CHAPTER 126

Pulmonary-Renal Syndrome

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OBJECTIVES

This chapter will:

1. Define the range of conditions causing immune-mediated alveolar and glomerular injury resulting in acute pulmonary complications, especially hemorrhage and acute kidney injury.
2. Explore the immunopathogenesis and clinical features of pulmonary-renal syndrome.
3. Describe relevant diagnostic techniques.
4. Discuss treatment in the context of recent evidence.

Acute kidney injury and respiratory failure are common problems affecting patients in the intensive care setting. This chapter discusses systemic conditions that affect the lung and kidney simultaneously, with a focus on immune-mediated diseases. The eponymous term *Goodpasture syndrome* sometimes is used to describe clinical presentations of disease that cause both acute pulmonary, parenchymal, immune-mediated inflammation and acute proliferative glomerulonephritis. By contrast, the term *Goodpasture disease* is used to refer to pulmonary hemorrhage and crescentic glomerulonephritis, specifically associated with circulating anti–glomerular basement membrane (anti–GBM) antibodies. For the purposes of this chapter, the term *pulmonary-renal syndrome* is used preferentially instead of *Goodpasture syndrome.*

Small vessel vasculitis encompasses many pathologies that may be seen as pulmonary-renal syndrome[1]:

1. Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV)
   a. Granulomatous polyangiitis (GPA, previously known as Wegener granulomatosis)
   b. Microscopic polyangiitis (MPA)
   c. Eosinophilic granulomatous polyangiitis (EGPA, also known as Churg-Strauss syndrome)
2. Anti–GBM disease, also known as Goodpasture disease
3. Immune complex–mediated
   a. Anti–GBM disease (Goodpasture disease)
   b. Cryoglobulinemic vasculitis
   c. IgA vasculitis (IgAV, also known as Henoch-Schönlein purpura)
   d. Hypocomplementemic urticarial vasculitis (also known as anti-C1q vasculitis)

IMMUNOPATHOGENESIS OF IMMUNE-MEDIATED PULMONARY-RENAL SYNDROMES

Pulmonary-renal syndrome is typically the result of immune-mediated disease. Rapid access to diagnosis is essential because severe cases may result in fatal pulmonary hemorrhage and oliguric kidney failure, and cases of all severities are potentially reversible with early recognition and aggressive management. The pathogenesis of immune-mediated pulmonary-renal syndrome is complex and involves either autoantibody deposition or local recognition of autoantigen peptides by autoimmune effector T cells. Tissue damage results from small vessel inflammation triggered by these humoral and cellular mechanisms in addition to their downstream activation of the complement pathway, leukocyte recruitment, and subsequent release of soluble tissue-damaging mediators, including enzymes, reactive oxygen species, arachidonic acid–derived products, cytokines, and chemokines. This cascade of immune activation results in local inflammation, tissue injury, increased capillary permeability, and loss of affected tissue structure and function. In the lung and kidney this results in necrosis, hemorrhage, and loss of effective glomerular filtration and pulmonary gas exchange, causing the clinical syndromes of respiratory failure and oliguric kidney failure.

ANTINEUTROPHIL CYTOPLASMIC ANTIBODY–ASSOCIATED VASCULITIS

AAV is an autoimmune-mediated, necrotizing, small vessel vasculitis targeting arterioles, venules, and capillaries. Such small vessel necrosis affects glomerular filtration in the kidney and gas exchange in the lung. ANCAs are likely to be pathogenic and result from autoimmunity to leukocyte lysosomal enzymes. The two major target autoantigens in AAV are myeloperoxidase (MPO)[2] and proteinase 3 (PR3).[3] Although ANCAs are likely to be pathogenic, the affected tissues frequently are injured without the local deposition of ANCA. In vitro studies demonstrate that MPO and PR3 are expressed in neutrophils, and ANCA can activate these neutrophils, resulting in degranulation, release of reactive oxygen species, and increased neutrophil adhesion to endothelial cells.[4–6] It is likely that ANCAs bind their target autoantigens in response to a trigger such as sepsis, which induces a translocation of PR3 and/or MPO to the neutrophil cell membrane.[7] As neutrophils circulate freely, the impact of AAV is systemic. Those neutrophils expressing PR3 or MPO that are bound by ANCA become localized to the small vessels of glomeruli, pulmonary endothelium, and perineural microcirculation,[8] acting as local targets for autoimmune effector T cells and leading to further recruitment of macrophages and neutrophils. In each location affected by ANCA-bound neutrophils, disease-specific manifestations arise.

In the kidney, inflammation induces acute proliferative, focal and segmental, necrotizing, crescentic glomerulonephritis with little antibody deposition, hence the term "pauci-immune crescentic glomerulonephritis." In the lung, interstitial infiltrates and hemorrhage are major features. The inflammation may include granulomas, which are typically a feature of PR3-ANCA autoimmunity in GPA.[9] Pulmonary infiltrates, glomerulonephritis, and/or other organ involvement without the presence of granulomas is present in MPA and typically is associated with MPO-ANCA autoimmunity.[2]

ANTI–GLOMERULAR BASEMENT MEMBRANE DISEASE (GOODPASTURE DISEASE)

Anti–GBM disease is an immune complex–mediated condition affecting the lung and kidney. The autoimmune target in anti–GBM disease is the noncollagenous domain of the alpha-3 chain of type IV collagen.[10] This target antigen is expressed in the glomerular basement membrane and alveolar capillaries. It is a cryptic epitope, and case studies implicate hydrocarbons, infections, cigarette smoking, and lithotripsy[11] in the onset of disease, perhaps through revealing the epitope to the systemic autoimmune process.

In vitro, anti–GBM disease can be induced via development of an immune response to a peptide that is antisense or complementary to the autoantigen.[12] The anti–GBM antibody is directly pathogenic and can induce nephritis in primates,[13] and in the presence of circulating anti–GBM antibody, renal allografts rapidly develop recurrent nephritis.[14] The presence of T cells and macrophages in glomerular lesions suggests cellular immunity also is involved. Histologically, strong linear deposition of IgG is seen in affected kidney and lung biopsy specimens. Interestingly, one third of patients with anti–GBM disease have concurrent circulating ANCAs.[15] Class II major histocompatibility complex (MHC), in particular HLA-DR2, is associated with anti–GBM disease. Specifically, HLA-DRB1*1501 and 1502 alleles confer increased susceptibility, whereas DRB1*07 and 01 confer protection.[16]

IMMUNE COMPLEX–MEDIATED PULMONARY-RENAL SYNDROME

The best-described immune complex–mediated cause of pulmonary-renal syndrome is systemic lupus erythematosus (SLE). Although pulmonary involvement is uncommon, it may occur and can present as pulmonary hemorrhage. Consistent with all manifestations of SLE, the target autoantigens are multiple and typically include antinuclear antigens (ANA) and anti–double-stranded DNA (anti-dsDNA). SLE-induced immune complex deposition in the kidneys and lungs has a characteristic pattern of injury with granular deposition of multiple subclasses of immunoglobulin in the affected organs. SLE-related, or lupus, nephritis may be divided into six different histopathologic patterns or classes, according to the Renal Pathology Society/International Society of Nephrology (RPS/ISN) classification system. Of these, class IV diffuse proliferative glomerulonephritis is associated most commonly with pulmonary disease and portends the worst prognosis.

Other forms of crescentic glomerulonephritis, such as mesangiocapillary glomerulonephritis, IgAV,[17] inflammatory myopathies, and idiopathic cryoglobulinemia[18] are likely to be immune-mediated and also can occur as pulmonary-renal syndrome.

Immune complex deposition also may be associated with several non–immune-mediated causes of rapidly progressive glomerulonephritis, which simultaneously can involve the lung. These include subacute bacterial endocarditis, in which host immunity to persistent intravascular microbiologic

antigens causes immune complex–mediated vasculitis,[19] as well as postinfectious glomerulonephritis[20] and hepatitis C–induced cryoglobulinemia.[21]

DIAGNOSTIC APPROACH TO PULMONARY-RENAL SYNDROME

The diagnosis of pulmonary-renal syndrome requires the presence of acute kidney injury resulting from glomerulonephritis, with or without pulmonary hemorrhage. Patients may present with a nonspecific inflammatory prodrome; rash; ear, nose, and throat symptoms; features of kidney failure; and respiratory complaints, or fulminant organ failure (Fig. 126.1). Because pulmonary-renal syndrome is typically a manifestation of a systemic immune-mediated process, features such as skin rash, serositis, neurologic involvement, mononeuritis multiplex, and gastrointestinal symptoms should be sought on history taking and clinical examination.

Glomerulonephritis in pulmonary-renal syndrome is associated with an active urinary sediment, which can be detected at the bedside via urine analysis demonstrating hematuria and proteinuria. Urine microscopy may confirm the glomerular origin of hematuria by the presence of dysmorphic red blood cells. Red cell casts on microscopy are suggestive of heavy glomerular bleeding and glomerular necrosis. The presentation of pulmonary hemorrhage ranges from clinical silence to severe respiratory failure. Symptoms may include dyspnea, cough, and chest pain, whereas signs such as overt hemoptysis or rusty-colored sputum are often less prominent. Chest x-ray may demonstrate diffuse alveolar shadowing. Diagnostic features of diffuse alveolar hemorrhage on CT include widespread lobular ground-glass opacities with areas of consolidation. Other radiologic changes such as cavitating lesions and pleural effusions suggest specific causes, such as GPA or SLE. Sputum microscopy may demonstrate hemosiderin-laden macrophages or frank blood. Pulmonary hemorrhage is associated with a transient and reversible increase in the diffusing capacity of the lungs for carbon monoxide (DLCO), resulting from increased uptake by extravascular blood, and is of particular value when monitoring for disease relapse.[22]

Serology is a key factor in the diagnosis of pulmonary-renal syndrome because the presence of antibodies may suggest a diagnosis of AAV, anti–GBM disease, or other autoimmune diseases, such as SLE. ANCA typically are detected by indirect immunofluorescence of ethanol-fixed neutrophils and using ELISA-based assays. A cytoplasmic pattern of staining (cANCA) on indirect immunofluorescence most commonly is associated with anti-PR3 antibodies by ELISA, whereas perinuclear staining (pANCA) is associated more commonly with the presence of anti-MPO antibodies. ELISA assays for anti–GBM antibodies are also available and are highly sensitive and specific for anti–GBM disease. Interestingly, one third of patients with anti–GBM disease have concurrently positive ANCA, and these dual-positive patients have a significantly greater mortality rate than those with ANCA alone.[23,24] Additional relevant serologic testing may include ANA, anti-dsDNA, cryoglobulins, complements, hepatitis serology, rheumatoid factor, anticyclic citrullinated peptide (anti-CCP), and serum protein immunoelectrophoresis. Urgent kidney biopsy is indicated in the presence of acute kidney injury and an active urinary sediment, with or without evidence of pulmonary hemorrhage. Histopathology not only establishes the diagnosis but also provides information regarding disease activity, prognosis, and comorbid conditions, all of which may influence therapeutic options. Despite this, in anti–GBM disease, a recent retrospective review of patients found that oliguria and age were the

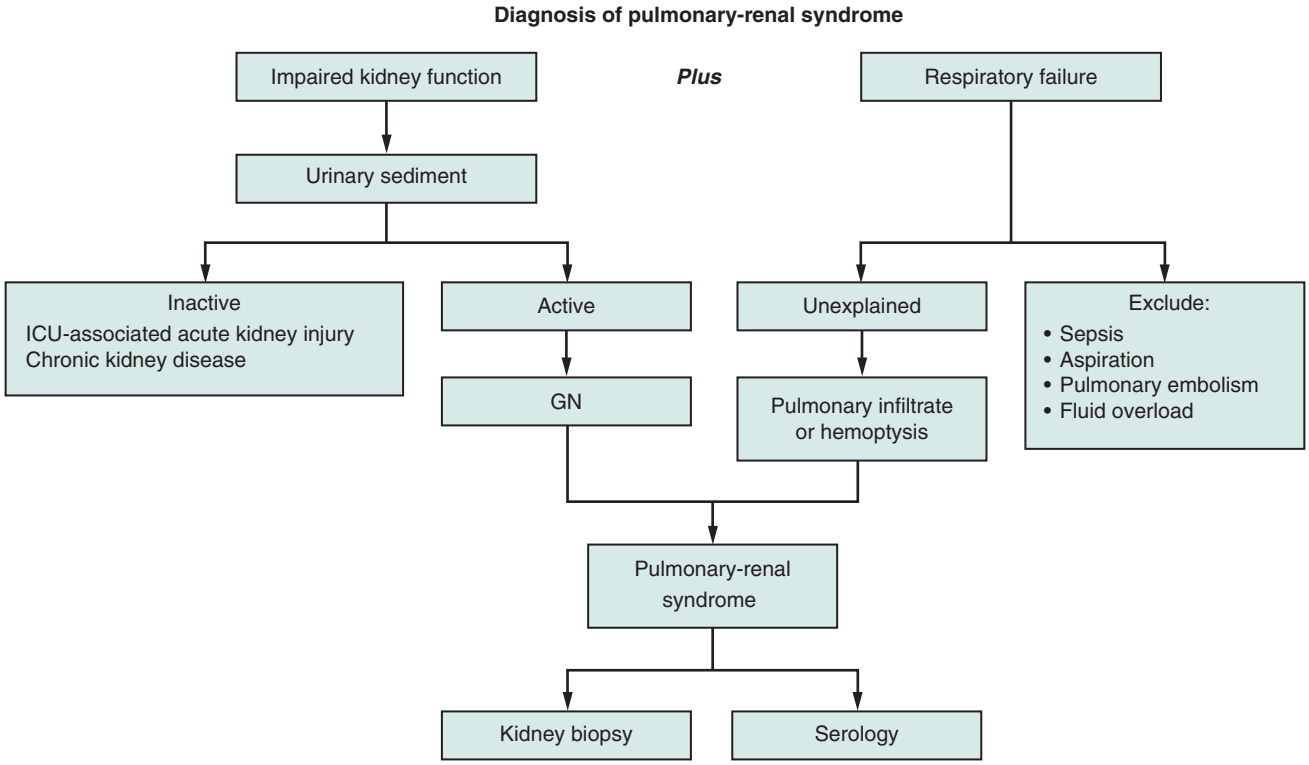

FIGURE 126.1 Diagnosis of Pulmonary-Renal Syndrome.

greatest determinants of survival, and the presence of crescents and chronic histopathology changes added little in determining need for chronic dialysis.[23,24]

Open or transbronchial lung biopsy also can be performed to determine the cause of pulmonary hemorrhage and confirm the diagnosis of vasculitis.[22] Open biopsy has a greater diagnostic yield than transbronchial biopsy and is of most benefit when the result of a kidney biopsy is inconsistent with the clinical and/or serologic picture. Additional histopathology or immunopathology of skin and mucosal samples may be of benefit in some cases such as GPA.

NONIMMUNE CAUSES OF PULMONARY DISEASE IN PATIENTS WITH RENAL DISEASE

Pulmonary complications are common in patients with renal impairment and in the intensive care population. Despite this, perhaps only one third of patients with pulmonary hemorrhage have an immune-mediated cause.[24,25] Common nonimmune causes may include pulmonary edema, pneumonia, aspiration pneumonitis, and pulmonary embolism. In addition, kidney failure may be associated with pericardial and pleural effusions. Nevertheless, unexplained pulmonary infiltrates should be evaluated promptly for the presence of an immune-mediated process using urine analysis, serology, and tissue histopathology to guide appropriate management.

PRINCIPLE DISEASES CAUSING PULMONARY-RENAL SYNDROME: CLINICAL FEATURES AND MANAGEMENT

Patients with pulmonary-renal syndrome often have aggressive, immune-mediated, vascular inflammation and necrosis, causing tissue damage that also potentially may respond to immunosuppressant therapy. Those conditions with the greatest evidence in support of immune suppression include anti–GBM disease, AAV, and lupus nephritis. Other causes with immune dysregulatory mechanisms may respond to immune suppressive therapies; however, the evidence to support this is not as robust.

Anti–glomerular Basement Membrane Disease

Clinical Features

Anti–GBM disease is a small-vessel vasculitis mediated by autoantibody production directed against the noncollagenous domain of the alpha-3 chain of type IV collagen. This antigen is expressed in the alveolar and glomerular basement membranes as well as the testis and choroid plexus. Anti–GBM disease is rare, reported to affect 0.5 to 1 person/million/year. The age distribution is bimodal, peaking in the third and seventh decades. In some studies, males are affected more commonly; however, this is inconsistent as are studies of racial bias.

Kidney manifestations of anti–GBM disease include microscopic hematuria and oliguric acute kidney injury, consistent with rapidly progressive glomerulonephritis (RPGN), whereas the pulmonary presentation may vary from dyspnea and cough to overt hemoptysis. Associated clinical features such as fever and malaise may precede the renal and pulmonary symptoms by weeks to months, whereas isolated pulmonary involvement is rare. Diagnosis is dependent upon serologic presence of anti–GBM antibody and/or tissue biopsy confirming the typically linear deposition of IgG along the glomerular basement membrane, commonly in the presence of cellular glomerular crescents. The titer of circulating anti–GBM correlates with disease severity and prognosis in renal but not pulmonary disease.[23,26,27] Up to one third of patients with anti–GBM disease have concurrent ANCA (particularly MPO-ANCA), and this is associated typically with a poorer prognosis than patients who have ANCA alone. Left untreated, anti–GBM disease has a poor prognosis and high mortality rate.[28]

Treatment

Early diagnosis and treatment is essential in the management of anti–GBM disease because it carries the greatest morbidity and mortality of the pulmonary-renal syndromes. Currently accepted standard therapy for anti–GBM disease comprises high-dose glucocorticoids, cyclophosphamide, and plasma exchange. The rationale behind these therapies is directed at removal and inhibition of the pathogenic anti–GBM antibody. Glucocorticoids reduce the toxic complications of activated neutrophils, plasma exchange removes circulating anti–GBM antibody, and cyclophosphamide reduces antibody production. Case reports suggest that rituximab may be useful in cases of refractory anti–GBM disease.[29] The largest and best-documented experience in anti–GBM disease comes from the Hammersmith group,[11,30,31] using high-dose prednisolone (1 mg/kg/day tapered over 6 months), oral cyclophosphamide (2 mg/kg/day) for 2 to 3 months, and daily plasma exchange (60 mL/kg with albumin or fresh frozen plasma if bleeding is a risk) for 14 days or until anti–GBM antibody is no longer detectable. In one small randomized trial, the addition of plasma exchange to prednisolone and cyclophosphamide increased the proportion of patients with retained renal function from 33% to 75%.[32] Histologically, those who require dialysis at diagnosis are likely to have kidney biopsies demonstrating near 100% crescent formation and interstitial damage. This group typically remains dialysis-dependent despite therapy (7% compared with 90%).[33] Kidney biopsy is therefore essential to guide the amount of immunosuppressive therapy in anti–GBM disease. Importantly, pulmonary presentations of anti–GBM disease respond well to plasma exchange, cyclophosphamide, and prednisolone. Should delayed pulmonary complications arise, aggressive immunosuppression should be initiated regardless of kidney disease prognosis.[34] Relapsed anti–GBM disease is uncommon but treatable,[33] although circulating antibody can be self-limited in those who are left untreated. Kidney transplantation is performed in those with anti–GBM disease who demonstrate absence of circulating antibody for extended periods.

ANTINEUTROPHIL CYTOPLASMIC ANTIBODY–ASSOCIATED VASCULITIS

Clinical Features

AAV is the most common cause of pulmonary-renal syndrome.[35–38] The presentation of patients with AAV varies with the organs affected and can include mononeuritis

multiplex, leukocytoclastic vasculitis, gut ischemia, pulmonary hemorrhage, and RPGN. The histologic features of AAV include crescent formation, glomerular necrosis, and vasculitis of the small and medium-sized vessels of the kidney. AAV can be categorized further as GPA, MPA, or EGPA. Most cases of GPA are associated with PR3-ANCA, whereas most cases of MPA are associated with MPO-ANCA, as are most cases of EGPA. Around 10% of patients with pauci-immune crescentic glomerulonephritis are ANCA-negative. Pulmonary hemorrhage is associated with a poorer prognosis than renal-limited AAV and is present in 42%, 29%, and 3% of patients with GPA, MPA, and EGPA, respectively.[39,40]

GPA is differentiated by symptoms affecting the upper respiratory tract such as sinusitis, subglottic stenosis, otitis media, and nasal congestion. The presence of necrotizing granulomas on tissue biopsy in association with PR3-ANCA confirms the diagnosis of GPA. MPA is characterized by necrotizing, small vessel inflammation, pauci-immune glomerulonephritis without granuloma formation. EGPA is rare, and clinical features include the triad of asthma, eosinophilia, and the presence of eosinophils and granulomas on tissue biopsy.

Treatment

Aggressive induction therapy is indicated in those with pulmonary hemorrhage and/or acute kidney injury. Therapy with cyclophosphamide and corticosteroids is effective and leads to a complete remission rate of 75% to 85%.[41–43] More recently, B cell depletion with rituximab (anti-CD20 chimeric monoclonal antibody) has been compared with standard therapy for inducing remission in those with severe AAV. In a randomized, double-blind, double-dummy, noninferiority trial comparing rituximab (375 mg/m^2/week × 4) corticosteroids with oral cyclophosphamide-azathioprine (CYC-AZA) corticosteroids, those who received rituximab had complete remission rates at 6, 12, and 18 months of 64%, 48%, and 39%, respectively, compared with 53%, 39%, and 33%.[44] Rituximab was noninferior, but not superior, to CYC-AZA at 6 and 12 months. However, at 18 months, rituximab was no longer noninferior, likely because of reconstitution of the B cell population. Most important, the use of rituximab was not associated with increased adverse events. These findings were similar to those in larger open-label trials RITUXVAS[45] and RAVE.[46] Treatment toxicity is an important determinant of therapy choice. Cyclophosphamide toxicity may include leukopenia, hemorrhagic cystitis, bladder cancer, infertility, and opportunistic infections, all of which may limit its utility in younger patients and in patients with relapsed disease. As a minimum standard of care, those receiving cyclophosphamide should receive maintenance hydration, and mercaptoethane sulfonate (Mesna) and trimethoprim-sulfamethoxazole to prevent hemorrhagic cystitis and *Pneumocystis jiroveci* pneumonia, respectively. Strategies that reduce cyclophosphamide exposure include intravenous administration, the use of alternative induction agents (such as rituximab), and early conversion to maintenance immunosuppression. Pulse intravenous cyclophosphamide has equivalent efficacy to daily oral therapy in terms of survival and remission induction; however, pulse therapy results in approximately 50% lower, cumulative cyclophosphamide dose.[47] Rituximab side effects include infusion reactions, anaphylaxis, opportunistic infections, such as reactivation of tuberculosis, and progressive multifocal leukoencephalopathy. Corticosteroid toxicities are well defined.

Most authors recommend the use of plasma exchange (60 mL/kg) in patients with severe AAV with pulmonary hemorrhage, dialysis-dependent kidney failure, or concurrent anti–GBM antibody-positive disease.[48] Dhaun et al.[49] conducted a retrospective review of 104 patients who presented with creatinine of more than 500 μmol/L, pulmonary hemorrhage or more than 30% renal necrotizing lesions and were treated with either rituximab or cyclophosphamide induction, with or without plasma exchange. Those who received plasma exchange demonstrated more rapid induction of remission and earlier weaning of steroids but with no difference in the rate of relapsed disease.[49] Patients who are dialysis-dependent at presentation likely derive the greatest benefit from receiving plasma exchange.

Despite high rates of complete remission in the first 18 months of therapy, relapse remains common, affecting 30% to 50% of those treated with a cyclophosphamide-based regimen[31,44] and 32% of those receiving rituximab-based induction.[44] Consequently, maintenance therapy is required after induction of remission in an attempt to reduce the risk of relapse. Relapse risk predictably is increased in the presence of high titers of ANCA as well as following reconstitution of the B cell population after rituximab therapy.[44,46,50,51] Maintenance therapy options including methotrexate, etanercept, cyclophosphamide, azathioprine, and rituximab have been examined. Neither methotrexate nor etanercept provide additional benefit,[52,53] and there is an increased risk of harm related to kidney function in those taking methotrexate and solid organ cancer in trials of etanercept.[53] The CYCAZAREM study examined 155 patients who were randomized to maintenance therapy with either azathioprine or cyclophosphamide and found that there was no difference in the rate of relapse.[54] More recently, azathioprine was compared with rituximab maintenance therapy in patients who received cyclophosphamide-corticosteroid induction.[55] The rituximab group received 500 mg on days 0 and 14, and at 6, 12, and 18 months, whereas the azathioprine group received daily doses for 22 months. After 28 months' follow-up, 29% of those on azathioprine relapsed compared with 5% of those on rituximab without an increase in adverse events.[55]AAV has a poor prognosis and, if left untreated, has an 80% mortality within 1 year. Cyclophosphamide-based induction therapy results in improved 5-year survival, whereas long-term data for rituximab are still awaited. Relapse is most common in those with pulmonary involvement, PR3-ANCA, and higher ANCA titres.[42,44] End-stage kidney disease occurs in around one quarter of patients, especially those with severe biopsy changes and kidney failure at diagnosis.

Key Points

1. There are three main groups of disorders causing immune-mediated, pulmonary-renal syndrome, including AAV, anti–glomerular basement membrane disease, and immune complex–mediated diseases (including systemic lupus erythematosus and cryoglobulinemic vasculitis).
2. Diagnosis of the cause of pulmonary-renal syndrome requires a comprehensive clinical history and examination, urinary investigations including urine analysis and microscopy, appropriate serologic tests, and histopathology, typically by urgent kidney biopsy.

3. In patients with ANCA-associated vasculitis, rituximab has been shown to be noninferior to induction/maintenance therapy with cyclophosphamide-azathioprine, for at least 12 months after treatment.
4. Plasma exchange is recommended for most patients with pulmonary-renal syndrome who present with pulmonary hemorrhage and severe kidney failure (creatinine > 500 μmol/L) or concurrent anti–GBM antibody-positive disease.

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

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