CHAPTER 47

Acute Glomerulonephritis

Judy Savige, Graeme Duke, Francesco Pesce, and Loreto Gesualdo

OBJECTIVES

This chapter will:

1. Describe the clinical features and investigations that indicate rapidly progressive glomerulonephritis as the cause of acute renal failure.
2. Define the features that distinguish between different causes of rapidly progressive glomerulonephritis.
3. Review the principles of treatment for the common forms of rapidly progressive glomerulonephritis.

Glomerulonephritis is the cause of acute renal failure in fewer than 10% of all affected patients and is even less common in those patients admitted to the intensive care unit (ICU), most of whom have acute tubular necrosis (ATN). However, some patients admitted to the ICU for respiratory support also have acute renal failure from small-vessel vasculitis or anti–glomerular basement membrane (anti–GBM) disease.[1]

Acute renal failure in glomerular disease usually is due to rapidly progressive glomerulonephritis, in which renal function deteriorates over days or weeks. The most

common causes are granulomatosis with polyangiitis (Wegener granulomatosis), microscopic polyangiitis, anti–glomerular basement membrane (GBM) disease, and, less often, diffuse proliferative lupus nephritis, immunoglobulin A (IgA) disease, and poststreptococcal glomerulonephritis. Acute renal failure also may be a feature of mixed cryoglobulinemia, mesangiocapillary glomerulonephritis, membranous nephropathy, hemolytic uremic syndrome–thrombotic thrombocytopenic purpura (HUS-TTP), and scleroderma.

In addition, acute renal failure in glomerulonephritis also results from nonglomerular complications such as ATN from renal hypoperfusion or the nephrotic syndrome, drug- or radiocontrast agent–induced interstitial nephritis, macroscopic hematuria–associated cast nephropathy,[2] renal vein thrombosis, and malignant hypertension.

Early recognition of rapidly progressive glomerulonephritis as the cause of acute renal failure or of respiratory failure is critical, because kidney and lung function do not recover spontaneously, and specific and aggressive treatment greatly improves patient outcome.

APPROACH TO MANAGEMENT OF RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Diagnosis

With rapidly progressive glomerulonephritis, a prodrome of fever, malaise, arthralgia, and loin pain is characteristic. All patients have microscopic hematuria, but macroscopic hematuria, proteinuria, and oliguria are common too. Phase contrast microscopy of the urinary sediment confirms the glomerular origin of bleeding,[3] together with presence of red cell and granular casts (Fig. 47.1). Urinary red blood cell (RBC) counts are at least 500,000/mL, and an additional isomorphic population may be present.[4] Other clinical features depend on the underlying disease, but pulmonary hemorrhage occurs in granulomatosis with polyangiitis (Wegener granulomatosis), microscopic polyangiitis, anti–GBM disease, and sometimes systemic lupus erythematosus (SLE). Anemia, neutrophilia, and thrombocytosis are common. Inflammatory markers such as C-reactive protein are elevated, and the serum creatinine is increased.

A number of assays for autoantibodies (and antibodies) are helpful diagnostically. These include tests for antineutrophil cytoplasmic antibodies (ANCA) in granulomatosis with polyangiitis (Wegener granulomatosis) and microscopic polyangiitis (Fig. 47.2),[5,6] anti–GBM antibodies (in anti–GBM disease or Goodpasture syndrome), antinuclear antibodies (ANA) and anti–double-stranded DNA (anti–dsDNA) antibodies (in SLE), serum IgA levels (in IgA glomerulonephritis), antistreptolysin O and anti–DNase B antibodies (in poststreptococcal glomerulonephritis), and rheumatoid factor, cryoglobulins, and serologic hepatitis C markers (in mixed cryoglobulinemia and mesangiocapillary glomerulonephritis) (Table 47.1). Antiphospholipid antibodies (anticardiolipin, anti–β_2-glycoprotein 1 antibodies, lupus anticoagulant) can be detected in some of these diseases (especially SLE and microscopic polyangiitis) and are associated with an increased risk of venous thrombosis.[7] In patients with suspected rapidly progressive glomerulonephritis, assays for ANCA and anti–GBM antibodies are requested urgently, and new technologies test for both antibodies simultaneously.

Complement levels also are helpful diagnostically. These are normal or elevated in granulomatosis with polyangiitis (Wegener granulomatosis), microscopic polyangiitis, anti–GBM disease, and IgA glomerulonephritis but are low in conditions in which complement is consumed: SLE (low C3 and C4), poststreptococcal glomerulonephritis (low C3 and normal C4), HUS-TTP, mixed cryoglobulinemia, and mesangiocapillary glomerulonephritis.

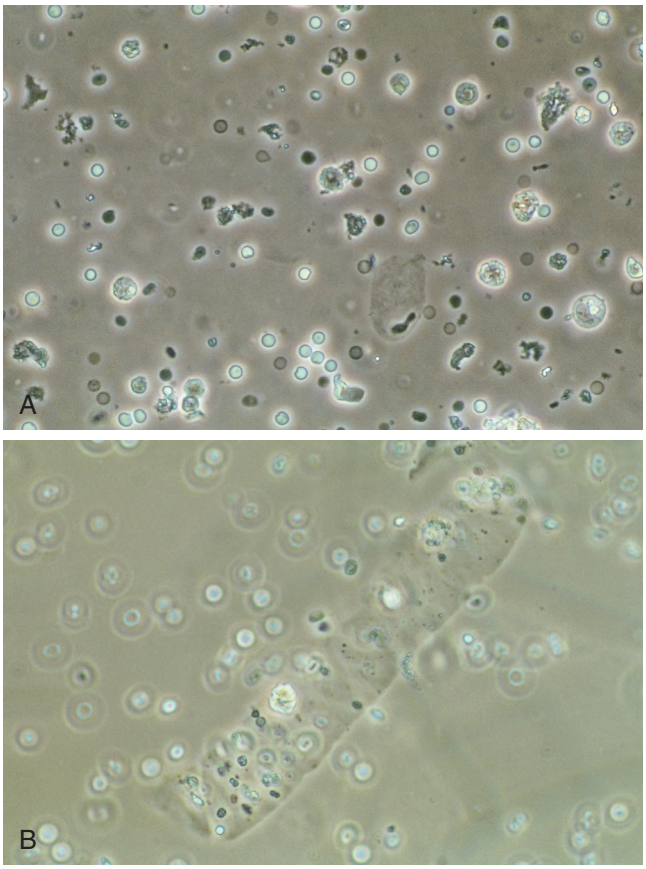

FIGURE 47.1 See also color plates. Phase contrast microscopy of the urinary sediment showing a mixed population of dysmorphic or "glomerular" red blood cells with fragments of varying size, shape, and hemoglobin content (A) and a cast containing red blood cells and red cell debris (B).

Chest radiography demonstrates lung nodules and the alveolar opacities seen with hemorrhage (Fig. 47.3). Chest computed tomography (CT) scans indicate cavitation of the lung nodules and air bronchograms in the alveolar shadows (see Fig. 47.3B). Abdominal ultrasound examination confirms normal kidney size and excludes some of the other causes of acute renal failure.

The underlying histologic diagnosis usually is obvious on urgent renal biopsy. The biopsy specimen also demonstrates the activity and reversibility of the glomerular lesion and the presence of any coincidental ATN (Fig. 47.4). Crescents with epithelial cells and inflammatory cell infiltrates are seen in Bowman's space. Immune deposits are present in one of three patterns: *few or none* ("pauci-immune") in granulomatosis with polyangiitis (Wegener granulomatosis) and microscopic polyarteritis[8]; *linear* in anti–GBM disease; and *granular* in SLE, IgA, and poststreptococcal glomerulonephritis.

Specific Treatment

The institution of urgent therapy with high-dose corticosteroids and cyclophosphamide is the mainstay of treatment for rapidly progressive glomerulonephritis resulting from

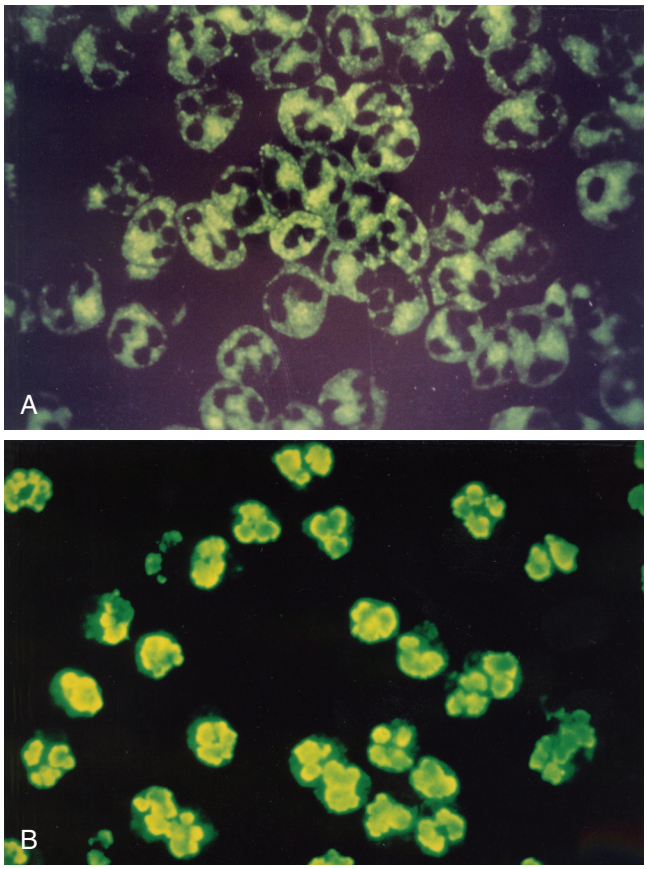

FIGURE 47.2 See also color plates. A, Cytoplasmic ANCA (C-ANCA) with coarse granular fluorescence of the neutrophil cytoplasm and interlobular accentuation. B, Perinuclear ANCA (P-ANCA) with perinuclear staining with nuclear extension. *ANCA,* antineutrophil cytoplasmic antibodies.

small-vessel vasculitis, anti–GBM disease, and many cases of lupus and IgA nephropathy. A typical protocol begins with daily intravenous methylprednisolone (1 g) for 3 days followed by oral prednisolone (1 mg/kg), together with oral cyclophosphamide (50 to 150 mg/day). An every-other-day regimen is associated with fewer side effects but is less effective, and a lower dose of cyclophosphamide must be used in the elderly and other patients with impaired renal function. Regimens vary slightly for the different types of glomerulonephritis, but the general principle is, as always, to use the smallest effective dose for the shortest duration to minimize toxicity without compromising efficacy. Plasma exchange is helpful in anti–GBM disease and in some cases of small-vessel vasculitis.

Complications of Treatment

The most severe complications of treatment are due to the use of cyclophosphamide.[9,10] If neutropenia or thrombocytopenia develops after 2 or 3 weeks, the cyclophosphamide should be stopped and then reinstituted at a lower dose after counts have recovered. Cyclophosphamide predisposes the patient to infection even when white cell counts are normal, and in one study, nearly half of the patients with vasculitis treated with cyclophosphamide required hospitalization for infection. Infections are particularly common with nosocomial bacteria, cytomegalovirus, *Pneumocystis* sp., and fungi, and all patients should receive prophylaxis for *Pneumocystis* infection. A common clinical difficulty is in determining whether a new abnormality on the chest radiograph is due to infection or to active vasculitis. In general, new vasculitic lesions are not seen when patients are on high-dose immunosuppressants and the disease is resolving elsewhere, but if doubt persists, an open lung biopsy is the most useful investigation.

TABLE 47.1

Clinical and Laboratory Features in the Different Causes of Rapidly Progressive Glomerulonephritis

DISEASE	TYPICAL CLINICAL FEATURES	SEROLOGIC FINDINGS	COMPLEMENT LEVELS	IMMUNE DEPOSITS IN GLOMERULUS ON RENAL BIOPSY
Vasculitis				Few/pauci-immune
Granulomatosis with polyangiitis (Wegener granulomatosis)	Prodrome of nasal stuffiness, blocked ears, arthralgia; then onset of hemoptysis, purpura, peripheral neuropathy	C-ANCA	Normal or increased	
Microscopic polyangiitis	Similar to granulomatosis with polyangiitis (Wegener granulomatosis) or affecting the kidneys only (renal-limited) or overlap with polyarteritis nodosa	P-ANCA	Normal or increased	
Anti–GBM disease	Macroscopic hematuria and hemoptysis	Anti–GBM antibodies	Normal or increased	Linear staining for IgG and C3
SLE (diffuse proliferative, WHO class IV)	Previous history of SLE, marked hematuria and proteinuria, hypertension "telescoping" urinary sediment	ANA, anti–dsDNA antibodies	Low C3, low C4	Granular immune deposits
IgA disease	Persistent microscopic hematuria with episodes of synpharyngitic macroscopic hematuria, with proteinuria, hypertension	IgA (increased in about half of cases)	Normal or increased	
Poststreptococcal glomerulonephritis	At 1 to 3 weeks after streptococcal pharyngitis or impetigo, macroscopic hematuria, edema, hypertension, oliguria	ASO, anti-DNase B antibodies	Low C3, normal C4	

ANA, Antinuclear antibodies; *anti–dsDNA,* anti–double-stranded DNA; *ASO,* antistreptolysin O; *C-ANCA,* cytoplasmic antineutrophil cytoplasmic antibodies; *GBM,* glomerular basement membrane; *IgA,* immunoglobulin A; *P-ANCA,* perinuclear antineutrophil cytoplasmic antibodies; *SLE,* systemic lupus erythematosus; *WHO,* World Health Organization.

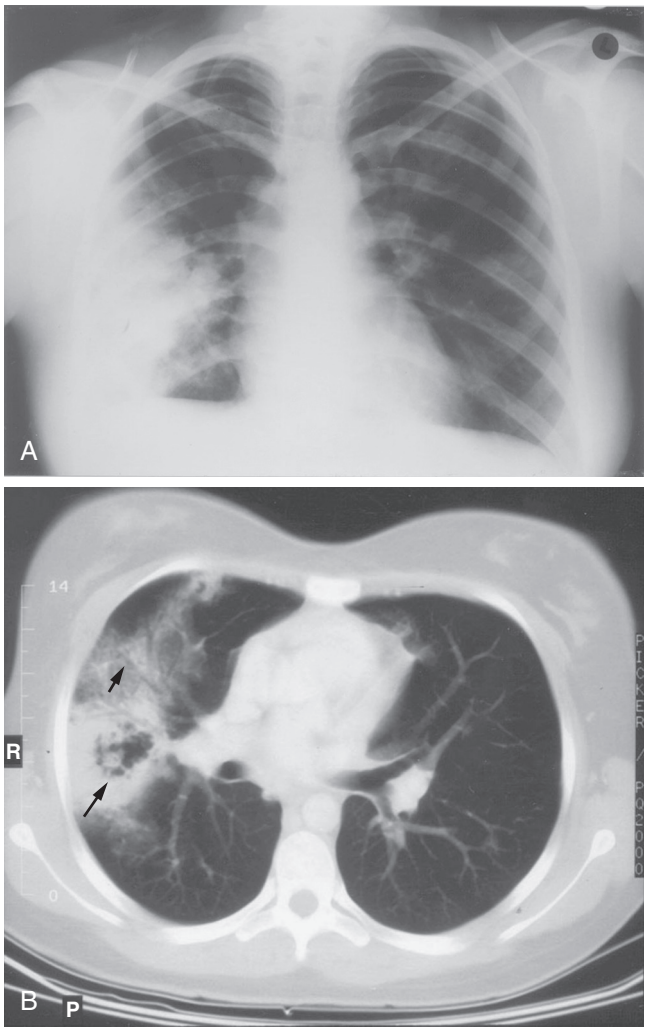

FIGURE 47.3 **A,** Chest x-ray film showing alveolar hemorrhage in the right *(R)* lung in a patient with Granulomatosis with polyangiitis (Wegener granulomatosis). **B,** Chest computed tomography scan taken at about the same time showing an air bronchogram *(long arrow)*, typical of alveolar hemorrhage, and cavitation in a nodule *(short arrow)*.

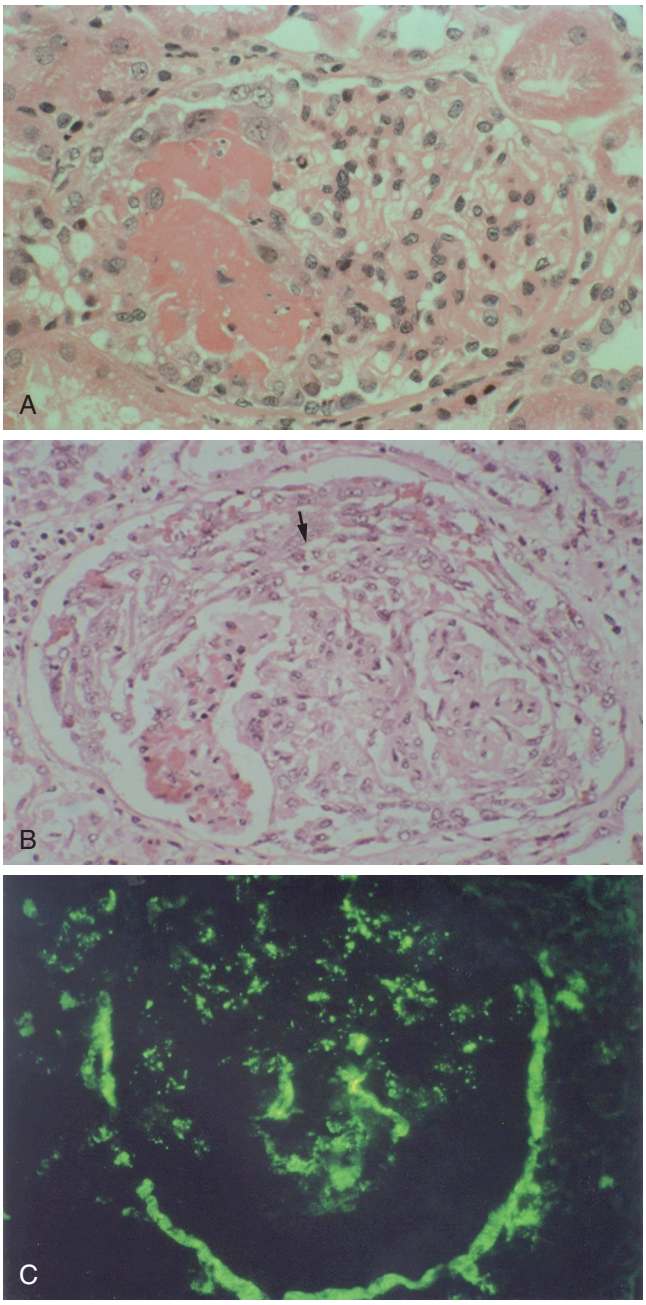

FIGURE 47.4 See also color plates. **A,** Segmental necrotizing lesion typical of that seen in granulomatosis with polyangiitis (Wegener granulomatosis) and microscopic polyangiitis. **B,** Cellular crescent *(arrow)* in Bowman's space, enveloping the glomerular tuft. **C,** "Pauci-immune" pattern, with only a few scattered C3 deposits in the glomerulus.

Prolonged use of cyclophosphamide is associated with an increased risk of cancer, especially transitional cell bladder cancer, myelodysplasia, and lymphoma.[9,10] Approximately half of the patients who receive cyclophosphamide for more than 1 year have hematuria 8 years later, and 16% have bladder cancer after 15 years. The risk of bladder complications from cyclophosphamide is reduced with morning administration and a lower total dose, but all patients should be monitored for hematuria regularly and for life. A year's treatment with cyclophosphamide induces infertility in most patients, both male and female, as well as early menopause and low testosterone levels and impotence. When relevant, embryo, ovum, and sperm storage should be offered before treatment is started.

High-dose steroids may cause disturbed sleep and altered mood, hypertension, hyperglycemia, gastrointestinal bleeding, and predisposition to infections. Long-term complications include osteoporosis (contributed to by the low estrogen and testosterone), weight gain, increased skin fragility, cataracts, and myopathy. The bone loss is greatest in the first 6 months of steroid treatment,[11] and patients require calcium, vitamin D, or bisphosphonates from the initiation of therapy.

Management in the Intensive Care Unit

Patients with rapidly progressive glomerulonephritis usually are managed on the renal ward but may be admitted to the ICU for treatment of acute renal failure, or for respiratory support in cases of alveolar hemorrhage, pulmonary edema, or severe underlying lung disease.

Patients also may be hospitalized for the management of complications such as pneumonia or overwhelming sepsis.[12] Other challenges in the ICU include the need for vigilance for alveolar hemorrhage, anemia and hypoxemia, gastrointestinal hemorrhage, hyperglycemia, and sepsis, and the treatment of subglottic tracheal stenosis in patients with granulomatosis with polyangiitis (Wegener granulomatosis).

Prognosis

Patients with glomerulonephritis admitted to the ICU with a high Acute Physiology and Chronic Health Evaluation (APACHE) II score have an increased mortality rate and a 5-year survival rate of only 25% to 50%.[13] Most deaths in these patients are due to sepsis and other adverse effects of treatment.

CLINICAL PRESENTATION AND MANAGEMENT OF RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Small-Vessel Vasculitis

Granulomatosis with polyangiitis (Wegener granulomatosis) and microscopic polyangiitis account for the majority of cases of rapidly progressive glomerulonephritis. Microscopic polyangiitis includes a renal-limited form[14] consisting of glomerular disease only, as well as the overlap syndrome with polyarteritis nodosa, which affects medium-sized vessels and results in renal, mesenteric, and coronary artery aneurysms and ischemia.[15] Renal-limited microscopic polyangiitis is the most common presentation of small-vessel vasculitis.

All forms of small-vessel vasculitis are characterized histologically by a pauci-immune segmental necrotizing glomerulonephritis (see Fig. 47.4A) and necrotizing vasculitis of the other capillaries, venules, arterioles, and arteries within the kidney. Granulomas typically are present in granulomatosis with polyangiitis (Wegener granulomatosis).

Granulomatosis with polyangiitis (Wegener granulomatosis) affects both genders and all age groups, but the average age at presentation is 50 years. This disease rarely is observed in blacks.[16] The prodrome may be prolonged, and the diagnosis may be overlooked for months. Presenting features include rapidly progressive glomerulonephritis with extracapillary crescents, pulmonary hemorrhage, episcleritis, persistent sinusitis, hearing loss, rhinorrhea, purpura, peripheral neuropathy, and subglottic tracheal stenosis.[17–19] Sometimes disease is limited to the ear, nose, or respiratory tract. Granulomatosis with polyangiitis is a chronic relapsing disease that often recurs within the first few years after the initial presentation and remission.

Microscopic Polyangiitis

Males are affected more often than females, but patients generally are older than those with granulomatosis with polyangiitis (Wegener granulomatosis). Presenting features are similar, except that all patients have glomerulonephritis, and respiratory tract and ear and nose disease is less common.[18,19] Microscopic polyangiitis is less likely to relapse than granulomatosis with polyangiitis and may resolve permanently after several years.

Antineutrophil Cytoplasmic Antibodies in Small-Vessel Vasculitis

Granulomatosis with polyangiitis (Wegener granulomatosis) and microscopic polyangiitis are associated with ANCA, which are autoantibodies directed against enzymes found within the cytoplasmic granules of neutrophils and monocytes. Recognition of the association with ANCA has greatly increased the clinician's ability to diagnose small-vessel vasculitis,[5,6] but no patient should receive treatment on the basis of a positive result on ANCA testing without independent confirmation.

Sera from patients in whom small-vessel vasculitis is suspected are screened for ANCA by indirect immunofluorescence of normal peripheral blood neutrophils,[20] and all fluorescence-positive sera are confirmed by enzyme-linked immunosorbent assays (ELISAs) for the major ANCA specificities, proteinase 3 (PR3), and myeloperoxidase (MPO).[18,21] Ninety percent of patients with active generalized granulomatosis with polyangiitis (Wegener granulomatosis) have cytoplasmic ANCA (C-ANCA) directed against PR3. Nearly 80% of patients with active microscopic polyangiitis have perinuclear ANCA (P-ANCA) directed against MPO, and the few with P-ANCA and specificity for PR3 have disease that more closely resembles granulomatosis with polyangiitis (Wegener granulomatosis) with increased respiratory tract, ear, and nose disease and an increased tendency to relapse. In small-vessel vasculitis, ANCA levels usually are high at presentation, fall with treatment, and, in approximately half of the patients, increase just before relapse. These antibodies also are found in inflammatory bowel disease, autoimmune liver disease, rheumatoid arthritis, and chronic infections, but in such cases, the diagnosis usually is obvious, ANCA levels are low, and the major antigens are not PR3 and MPO.[19]

Antineutrophil Cytoplasmic Antibodies and Disease Pathogenesis

The development of ANCA is more likely in persons with certain α_1-antitrypsin and neutrophil FcγR111 receptor genotypes,[22,23] but infections have a role in disease initiation too. Experimental models and evidence of disease transmission in utero indicate that MPO-ANCA and probably PR3-ANCA are pathogenetic.[24,25] The mechanism is as follows: infections increase levels of circulating tumor necrosis factor (TNF),[26,27] which induces neutrophils to express surface PR3 and MPO.[28] ANCA bind to these molecules and activate the neutrophils, which degranulate and release cytokines, reactive oxygen species, and lytic enzymes. These damage the vascular endothelium. The activated neutrophils also release PR3 and MPO, which adhere to the endothelial cells, allowing further ANCA to bind, resulting in increased inflammation. Patients with granulomatosis with polyangiitis (Wegener granulomatosis) appear to have more neutrophils that constitutively express membrane PR3 and can be stimulated by ANCA without priming by infection.[29] Cellular and extracellular MPO may both cause glomerular and interstitial damage.[30] Humoral and T cell responses are involved, for neutrophil localization and attraction and monocyte/macrophage activation and crescent formation, respectively.[31] In patients with PR3 vasculitis

more organs are affected, whereas in those with MPO a renal limited vasculitis is often identified.[32] A histopathologic classification of ANCA-associated glomerulonephritis, based on different glomerular lesions, has been proposed as a method of prognostication of outcomes at diagnosis. The four categories of glomerular lesions are referred to as focal, crescentic, mixed, and sclerosing; the different lesions correlate with the loss of function in order of increasing severity.[33]

Treatment

The major aim of treatment is to prevent renal involvement in granulomatosis with polyangiitis (Wegener granulomatosis) and to delay renal failure in cases in which kidney involvement is already present in granulomatosis with polyangiitis and microscopic polyangiitis. Fewer than 20% of patients with small-vessel vasculitis and kidney disease survive without treatment for 1 year, and those given steroids alone exhibit a transient and incomplete response. Thus all patients, including the elderly, should have at least a trial of steroids and immunosuppressants if the intent is to salvage renal function.

Induction therapy for patients with small-vessel vasculitis and rapidly progressive glomerulonephritis, pulmonary hemorrhage, inflammatory tracheal stenosis, and other serious manifestations is high-dose corticosteroids and cyclophosphamide.[27]

Disease that is resistant to these regimens is rare but responds to rituximab and certain TNF antagonists such as infliximab.[34,35] Although rituximab can induce remission in patients with mild to moderate kidney involvement in ANCA-associated glomerulonephritis, this anti–CD20 monoclonal antibody is essentially equivalent to cyclophosphamide in terms of efficacy and it also has a similar risk profile.[36] Patients with ANCA glomerulonephritis and rapid worsening of function should receive at least corticosteroids and cyclophosphamide. Additional benefits could derive from plasma exchange because this treatment reduces the development of end-stage renal disease (ESRD) by approximately 40%.[37] Remission induction with cyclophosphamide and corticosteroids followed by rituximab to maintain remission is suggested as approach for severe disease.[38,39]

Response to Treatment

Patients should be monitored for general well-being and specific symptoms, as well as urinary RBC counts, FBE, C-reactive protein, serum creatinine, and ANCA. A rapid response to treatment is typical.[19] Hemoptysis resolves in days, and radiologic evidence of pulmonary hemorrhage and nodules clears within 1 week and 1 month, respectively. Urinary RBC counts and C-reactive protein levels stabilize and begin to fall within days. Maximal improvement in serum creatinine occurs between 10 days and 2 months. Deafness and neuropathy resolve more slowly, and recovery may be incomplete. Proteinuria decreases gradually and does not necessarily return to baseline. ANCA persist for at least 4 months.

Clinical Course

After the initial course of therapy, cyclophosphamide typically is substituted with another agent, usually azathioprine, but sometimes methotrexate, mycophenolate, or tacrolimus; this regimen is continued for 3 years in granulomatosis with polyangiitis (Wegener granulomatosis) and 2 years in microscopic polyangiitis if no relapses occur. However, relapses are common and often occur when the medication dose is reduced too quickly. Relapses tend to be less severe than the initial disease and to respond more rapidly to increased medication, but sometimes a further short course of cyclophosphamide is necessary.

When renal transplantation is required, it is delayed for at least 6 months after the initial presentation or the most recent relapse to prevent disease recurrence in the graft.[40] Elective surgery such as nasal reconstruction should be delayed for a year after presentation, but a tracheal stricture that predisposes the patient to infections should be corrected immediately with surgery or, if necessary, a tracheostomy.

Disease-Associated Morbidity and Mortality

Disease-related morbidity occurs in possibly 90% of patients with small-vessel vasculitis and arises from delays in instituting treatment, progression of subclinical disease, and relapse. Nearly half of all patients have some degree of renal impairment at presentation, and 20% have moderate to severe respiratory disease. Overall, the single most important determinant of outcome in these patients is the presence of renal disease, and the strongest predictor of renal outcome is the serum creatinine level at presentation.[41]

In ANCA-associated pauci-immune glomerulonephritis a 20% mortality rate is observed within the first year of diagnosis. In those who survive, ESRD occurs in up to 25% of the patients within the first 4 years after diagnosis.[42–45] The overall survival in patients with ANCA-associated vasculitis receiving a kidney transplant is similar to that for patients with other glomerulonephtitis.[46]

A study conducted in very elderly patients has shown that the use of immunosuppression is able to reduce the incidence of ESRD within the first year of diagnosis. The immunosuppressive treatment and peak serum creatinine before biopsy are the only factors influencing progression to ESRD. Immunosuppression is associated with lower risk of death and/or ESRD in multivariable models only with a follow-up longer than 2 years.[47]

Anti–Glomerular Basement Membrane Disease

Anti–GBM disease[48,49] accounts for less than 5% of all cases of rapidly progressive glomerulonephritis. It affects patients of all ages, but especially young males and the elderly. Anti-GBM disease is strongly associated with human leukocyte antigen (HLA) DRB1*1501 and is seen occasionally after renal injury—for example, with lithotripsy and after pyelonephritis.[50,51]

Clinical Features

The prodrome usually is mild, and patients often present late in the clinical course with hemoptysis, macroscopic hematuria, or acute renal failure. One third have dyspnea or hemoptysis (Goodpasture syndrome), which may be precipitated by cigarette smoking, hydrocarbon exposure, pulmonary infection, or fluid overload.[52] The severity of hemoptysis is a poor indicator of the extent of alveolar hemorrhage. Hypertension is uncommon.

Anti–GBM disease may be differentiated from small-vessel vasculitis by the paucity of systemic features, the presence of a very active urinary sediment (often with RBC counts higher than 1 million/mL, with many red cell casts and marked proteinuria), and the rapidity of the deterioration in renal function. Patients often require dialysis at presentation.

A rare atypical anti–GBM variant is characterized by an indolent course with no pulmonary involvement and undetectable circulating antibodies against noncollagenous (NC1) domain of the α3-chain of type IV collagen.[53]

Diagnosis

The diagnosis of anti–GBM disease is confirmed with the demonstration of circulating anti–GBM antibodies or linear IgG bound to the glomerular basement membrane in a renal biopsy specimen. Anti–GBM antibodies usually are detected in a sensitive and specific ELISA, but antibody levels do not correlate with disease activity and are undetectable in 10% of patients. Anti–GBM antibodies also are found occasionally in patients with small-vessel vasculitis.[54]

A renal biopsy is critical in determining the severity and reversibility of the glomerular disease and the presence of tubular damage. The glomerular lesion varies, ranging from mild mesangial hypercellularity to a diffuse proliferative glomerulonephritis with extensive crescent formation. ATN and interstitial inflammation often are present. Bright linear polyclonal staining of GBM for IgG on immunofluorescence is the hallmark of anti–GBM glomerulonephritis.[53] IgG and C3 are found in the glomerular basement membrane, Bowman's capsule, and the distal tubular membrane within the kidney and in the alveolar membrane in the lung.

Disease Pathogenesis

The adult glomerular and alveolar basement membranes comprise mainly type IV collagen heterotrimers with a1(IV)-a5(IV) collagen chains, and the Goodpasture antigen target is found within the a3(IV) chain.[55] Antibody binding, complement activation, phagocyte accumulation, and T cells contribute to glomerular damage.

Treatment and Outcome

Renal function declines more rapidly in anti–GBM disease than in any other form of rapidly progressive glomerulonephritis; without treatment, affected patients die of renal failure or pulmonary hemorrhage. Thus all patients with anti–GBM disease, except those with minimal renal involvement or irreversible renal damage, should undergo early treatment. The aim is to remove circulating anti–GBM antibodies and inflammatory mediators[56,57] using plasma exchange together with high-dose cyclophosphamide and prednisolone. Some physicians do not perform plasma exchange in patients with a creatinine level greater than 600 μmol/L with oliguria,[56] but acute renal failure in patients with anti–GBM disease often is at least partly due to ATN, which is reversible. Because the disease is not common and the presentation is typically acute and severe, clinical trials are not easy to perform and the treatment is still based on this combination therapy.[58] The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for glomerulonephritis have recommended a trial of rituximab versus cyclophosphamide in anti–GBM disease. Interestingly, the use of other biologic agents for this condition is possible.[59]

With this treatment, the urinary glomerular RBC counts stabilize and fall, and the creatinine begins to improve within a week. The response is slower in patients who require dialysis. Hemoptysis ceases within a few days, and alveolar hemorrhage clears radiologically within a week. Oral prednisolone and cyclophosphamide are reduced over 3 months and then ceased if the disease is inactive and anti–GBM antibodies are undetectable.

Anti–GBM disease is not a common cause of ESRD and is not associated with altered dialysis survival. Moreover renal transplant patients' survival and renal allograft survival rates are not influenced by the disease. Older age and history of pulmonary hemorrhage are predictors of death on dialysis in patients affected by anti–GBM disease.[60] Renal transplantation should be delayed until anti–GBM antibodies are undetectable at least 6 months after the initial presentation, to prevent disease recurrence in the graft.

OTHER TYPES OF GLOMERULONEPHRITIS THAT CAUSE ACUTE RENAL FAILURE

Less common causes of glomerulonephritis account for less than 40% of all cases of rapidly progressive glomerulonephritis.

Systemic Lupus Erythematosus

SLE is associated with a variety of renal histologic patterns, but rapidly progressive glomerulonephritis in this disorder most often is associated with diffuse proliferative glomerulonephritis (class IV in the World Health Organization [WHO] classification). This occurs in less than 10% of all patients with lupus nephritis.

The diagnosis of diffuse proliferative lupus glomerulonephritis is suspected in patients who fulfill the American Rheumatology Association criteria for SLE and who have high urinary RBC counts and marked proteinuria. Renal function usually is impaired, and hypertension is common. Other findings include anti–dsDNA antibodies and low complement levels. In the renal biopsy specimen, more than 50% of the glomeruli demonstrate a proliferative lesion, crescents are common, and the capillary walls are thickened with "wireloop" subendothelial deposits. A "full hand" of IgG, IgM, IgA, C3, and C1q immune deposits is characteristic.

In class III and IV disease, induction consists of intravenous cyclophosphamide (low-dose: 500 mg fortnightly for 3 months or high-dose: 0.5–1 g/m^2 monthly for 6 months) or mycophenolate mofetil (2–3 g total daily dose) plus oral glucocorticoids (0.5–1.0 mg/kg/day) with or without three pulses of intravenous methylprednisolone at start of induction treatment. For postinduction maintenance therapy, oral mycophenolate mofetil (1–2 g/day) and oral azathioprine (1.5–2.5 mg/kg/day) are well tolerated and effective over a 3- to 4-year period, although mycophenolate mofetil may be superior particularly in higher-risk patients.[61–63] In class V with a nephrotic range proteinuria, glucocorticoids, and mycophenolate mofetil or other immunosuppressives should be used as induction treatment, whereas the recommendation for the maintenance therapy is equivalent to that in class

III/IV.[64,65] The efficacy of tacrolimus is comparable with mycophenolate mofetil and cyclophosphamide. Rituximab and biologic agents may be promising in refractory lupus nephritis as induction therapy.[66]

Immunoglobulin A Glomerulonephritis

Most patients with IgA glomerulonephritis (IgAN) have a benign disease with persistent microscopic hematuria, mild proteinuria, and episodes of infection-associated macroscopic hematuria, but one third progress to renal failure over years.[67] The MEST criteria (mesangial hypercellularity [M], endocapillary hypercellularity [E], segmental glomerulosclerosis [S], and tubular atrophy/interstitial fibrosis [T]) in the Oxford classification are useful prognostic indicators at the time or renal biopsy.[68]

In a small group of patients, a rapidly progressive glomerulonephritis with crescentic change and tubulointerstitial inflammation develops. Crescentic IgAN accounts for 1% of biopsies in the Oxford classification cohort.[68] About 70% of patients with crescentic IgAN progress to end-stage renal disease (ESRD) in 5 years, and initial serum creatinine level is the strongest risk factor for kidney failure.[69]

High-dose corticosteroids and immunosuppressants are useful in these patients.[70] Although corticosteroids may reduce the risk of progression, the optimal management of IgAN remains uncertain.[71,72]

Poststreptococcal Glomerulonephritis

Poststreptococcal glomerulonephritis is common in children[73] in developing countries 1 to 3 weeks after pharyngitis or impetigo. Most cases are asymptomatic, but in 20% of affected patients, the nephritic syndrome develops, manifesting as hematuria, hypertension, oliguria, and an elevated serum creatinine. Antistreptolysin O and anti–DNase B antibodies are detectable after throat and skin infections, respectively, and C3 levels are low. The prognosis usually is excellent, and no specific treatment is needed. In up to 1% of patients, however, acute renal failure with a crescentic glomerulonephritis develops, sometimes associated with ANCA.[74] The role of corticosteroids and immunosuppressants in these patients is controversial.

Key Points

1. Glomerulonephritis is a rare cause of acute renal failure, especially in the intensive care unit, and may be misdiagnosed as acute tubular necrosis.
2. Rapidly progressive glomerulonephritis constitutes a medical emergency, and an urgent renal biopsy is indicated to make an accurate diagnosis and to determine the extent of irreversible renal damage.
3. An urgent diagnosis is critical because renal function does not recover spontaneously, and because aggressive treatment improves function and delays the onset of end-stage renal failure.

ACKNOWLEDGMENTS

I thank the following colleagues for providing illustrations: Dr. Ian Forbes (urinary sediment); Dr. Roger Sinclair (renal histology and immunofluorescence); and Professor Don Campbell (chest radiology).

Key References

30. O'Sullivan KM, Lo CY, Summers SA, et al. Renal participation of myeloperoxidase in antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis. *Kidney Int.* 2015;88:1030-1046.
38. Pendergraft WF 3rd, Falk RJ. Understanding the role of rituximab in ANCA GN: regressing toward the mean. *J Am Soc Nephrol.* 2015;26:771-774.
59. Holdsworth SR, Gan PY, Kitching AR. Biologics for the treatment of autoimmune renal diseases. *Nat Rev Nephrol.* 2016;12:217-231.
64. Wilhelmus S, Bajema IM, Bertsias GK, et al. Lupus nephritis management guidelines compared. *Nephrol Dial Transplant.* 2016;31:904-913.
71. Vecchio M, Bonerba B, Palmer SC, et al. Immunosuppressive agents for treating IgA nephropathy. *Cochrane Database Syst Rev.* 2015;(8):CD003965.

A complete reference list can be found online at ExpertConsult.com.

References

1. Semple D, Keogh J, Forni L, et al. Clinical review: Vasculitis on the intensive care unit–part 1: diagnosis. *Crit Care*. 2005;9:92-97.
2. Griffith M, Brett S. The pulmonary physician in critical care * illustrative case 3: pulmonary vasculitis. *Thorax*. 2003;58:543-546.
3. Kincaid-Smith P, Bennett WM, Dowling JP, et al. Acute renal failure and tubular necrosis associated with hematuria due to glomerulonephritis. *Clin Nephrol*. 1983;19:206-210.
4. Fairley KF, Birch DF. Hematuria: a simple method for identifying glomerular bleeding. *Kidney Int*. 1982;21:105-108.
5. van der Woude FJ, Rasmussen N, Lobatto S, et al. Autoantibodies against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosis. *Lancet*. 1985;1:425-429.
6. Savage CO, Winearls CG, Jones S, et al. Prospective study of radioimmunoassay for antibodies against neutrophil cytoplasm in diagnosis of systemic vasculitis. *Lancet*. 1987;1:1389-1393.
7. Cohney S, Savige J, Stewart MR. Lupus anticoagulant in anti-neutrophil cytoplasmic antibody-associated polyarteritis. *Am J Nephrol*. 1995;15:157-160.
8. Jennette JC, Wilkman AS, Falk RJ. Anti-neutrophil cytoplasmic utoantibody-associated glomerulonephritis and vasculitis. *Am J Pathol*. 1989;135:921-930.
9. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med*. 1992;116:488-498.
10. Talar-Williams C, Hijazi YM, Walther MM, et al. Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. *Ann Intern Med*. 1996;124:477-484.
11. Reid IR, Heap SW. Determinants of vertebral mineral density in patients receiving long-term glucocorticoid therapy. *Arch Intern Med*. 1990;150:2545-2548.
12. Semple D, Keogh J, Forni L, et al. Clinical review: Vasculitis on the intensive care unit – part 2: treatment and prognosis. *Crit Care*. 2005;9:193-197.
13. Cruz BA, Ramanoelina J, Mahr A, et al. Prognosis and outcome of 26 patients with systemic necrotizing vasculitis admitted to the intensive care unit. *Rheumatology (Oxford)*. 2003;42:1183-1188.
14. Savage CO, Winearls CG, Evans DJ, et al. Microscopic polyarteritis: presentation, pathology and prognosis. *Q J Med*. 1985;56:467-483.
15. Kirkland GS, Savige J, Wilson D, et al. Classical polyarteritis nodosa and microscopic polyarteritis with medium vessel involvement–a comparison of the clinical and laboratory features. *Clin Nephrol*. 1997;47:176-180.
16. Comarmond C, Cacoub P. Granulomatosis with polyangiitis (Wegener): clinical aspects and treatment. *Autoimmun Rev*. 2014;13:1121-1125.
17. DeRemee RA. Antineutrophil cytoplasmic autoantibody-associated diseases: a pulmonologist's perspective. *Am J Kidney Dis*. 1991;18:180-183.
18. Falk RJ, Jennette JC. Anti-neutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. *N Engl J Med*. 1988;318:1651-1657.
19. Savige J, Davies D, Falk RJ, et al. Antineutrophil cytoplasmic antibodies and associated diseases: a review of the clinical and laboratory features. *Kidney Int*. 2000;57:846-862.
20. Savige J, Gillis D, Benson E, et al. International Consensus Statement on Testing and Reporting of Antineutrophil Cytoplasmic Antibodies (ANCA). *Am J Clin Pathol*. 1999;111:507-513.
21. Niles JL, McCluskey RT, Ahmad MF, et al. Wegener's granulomatosis autoantigen is a novel neutrophil serine proteinase. *Blood*. 1989;74:1888-1893.
22. Esnault VL, Testa A, Audrain M, et al. Alpha 1-antitrypsin genetic polymorphism in ANCA-positive systemic vasculitis. *Kidney Int*. 1993;43:1329-1332.
23. Tse WY, Abadeh S, Jefferis R, et al. Neutrophil FcgammaRIIIb allelic polymorphism in anti-neutrophil cytoplasmic antibody (ANCA)-positive systemic vasculitis. *Clin Exp Immunol*. 2000;119:574-577.
24. Xiao H, Heeringa P, Hu P, et al. Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. *J Clin Invest*. 2002;110:955-963.
25. Pfister H, Ollert M, Frohlich LF, et al. Antineutrophil cytoplasmic autoantibodies against the murine homolog of proteinase 3 (Wegener autoantigen) are pathogenic in vivo. *Blood*. 2004;104:1411-1418.
26. Jennette JC, Xiao H, Falk RJ. Pathogenesis of vascular inflammation by anti-neutrophil cytoplasmic antibodies. *J Am Soc Nephrol*. 2006;17:1235-1242.
27. Kallenberg CG, Heeringa P, Stegeman CA. Mechanisms of Disease: pathogenesis and treatment of ANCA-associated vasculitides. *Nat Clin Pract Rheumatol*. 2006;2:661-670.
28. Falk RJ, Terrell RS, Charles LA, et al. Anti-neutrophil cytoplasmic autoantibodies induce neutrophils to degranulate and produce oxygen radicals in vitro. *Proc Natl Acad Sci USA*. 1990;87:4115-4119.
29. Schreiber A, Luft FC, Kettritz R. Membrane proteinase 3 expression and ANCA-induced neutrophil activation. *Kidney Int*. 2004;65:2172-2183.
30. O'Sullivan KM, Lo CY, Summers SA, et al. Renal participation of myeloperoxidase in antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis. *Kidney Int*. 2015;88:1030-1046.
31. Couser WG, Johnson RJ. What is myeloperoxidase doing in ANCA-associated glomerulonephritis? *Kidney Int*. 2015;88: 938-940.
32. Hilhorst M, van Paassen P, Tervaert JW, et al. Proteinase 3-ANCA Vasculitis versus Myeloperoxidase-ANCA Vasculitis. *J Am Soc Nephrol*. 2015;26:2314-2327.
33. Berden AE, Ferrario F, Hagen EC, et al. Histopathologic classification of ANCA-associated glomerulonephritis. *J Am Soc Nephrol*. 2010;21:1628-1636.
34. Arzoo K, Sadeghi S, Liebman HA. Treatment of refractory antibody mediated autoimmune disorders with an anti-CD20 monoclonal antibody (rituximab). *Ann Rheum Dis*. 2002;61:922-924.
35. Zhou A, Ueno H, Shimomura M, et al. Blockade of TGF-beta action ameliorates renal dysfunction and histologic progression in anti-GBM nephritis. *Kidney Int*. 2003;64:92-101.
36. Geetha D, Specks U, Stone JH, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis with renal involvement. *J Am Soc Nephrol*. 2015;26:976-985.
37. Walters G. Role of therapeutic plasmapheresis in ANCA-associated vasculitis. *Pediatr Nephrol*. 2016;31:217-225.
38. Pendergraft WF 3rd, Falk RJ. Understanding the role of rituximab in ANCA GN: regressing toward the mean. *J Am Soc Nephrol*. 2015;26:771-774.
39. Walters G, Willis NS, Craig JC. Interventions for renal vasculitis in adults. *Cochrane Database Syst Rev*. 2015;(9):CD003232.
40. Grotz W, Wanner C, Rother E, et al. Clinical course of patients with antineutrophil cytoplasm antibody positive vasculitis after kidney transplantation. *Nephron*. 1995;69:234-236.
41. Hogan SL, Nachman PH, Wilkman AS, et al. Prognostic markers in patients with antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol*. 1996;7:23-32.
42. de Groot K, Adu D, Savage CO, et al. The value of pulse cyclophosphamide in ANCA-associated vasculitis: meta-analysis and critical review. *Nephrol Dial Transplant*. 2001;16:2018-2027.
43. Booth AD, Almond MK, Burns A, et al. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. *Am J Kidney Dis*. 2003;41:776-784.
44. Weidner S, Geuss S, Hafezi-Rachti S, et al. ANCA-associated vasculitis with renal involvement: an outcome analysis. *Nephrol Dial Transplant*. 2004;19:1403-1411.
45. Hogan SL, Falk RJ, Chin H, et al. Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. *Ann Intern Med*. 2005;143:621-631.
46. Hruskova Z, Stel VS, Jayne D, et al. Characteristics and Outcomes of Granulomatosis With Polyangiitis (Wegener) and Microscopic Polyangiitis Requiring Renal Replacement Therapy: Results From the European Renal Association-European Dialysis and Transplant Association Registry. *Am J Kidney Dis*. 2015;66:613-620.
47. Bomback AS, Appel GB, Radhakrishnan J, et al. ANCA-associated glomerulonephritis in the very elderly. *Kidney Int*. 2011;79:757-764.

48. Pusey CD. Anti-glomerular basement membrane disease. *Kidney Int*. 2003;64:1535-1550.
49. Cui Z, Zhao MH. Advances in human antiglomerular basement membrane disease. *Nat Rev Nephrol*. 2011;7:697-705.
50. Rees AJ, Peters DK, Compston DA, et al. Strong association between HLA-DRW2 and antibody-mediated Goodpasture's syndrome. *Lancet*. 1978;1:966-968.
51. Iwamoto I, Yonekawa S, Takeda T, et al. Anti-glomerular basement membrane nephritis after extracorporeal shock wave lithotripsy. *Am J Nephrol*. 1998;18:534-537.
52. Donaghy M, Rees AJ. Cigarette smoking and lung haemorrhage in glomerulonephritis caused by autoantibodies to glomerular basement membrane. *Lancet*. 1983;2:1390-1393.
53. Nasr SH, Collins AB, Alexander MP, et al. The clinicopathologic characteristics and outcome of atypical anti-glomerular basement membrane nephritis. *Kidney Int*. 2016;89:897-908.
54. Jayne DR, Marshall PD, Jones SJ, et al. Autoantibodies to GBM and neutrophil cytoplasm in rapidly progressive glomerulonephritis. *Kidney Int*. 1990;37:965-970.
55. Saus J, Wieslander J, Langeveld JP, et al. Identification of the Goodpasture antigen as the alpha 3(IV) chain of collagen IV. *J Biol Chem*. 1988;263:13374-13380.
56. Lockwood CM, Rees AJ, Pearson TA, et al. Immunosuppression and plasma-exchange in the treatment of Goodpasture's syndrome. *Lancet*. 1976;1:711-715.
57. Savige JA, Dowling J, Kincaid-Smith P. Superimposed glomerular immune complexes in anti-glomerular basement membrane disease. *Am J Kidney Dis*. 1989;14:145-153.
58. Lahmer T, Heemann U. Anti-glomerular basement membrane antibody disease: a rare autoimmune disorder affecting the kidney and the lung. *Autoimmun Rev*. 2012;12:169-173.
59. Holdsworth SR, Gan PY, Kitching AR. Biologics for the treatment of autoimmune renal diseases. *Nat Rev Nephrol*. 2016;12:217-231.
60. Tang W, McDonald SP, Hawley CM, et al. Anti-glomerular basement membrane antibody disease is an uncommon cause of end-stage renal disease. *Kidney Int*. 2013;83:503-510.
61. Houssiau FA, D'Cruz D, Sangle S, et al. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. *Ann Rheum Dis*. 2010;69:2083-2089.
62. Dooley MA, Jayne D, Ginzler EM, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. *N Engl J Med*. 2011;365:1886-1895.
63. Morris HK, Canetta PA, Appel GB. Impact of the ALMS and MAINTAIN trials on the management of lupus nephritis. *Nephrol Dial Transplant*. 2013;28:1371-1376.
64. Wilhelmus S, Bajema IM, Bertsias GK, et al. Lupus nephritis management guidelines compared. *Nephrol Dial Transplant*. 2016;31:904-913.
65. Chan TM. Treatment of severe lupus nephritis: the new horizon. *Nat Rev Nephrol*. 2015;11:46-61.
66. Mok CC. Towards new avenues in the management of lupus glomerulonephritis. *Nat Rev Rheumatol*. 2016;12:221-234.
67. Wyatt RJ, Julian BA. IgA nephropathy. *N Engl J Med*. 2013;368:2402-2414.
68. Working Group of the International IgA Nephropathy Network and the Renal Pathology Society, Roberts IS, Cook HT, et al. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. *Kidney Int*. 2009;76:546-556.
69. Lv J, Yang Y, Zhang H, et al. Prediction of outcomes in crescentic IgA nephropathy in a multicenter cohort study. *J Am Soc Nephrol*. 2013;24:2118-2125.
70. Barratt J, Feehally J. Treatment of IgA nephropathy. *Kidney Int*. 2006;69:1934-1938.
71. Vecchio M, Bonerba B, Palmer SC, et al. Immunosuppressive agents for treating IgA nephropathy. *Cochrane Database Syst Rev*. 2015;(8):CD003965.
72. Rauen T, Eitner F, Fitzner C, et al. Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. *N Engl J Med*. 2015;373:2225-2236.
73. Eison TM, Ault BH, Jones DP, et al. Post-streptococcal acute glomerulonephritis in children: clinical features and pathogenesis. *Pediatr Nephrol*. 2011;26:165-180.
74. Walters MD, Savage CO, Dillon MJ, et al. Antineutrophil cytoplasm antibody in crescentic glomerulonephritis. *Arch Dis Child*. 1988;63:814-817.