCAs. Recent experimental work suggests that passive transfer of such ANCAs, specifically antineutrophil cytoplasmic antibodies, can elicit focal necrotizing lesions in glomeruli in the absence of B or T cells.⁴⁰ It is additionally possible that the full expression of pauci-immune crescentic GN

requires activated T cells as an effector mechanism.⁴¹ The major ANCA-associated renal syndromes are WG, microscopic polyangiitis (MPA), and Churg-Strauss syndrome (CSS).

WG and MPA

One-third of individuals with pauci-immune GN have renal-limited disease, whereas the remainder present with associated systemic small-vessel vasculitis (svv) symptoms. Disease is often preceded by a flu-like prodrome, followed by nonspecific symptoms such as fever, myalgias, arthralgias, and fatigue. WG is characterized by a systemic granulomatous vasculitis involving the upper and lower respiratory tracts and the kidney. MPA is distinguished by nongranulomatous vasculitic lesions of the lower respiratory tract.⁴² Mononeuritis multiplex, skin, joint, and abdominal involvement occur, and renal manifestations can vary from proteinuria and hematuria associated with mild renal insufficiency to rapid declines in renal function. Unlike anti-GBM disease, relapsing courses of disease are common. ANCA svv is more common in Caucasians and generally affects people over 50 years of age. There is an association between treatment with propylthiouracil, hydralazine, penicillamine, and minocycline and the development of ANCA-associated vasculitides. Chronic nasal carriage of *Staphylococcus aureus* is a risk factor for relapse of WG.⁴³

Diagnosis is based on the clinical presentation, renal pathology, and serologic findings. C-ANCA is generally associated with WG, and p-ANCA is associated with MPA and CSS. However, significant overlap occurs. Current recommendations are to perform direct antigen-driven enzyme-linked immunosorbent assays to detect the more specific antineutrophil cytoplasmic antibody (p-ANCA) and antiproteinase 3 (c-ANCA) markers.^{44,45} Pathologically, the glomerular lesions can resemble anti-GBM disease at the light microscopic level; however, WG and CSS can have accompanied granulomata in the interstitium or arteries.

Treatment includes corticosteroids and cyclophosphamide. Plasmapheresis is recommended for the patients who require hemodialysis at the time of presentation.⁴⁶ Cotrimoxazole may reduce relapse rates, and methotrexate is contraindicated in patients with creatinine clearances of less than 60 mL/min. Pauci-immune GN and svv can recur after transplantation, but a positive ANCA at the time of transplantation does not seem to increase risk of recurrence.

CSS

CSS is associated with new onset asthma, allergic rhinitis, and eosinophilia in association with an svv. Cardiac, abdominal, and peripheral nervous system involvement are common. The incidence of renal disease in CSS has varied from 20% to 88% in published reports and has generally been characterized as mild. Patients present with hematuria and proteinuria, and renal biopsy typically reveals focal segmental or diffuse necrotizing lesions. Characteristic interstitial granulomata are only rarely seen. Similar to other ANCA-GNs, immunofluorescence

and EM studies reveal a paucity of immunoglobulin or dense deposit staining.⁴⁷ CSS is effectively treated with corticosteroids. The use of cyclophosphamide and interferon- α are currently being investigated.⁴⁸

IC-mediated RPGN

In children, IC diseases account for most of the cases of RPGN. Hemolytic uremic syndrome is the primary cause of RPGN, and manifestations include microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. IgA NP, postinfectious GN, MPGN, SLE, cryoglobulinemia, and HSP can also present as an RPGN. In IC GN, intact glomeruli are distinguished by features of the underlying disease, and EM studies should reveal glomerular electron-dense ICs. Treatment of IC-mediated RPGN is dictated by the primary disease. Supportive therapy is recommended, and once infection is ruled out, then prednisone and cytotoxic agents can be initiated. The response to conventional therapies with IC-mediated RPGN is worse than in the other RPGNs, and plasmapheresis does not offer benefit in patients already on dialysis.⁴⁹

Renal manifestations of other rheumatologic diseases

There is a variable incidence of renal dysfunction in patients with mixed connective tissue disease. Most patients present with microscopic hematuria and low-grade proteinuria. As the disease can evolve into lupus or systemic sclerosis, the renal lesions characteristically resemble the new disorder.

Evidence of renal involvement in Behçet's disease has ranged from 0% to 55%. The most common manifestations are asymptomatic hematuria, proteinuria, amyloidosis, GN, and vascular involvement.⁵⁰

There are multiple manifestations of RA renal disease; however, renal dysfunction tends to be mild. Drug therapy and secondary amyloidosis account for the majority of cases. Mesangioproliferative GN and MN are also seen in RA patients.⁵¹ RA patients usually have lower Scr due to reduced muscle mass. Therefore, Scr can underestimate the true GFR and lead to inappropriate drug dosing. The Cockcroft-Gault estimation of GFR ($GFR = \{[140 - \text{age}] \times \text{body weight} / \{72 \times \text{Scr}\}\} \times 0.85$ for females)) has been determined to be a reliable predictor of renal function in these patients.⁵²

Scleroderma renal disease

Scleroderma renal crisis affects 10% to 20% of patients with systemic sclerosis. The renal manifestations characteristically develop early in the course of disease and generally affect patients with diffuse scleroderma. The initiating pathological event is unknown, however, endothelial cell damage and resultant tissue ischemia seem to precipitate the "vicious cycle of spasm and ischemia."⁵³ The alteration in vasomotor tone contributes to the excess release of renin, which has been diagnostic in these patients.⁵⁴ Patients silently develop rapidly progressive renal failure associated with hypertension, hematuria, and proteinuria. Microangiopathic hemolytic

anemia occurs in about 40% of the cases. Normotensive patients with scleroderma can also develop renal failure. Renal biopsy specimens reveal intimal thickening of arteries and nonspecific deposition of IgM and C3 in renal vessels. Fatal outcomes were universal in the past. Today, the use of ACE inhibitors has obviated the need for nephrectomy and decreased the mortality rate greatly. Stem cell transplantation and renal transplantation have been successful in select cases. Recommendations also include close blood pressure monitoring of all patients with diffuse systemic sclerosis.

Immune-mediated disorders of the tubulointerstitium

AIN is characterized pathologically by inflammation of the interstitial compartment of the renal cortex. Nephrologists typically make a distinction between primary tubulointerstitial nephritis, where the pathologic findings are limited to the interstitial compartment, and secondary interstitial nephritis, where interstitial inflammation is seen in conjunction with pathology in the glomeruli and/or small vessels of the kidney. The latter is frequently seen in many forms of primary glomerular disease, and in fact, interstitial abnormalities (including inflammation, fibrosis, and tubular atrophy) correlate better with loss of GFR than do abnormalities within the glomerular compartment.

The pathogenesis of AIN is presumed to relate to either an immune response to antigens present within the tubules or interstitial compartment of the kidney, or a response that cross-reacts to such antigens. Clinical AIN can be associated with interstitial inflammation with mononuclear cells, mononuclear cells and eosinophils, mononuclear cells and antibody, or mononuclear cells and ICs. The form of immune injury is likely dependent on a complex interplay between the nature of the inciting insult, and host factors. Pathogenesis and clinical features of interstitial nephritis have been recently reviewed.⁵⁵

The most common cause of AIN is a hypersensitivity reaction to medication. Antibiotics, especially penicillin and cephalosporin-type agents, are the most common offenders. The classic presentation is that of acute renal failure in association with fever, rash, and eosinophilia. This latter triad of symptoms is most typical with AIN induced by penicillin-like drugs, and even in those settings all 3 symptoms are probably only seen in one-third of patients. Many patients with biopsy-proven AIN never exhibit fever, rash, or eosinophilia. Typically, acute renal failure develops following 10 to 14 days of antibiotic therapy. This time course can be markedly accelerated in patients previously exposed to the incriminated drug. The acute renal failure is typically nonoliguric, and has a fractional excretion of sodium of $> 1\%$. The urinalysis may show striking numbers of white blood cells, including eosinophils. There is frequently microscopic hematuria, as well. Serum complements are typically normal. The typical clinical course following discontinuation of the offending medication is resolution of the acute renal failure over days to weeks, with a

second slower phase of resolution to baseline renal function that occurs over several months.

Other common medications associated with AIN are sulfonamide antibiotics, fluoroquinolones, antiviral agents (acyclovir, foscarnet), diuretics (thiazides and furosemide), and NSAIDs. AIN secondary to diuretics is distinctly uncommon, compared to diuretic-induced azotemia secondary to volume depletion. The AIN seen with NSAIDs is atypical, in that it frequently occurs after months of drug use and is not infrequently associated with nephrotic syndrome (nil lesion by renal biopsy). The reader is referred to textbooks for exhaustive listing of drugs associated with AIN.

Infectious agents associated with AIN include streptococci, staphylococci, *Legionella*, *Yersinia*, *Brucella*, *Pseudomonas*, leishmania, Epstein-Barr virus, and measles. The interstitial nephritis does not seem to be due to infection of the renal parenchyma, but rather an immune response targeting the interstitium.

AIN can occur in the setting of systemic diseases such as SLE, sarcoidosis (where the pathology can demonstrate granulomatous interstitial infiltrates), and Sjögren's syndrome. It can also occur in conjunction with uveitis and iritis (so-called TINU syndrome, tubulointerstitial nephritis and uveitis), most frequently in young females, or rarely as a primary autoimmune disease associated with antitubular basement membrane antibodies and mononuclear cell infiltration. TINU can be associated with hypergammaglobulinemia, positive rheumatoid factors, and elevated erythrocyte sedimentation rate.

Therapy of AIN depends on the underlying cause. For all causes, careful attention must be paid to electrolyte, and acid-base imbalance, as well as monitoring of the need for temporary dialytic intervention. Drug discontinuation is of critical importance for drug-induced AIN, in order to avoid progression to chronic interstitial nephritis. For infection-related AIN, typically treatment or resolution of the underlying infection is sufficient to result in improvement in renal function. For systemic diseases, or primary autoimmune causes of interstitial nephritis, systemic immunosuppression typically is required. There are no controlled clinical trials of corticosteroid therapy in drug-induced interstitial nephritis. Retrospective and anecdotal evidence suggests that patients improve more rapidly on steroids, and may have a lower ultimate serum creatinine, than those allowed to improve without corticosteroids. There are case reports supporting the efficacy of cyclosporine and cyclophosphamide in AIN.

Renal toxicity of medications commonly used by rheumatologists

Several antirheumatic therapies are nephrotoxic, and simultaneous use of these medications with NSAIDs can precipitate renal disease. NSAIDs can cause MCNS associated with interstitial nephritis (see above). Eosinophilia and rash are typically absent. Fortunately, NSAID-induced NP is often reversible, though steroids can prove helpful in severe cases.⁵⁶ NSAIDs can also cause renal

papillary necrosis and functional alterations in renal function related to changes in renal hemodynamics.

Gold therapy has been associated most commonly with MN; however, MCNS and mesangial GN have been reported. Proteinuria has also been observed in 7% to 18% of patients treated with D-penicillamine. Proteinuria classically begins after 6 to 12 months of therapy with these antirheumatic agents. The proteinuria is generally reversible but can take over a year to abate after drug withdrawal.⁵⁷ Cyclosporine causes renal afferent arteriolar constriction, and biopsies reveal focal interstitial fibrosis, tubular atrophy, and arteriolar hyaline sclerosis. Toxicity is related to the doses used (≥ 5 mg/kg/d), age of patients (> 65 years of age) and degree of underlying kidney disease. It is recommended to follow renal function closely, especially in the elderly, and to avoid combination therapy with NSAIDs.⁵⁸ Methotrexate rarely causes renal toxicity; however, it is excreted by the kidney and can accumulate in patients with renal insufficiency.

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