# Pulmonary renal syndrome: An update for the intensivist

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**Abstract: Objectives**: To provide the intensivist with an overview of pulmonary renal syndrome focusing on its pathogenesis and treatment innovations. **Data Sources:** Medline databases (PubMed, Medscape, ScienceDirect. EMF-Portal) and all materials available in the Internet from 2006 to 2016. **Study Selection:** The initial search presented 170 articles of which 44 met the inclusion criteria. **Data Extraction:** If the studies did not fulfill the inclusion criteria, they were excluded. Study quality assessment included whether ethical approval was gained, eligibility criteria specified, appropriate controls, adequate information and defined assessment measures. **Data Synthesis:** Comparisons were made by structured review with the results tabulated. **Findings:** Pulmonary-renal syndrome is defined as the combination of diffuse alveolar haemorrhage and glomerulonephritis. The pulmonary lesion in the majority of cases of pulmonary-renal syndrome is small-vessel vasculitis, characterized by a destructive inflammatory process that involved arterioles, venules and alveolar capillaries. The renal pathology in the majority of cases of pulmonary-renal syndrome is a form of focal proliferative glomerulonephritis. The term Goodpasture's syndrome is used for the clinical entity of diffuse alveolar haemorrhage and rapidly progressive glomerulonephritis associated with anti-glomerular basement membrane antibodies. Syndrome is extremekly rare. Human anti-GBM antibodies belong mostly to the IgG class and react with a limited number of epitopes on the non-collageneous domain of the α3 chain of type IV collagen (NC1 α3 IV), a molecule expressed in the basement membranes of renal glomerulus, renal tubule, alveoli, choroids plexus, retinal capillaries and Bruchs's membrane. Circulating ANCA autoantibodies are detected in the majority of patients presenting with pulmonary-renal syndrome. ANCA-negative systemic vasculitis is very rare. Porpylthiouracil and hydralazine and ANCA are detected in 20% of patients receiving propylthiouracil, but only a minority of these patients develop clinical manifestations of systemic vasculitis including pulmonary-renal syndrome. The most frequent diagnoses in patients with pulmonary-renal syndrome admitted to the ICU are perinuclear ANCA vasculitis, followed by cytoplasmic ANCA vasculitis, Goodpasture's syndrome, systemic lupus erythematosus and catastrophic APS. The possibility of a pulmonary-renal syndrome should be considered in those patients with bilateral pulmonary infiltrates. Haemoptysis is the most common clinical manifestation of diffuse alveolar haemorrhage. Chest roentgenograms and computerized tomography scanning are used to depict diffuse alveolar haemorrhage. **Conclusion:** Appropriate management of such patients includes early and accurate diagnosis, exclusion of infection, close monitoring and specialized. Maintenance therapy includes low-dodse corticosteroids with cytotoxic agents. Renal transplantation remains the only alternative for patients with pulmonary renal syndrome who developed end-stage renal disease.
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**Key words:** pulmonary renal syndrome**.**

## 1. Introduction

Pulmonary-renal syndromes are defined by the combination of diffuse alveolar haemorrhage and glomerulonephritis. The three most common causes of pulmonary renal syndrome presenting to the respiratory physician are ANCA-positive small vessel vasculitis, anti-glomerular basement membrane (anti-GBM) disease (Goodpasture's disease) and Systemic Lupus Erythematosus (SLE)[(1)].

These disorders exhibit considerable heterogeneity in clinical presentation both in severity and prognosis. Early recognition depends on a high index of clinical suspicion combined with a full assessment of the clinical picture, available serology, radiology and histology, and exclusion of alternative diagnoses. Whilst a frequent presentation of pulmonary renal syndrome is a patient presenting with breathlessness and fever with pulmonary infiltrates on a chest radiograph, a significant number of patients deteriorate rapidly and present with life threatening respiratory and/or renal failure requiring admission to ICU. Initially the diagnosis may not be clear-cut. Clinically apparent haemoptysis secondary to diffuse alveolar haemorrhage (DAH) occurs in about 55% of cases[(2)].

The management of pulmonary-renal syndromes centres on immunosuppression therapy supportive care. Therapy is subdivided into the induction-remission

phase and the maintenance phase. It is uncommon that the intensivist treats patients with pulmonary-renal syndrome in remission, unless drug toxicity and infectious immunosuppressive treatment complications ensue[3].

The aim of the present article is to provide the intensivist with an overview of pulmonary renal syndrome focusing on its pathogenesis and treatment innovations.

## 2. Materials and Methods

**Search Strategy:**

We reviewed papers on the pulmonary renal syndrome from Medline databases which are (Pub Med, Medscape, ScienceDirect) and also materials available in the Internet. We used pulmonary renal syndrome ey as searching terms. In addition, we examined references from the specialist databases EMF-Portal (http://www.emf-portal.de), reference lists in relevant publications and published reports. The search was performed in the electronic databases from 2006 to 2016.

**Study Selection**:

All the studies were independently assessed for inclusion. They were included if they fulfilled the following criteria:

Inclusion criteria of the published studies:

-Published in English language.

-Published in peer-reviewed journals.

-If a study had several publications on certain aspects we used the latest publication giving the most relevant data.

**Data Extraction:**

If the studies did not fulfill the above criteria, they were excluded such as reports without peer-review, not within national research programme, letters/comments/editorials/news and studies not focused on pulmonary renal syndrome.

**Quality Assessment:**

The quality of all the studies was assessed. Important factors included, study design, attainment of ethical approval, evidence of a power calculation, specified eligibility criteria, appropriate controls, adequate information and specified assessment measures. It was expected that confounding factors would be reported and controlled for and appropriate data analysis made in addition to an explanation of missing data.

**Data Synthesis:**

A structured systematic review was performed with the results tabulated.

## Results

The term *nonspecific PRS* refers to pulmonary edema, pulmonary thromboembolism, or pulmonary infection, complicating the course of glomerular disease. Nonspecific PRS also refers to glomerular disease after pulmonary disease, which is mostly an infection. The term *specific PRS* denotes simultaneous or continuous pulmonary hemorrhage and glomerulonephritis. Therefore, *specific PRS* implies a much more restricted range of possibilities, and the most frequent is the SVV (Table 1)[4].

Patients with pulmonary–renal syndrome may require admission to the ICU either because of the disease itself or because of a complication of the treatment. The most frequent diagnoses in patients with pulmonary–renal syndrome admitted to the ICU are perinuclear ANCA vasculitis, followed by cytoplasmic ANCA vasculitis, Goodpasture's syndrome, systemic lupus erythematosus and catastrophic APS (Figure 1)[5].

Although the lung is the most common organ involved in WG, pulmonary hemorrhage is uncommon. In patients with WG and PRS, the pulmonary hemorrhage is often the initial presentation of this disease. The authors also described an autopsy finding of a 46-yearold man with WG and fulminant PRS (Figures 2-5). The majority of patients with alveolar hemorrhage present with rapidly progressive glomerulonephritis and acute renal failure. Therefore, patients with PRS tend to have a fulminant variant of WG. Microscopic polyangiitis is a systemic SVV primarily associated with necrotizing glomerulonephritis and pulmonary capillaritis[6].

**Table (1):** Classification of the pulmonary-renal syndrome (pulmonary hemorrhage and glomerulonephritis)

| |
|---|
| Goodpasture's syndrome or antiglomerular basement membranes |
| Immune complex–induced |
| Systemic lupus erythematosus |
| Rheumatoid arthritis |
| Systemic sclerosis |
| Antineutrophil cytoplasmic antibody–associated vasculitis |
| Microscopic polyangiitis |
| Wegener's granulomatosis |
| Churg-Strauss syndrome |
| Drug-induced vasculitis |
| Pauci-immune necrotizing and crescentic glomerulonephritis |
| Non–antineutrophil cytoplasmic antibody–associated vasculitis |
| Henoch-Schönlein purpura |
| Essential cryoglobulinemia |
| Behçet's disease |
| Immunoglobulin A nephropathy |
| Antiphospholipid syndrome |
| Others |

Plain chest radiography or computed tomography of the chest may reveal a distribution of infiltrates from perihilar shadowing tending towards the lower zones to frank consolidation mimicking an ARDS appearance (Figures 6 and 7). In 25% of cases, chest radiography may be normal in which event pulmonary thromboembolic disease should be considered[3].

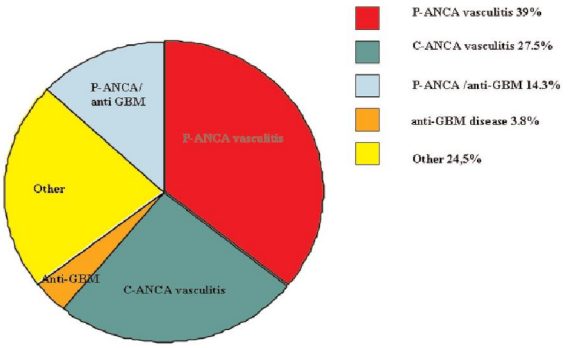


**Figure (1):** Relative frequencies of conditions contributing to pulmonary–renal syndrome in the intensive care unit. Relative frequencies of conditions contributing to pulmonary–renal syndrome in the intensive care unit based on mean values from data on patients' characteristics. Perinuclear antineutrophil cytoplasmic antibodies (P-ANCA) vasculitis is the most frequent cause of pulmonary–renal syndrome for patients admitted to the intensive care unit. 'Other' includes systemic lupus erythematosus, catastrophic antiphospholipid syndrome, polyarteritis nodosa, HIV-related vasculitis, cryoglobulinaemic vasculitis and Henoch–Schönlein purpura. C-ANCA, cytoplasmic antineutrophil cytoplasmic antibodies; anti-GBM, antiglomerular basement membrane **(Cruz *et al.*, 2003)**.

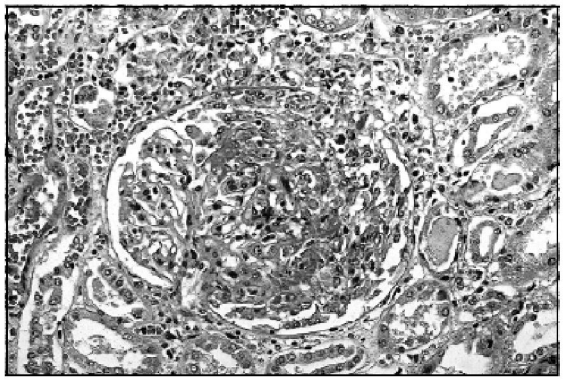

**Figure (2):** Necrotizing and crescentic glomerulonephritis in a patient with fulminant Wegener's granulomatosis.

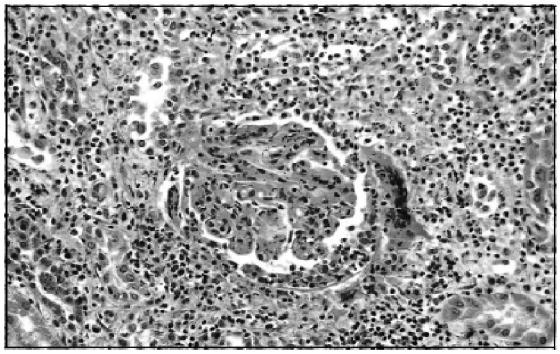

**Figure (3):** Glomerulonephritis with Bowman's capsule rupture and interstitial infiltration of giant cells

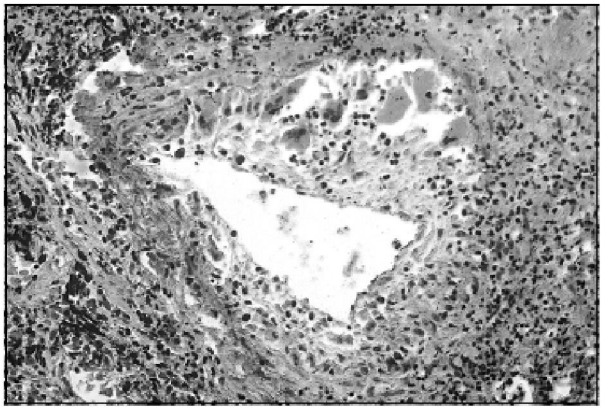

**Figure (4):** Pulmonary arteritis with giant cell infiltration

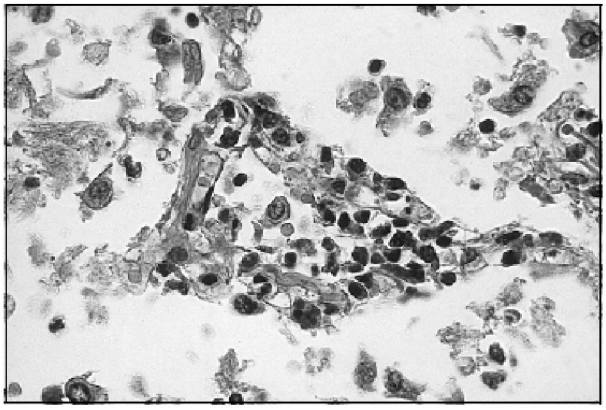

**Figure (5):** Pulmonary capillaritis

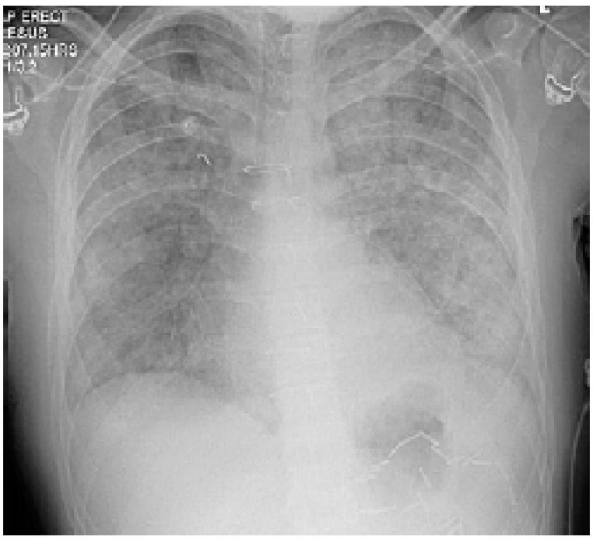

**Figure (6):** Chest radiograph showing acute pulmonary haemorrhage

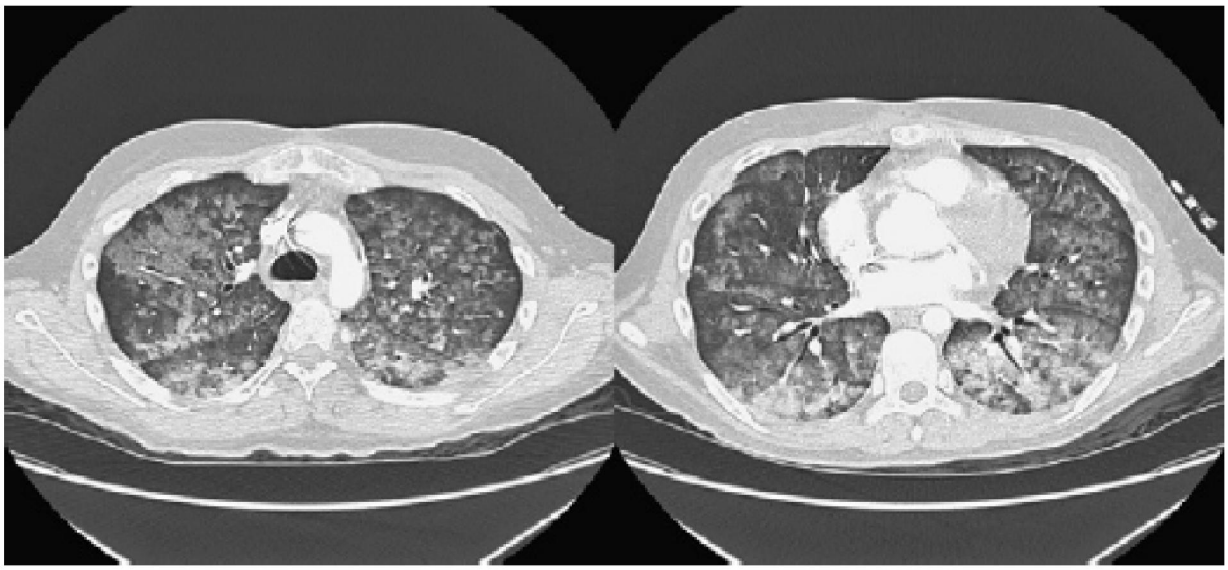

**Figure (7):** CT chest (2 slices) showing diffuse pulmonary haemorrhage

**4. Discussion**

**Niles *et al.*** [7] suggested that 60% to 70% of cases with PRS are associated with ANCAs, and 20% are associated with anti-GBM antibodies.

**Morita *et al.*** [8] suggested that hydralazine, propylthiouracil, and several other drugs may cause some cases of ANCA-positive vasculitis. The majority of these cases have been associated with anti-MPO antibodies. Penicillamine, propylthiouracil, and cocaine have been associated with PRS.

**Yashiro *et al.*** [9] supported the hypothesis that asbestos and silica exposition may induce PRS. They described 14 patients with ANCA related (anti-MPO) angiitis or nephritis identified within a 3-year period after the great earthquake of Kobe (Japan), and compared them with 15 patients with the same disease observed from 1990 to 1997 in Kyoto (poorly affected by the earthquake). Severe renal and pulmonary involvement was significantly higher in the Kobe group than in the Kyoto group. The asbestos and silica content after the earthquake produced acute and chronic lung damage with activation and induction of apoptosis from alveolar macrophages, T cells, and neutrophils, which are the main source of MPO. The surface expression of MPO during apoptosis may stimulate the immune response resulting in an amplified release of cytokines, oxygen radicals, lysosomal enzymes, and production of ANCAs (anti-MPO exposure to silica developed p-ANCA-associated vasculitis with pulmonary-renal syndrome (anti-MPO). Two siblings with similar environmental exposure to silica developed p-ANCA–associated vasculitis with PRS (anti-MPO). This is the first report of a family cluster of silica-induced, ANCA-associated systemic vasculitis and PRS with members sharing HLA antigens.

Studying the pathophysiologic role of ANCA *in vivo*, **Brouwer *et al.*** [10] reported an animal model for anti-MPO-associated pauci-immune necrotizing crescentic glomerulonephritis (NCGN). Recently, an animal model for anti-MPO associated pulmonary vasculitis was developed in analogy to the kidney model. In this model, rats were immunized with human MPO, and a single left lung perfusion with a neutrophil lysosomal extract was performed. The lesions were characterized by infiltration of polymorphonuclear leukocytes and monocytes and, in some rats, foci alveolar hemorrhage. **Foucher *et al.*** [11] suggested a pathogenic role of MPO-ANCA in PRS associated vasculitis.

**Salama *et al.*** [12] showed that during acute disease there were increased frequencies of CD4+ T cells reactive with 3 (IV) NC1, which decreased with time. The decrease in autoreactive CD4+ T cell numbers during recovery may be the reason why recurrences are infrequent, and may explain the loss of pathogenic autoantibodies with time, because of the lack of T cell help.

They also supported a key role for 3 (IV) NC1. However, it has been difficult to establish the antigen that is detected by the anti-GBM antibodies. These animal models recognize the 3 (IV) NC1, and T cell involvement in the development of glomerulonephritis suggests that linear peptides are important.

**Luo *et al.*** [13] examined overlapping peptides covering the length of the target domain, and found that none of them would reliably produce glomerulonephritis in an experimental model of GPS. Two peptides produced mild nephritis in a minority of animals; several could provoke a T cell mitogenic response in animals that already had the syndrome. It appears that more than

one antigen is necessary to produce glomerulonephritis, or that the antigen must undergo conformational change or post-translational modification in order to work its effect.

**Carreras *et al.*** [14] reported a 69-year-old patient with Henoch-Schönlein purpura with kidney involvement followed by pulmonary hemorrhage. The presence of an IgA linear pattern on the kidney biopsy specimen and circulating anti-GBM IgA antibodies led to the diagnosis of GPS. In cases of glomerulonephritis with lung involvement, clinicians should not limit the search for anti-GBM IgG.

**Salama *et al.*** [15] described three cases of GPS in which no circulating anti-GBM antibodies were detectable in serum by ELISA or western blotting techniques. The diagnosis of GPS was confirmed by renal biopsy with linear deposition of immunoglobulin along the GBM and crescentic glomerulonephritis.

**Hughson *et al.*** [16] investigated the relationship between alveolar hemorrhages to immune complex deposition in the lungs of six patients with SLE, and correlated the findings with glomerular and vascular disease in the kidneys. They indicated that alveolar hemorrhage in SLE, characterized by bland alveolar wall changes, was pathogenically similar to the lupus microangiopathy of the kidney. Therefore, the pathogenesis of the microvascular injury appears to be related to immune complex deposition and induction of apoptosis.

**Gallagher *et al.*** [17] studied 14 cases retrospectively from a single tertiary center over a 4-year period of follow-up. Thirteen patients had systemic vasculitis, and only one had SLE. Five patients were c-ANCA-positive, and seven patients were p-ANCA-positive; two of the latter patients also were positive for anti-GBM antibodies. Findings confirmed previous suggestions that PRS requiring intensive care treatment has high mortality rates and early survivors have good outcomes in the 1st and 2nd year.

**von Vigier *et al.*** [18] reported 21 pediatric patients with specific or nonspecific PRS. Three children had a systemic vasculitis associated with ANCA (WG, *n*=2; MPA, *n*=1) and two with SLE. They disclosed 52 cases of specific PRS other than SLE—28 cases with WG, 13 with GPS, and 11 Henoch-Schönlein purpura.

**Blanco-Filho *et al.*** [19] described the case of a 10-year-old girl with rapid and progressive loss of renal function and massive lung hemorrhage. The ANCA test with anti-MPO was positive, and the circulating anti-GBM showed an undetermined result.

**Henning *et al.*** [20] described the first three cases of PRS caused by APS. The patients presented dysnea, renal failure, and pulmonary infiltrates on the chest radiograph. Clinical findings, antiphospholipid antibodies, and histologic findings in transbronchial or renal biopsy proved the diagnosis of APS.

**Specks**[2] attested to the efficacy of anti-CD20 chimeric monoclonal antibody therapy in chronic relapsing c-ANCA–associated Wagener's granulomatosis.

**Hiemstra *et al.*** [21] looked at maintenance therapy with methotrexate, leflunomide and MMF have not shown any advantage over azathioprine to date. Biological therapies studied include the TNF-a inhibitor Infliximab and the TNFa receptor protein Etanercept. These along with Rituximab, which is an anti-CD20 antibody that depletes B cells, initially looked promising candidates for remission induction. Both anti-TNF-a agents tested however resulted in unacceptably high infection complication rates. However, **Stone *et al.*** [22] have demonstrated that rituximab is as effective as cyclophosphamide.

**Merrill *et al.*** [23] looked at rituximab as add-on therapy in SLE and have failed to show significant benefit but this is most likely due to poor trial design.

**Conclusion**:

Appropriate management of such patients includes early and accurate diagnosis, exclusion of infection, close monitoring and specialized. Maintenance therapy includes low-dodse corticosteroids with cytotoxic agents. Renal transplantation remains the only alternative for patients with pulmonary renal syndrome who developed end-stage renal disease.

**No Funds**
No Conflict of Interests

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