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REVIEW

Pulmonary-renal syndromes: An update for respiratory physicians

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Summary
Pulmonary-renal syndromes are a group of disorders characterised by necrotising glomerulonephritis and pulmonary haemorrhage. Small vessel systemic vasculitis is the most common cause of pulmonary-renal syndromes presenting to respiratory physicians. Rarer causes include systemic lupus erythematosus and connective tissue diseases though severe pneumonia or cardiac failure may mimic their presentation. Some forms of small vessel vasculitides have a predilection for the pulmonary and renal vascular beds and if left untreated can result in fulminant organ failure. Whilst the aetiology of these syndromes remains unclear, much is known about the disease mechanisms including the pathogenic role of autoantibodies, immune-complex mediated inflammation and microangiopathic *in-situ* thrombosis. Despite established treatments achieving successful remission induction, patient tolerability and side effect profiles have limited their use which has led to searches for more targeted treatments. Consequently newer biological therapies have gained wider acceptance despite little being known about their long term safety and efficacy. The European Vasculitis Study Group (EUVAS) have recently formulated guidelines to provide consensus on diagnosis and management in this area and work to define survival rates in these conditions with longer term follow-up studies is ongoing. This review summarises the current aetiopathogenesis

Abbreviations: ANCA, anti nuclear cytoplasmic antibody; PRS, pulmonary-renal syndromes; GPA, granulomatosis with polyangiitis; CSS, Churg–Strauss syndrome; MPA, Microscopic Polyangiitis; cANCA, cytoplasmic ANCA; pANCA, perinuclear ANCA; PR3, proteinase 3; MPO, myeloperoxidase.

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thought to underlie these complex diseases, the diagnostic definitions and classification criteria currently in use and the evidence base for modern therapies. Though unusual for respiratory specialists to coordinate overall management of these patients, an update on their current management is regarded as important to their practice given the recently changing trends in treatments.

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Introduction

Pulmonary-renal syndromes (PRS) are defined by the combination of diffuse alveolar haemorrhage and glomerulonephritis.[1,2] The three most common causes of PRS 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). The ANCA-positive vasculitides describe three major systemic syndromes namely granulomatosis with polyangiitis (Wegener's) (GPA), Microscopic Polyangiitis (MPA) and Churg—Strauss Syndrome (CSS) which between them have subtle differences in clinical and pathological features. ANCA-negative vasculitic syndromes such as Henoch Schonlein Purpura and IgA nephropathy are rarer but may present in a similar fashion and drug-induced pulmonary-renal syndromes are also well described.[3] Table 1 summarises possible aetiologies. This article aims to review the presentation, diagnosis and treatment of PRS with the aim of arming the general respiratory physician with up to date evidence and research developments in this complex field.

Pathology

The primary pathology in the majority of PRS is inflammation and necrosis of small calibre blood vessels grouped under the term small vessel vasculitides. Alveolar and glomerular inflammation arise via neutrophilic infiltration through vascular endothelium which predominantly affects arterioles, capillaries and venules. Within the lung, disruption and degradation of the pulmonary capillary wall and interstitial matrix results in vessel wall destruction and necrosis. Immune-complex mediated vasculitis can give rise to an isolated necrotic pulmonary capillaritis where damaged red blood cells extravasate directly into alveolar tissue resulting in alveolar haemorrhage.[4]

The predominant renal pathological finding in PRS is necrotising glomerulonephritis.[5] Within this there are multiple pathological variations depending on exact aetiology. Whilst fibrinoid necrosis and *in-situ* microangiopathy are common features, necrotising granulomata consistent with GPA are rarely seen on renal biopsy and direct evidence of small vessel vasculitis is uncommon.[6] Crescent formation signifies extensive glomerular

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Table 1 Causes of pulmonary-renal syndromes.

ANCA-positive vasculitis
— Granulomatosis with polyangiitis (Wegener's)
— Microscopic Polyangiitis
— Churg—Strauss syndrome
Anti-glomerular basement membrane antibodies (Anti-GBM) — Goodpasture's syndrome
Autoimmune connective tissue disease
— Systemic lupus erythematosus
— Polymyositis
— Scleroderma
ANCA-negative vasculitis
— Henoch Schonlein Purpura
— Mixed cryoglobulinaemia
— IgA nephropathy
— Behcet's disease
Drug-induced vasculitis — Hydralazine
— Propylthiouracil
— D-penicillamine
Idiopathic pulmonary-renal syndrome

involvement whereas fibrosis and tubular atrophy are poor prognostic features. Pauci-immune glomerulonephritis implies absence of immune-complex deposition, immunoglobulins or complement within the biopsy sample when examined using both immunoflourescence and electron microscopy. This is a feature of the necrotising vasculitis seen in MPA.

Epidemiology

GPA is a small vessel necrotising vasculitis with an incidence of 10 cases/million with equal male/female preponderance. It occurs predominantly in Caucasian populations and presents between the ages of 40 and 55 years in over 70% of cases.[7] Its prognosis has recently been characterised into a bimodal distribution in mortality with an increased risk of death from infection, vasculitis and renal failure in the first year followed by a second peak 8 years from diagnosis which is so far unexplained.[8] A north-south negative gradient in disease prevalence has been observed across Europe suggesting a latitude-dependant predisposition and there are suggestions this finding is reciprocated in the southern hemisphere.[9—11]. Studies evaluating occupational risk for systemic vasculitis have demonstrated a significant association between farming occupations and silica and solvent exposure (odds ratio 2.2—2.7) creating aetiological overlap with other occupational lung diseases such as hypersensitivity pneumonitis that are commonly encountered by respiratory physicians.[9,12]

MPA also causes a necrotising vasculitis and may be clinically difficult to distinguish from GPA. It has a similar incidence and mean age of onset around 50 years. As with GPA, it is more common in Caucasian populations and in its severest form causes a pauci-immune glomerulonephritis with alveolar haemorrhage.[13] In general pulmonary involvement occurs in 30—50% of cases whereas renal involvement extends to over 95% of cases.

CSS is a rare systemic and pulmonary vasculitis with an incidence of less than 3 cases/million. Though a higher incidence is quoted in asthmatic populations (64 cases/million) this may be due to misdiagnosis.[14] Males are affected twice as commonly as females and onset is in middle-age. It is considered by some to be a three-stage disease comprising the initial development of asthmatic symptoms following which a marked blood and tissue eosinophilia develops. The final stage is a vasculitic phase which can progress to severe respiratory and renal failure. Though the aetiology remains unknown, a possible role of the leukotriene receptor antagonist Montelukast was postulated[15] but this more likely represents a secondary effect of steroid withdrawal unmasking underlying vasculitis.[16,17] The presence of pANCA, present in 30—50% of cases, appears to determine a subgroup of patients predisposed to severe renal disease, pulmonary haemorrhage and central nervous system involvement.[18]

Anti-GBM (Goodpasture's) disease is an even more rare cause of PRS with an annual incidence of 1 case/million. Males are four times more likely to be affected with disease presenting most commonly between 20 and 30 years of age. A second peak in females over 60 appear to be at increased risk of isolated glomerulonephritis.[19] Though smokers are at greater risk of pulmonary haemorrhage, Goodpasture's disease is no more common in smokers than in non-smokers.[20] Familial trends have been proposed due to strong association with the HLA DR15 and DR4 alleles[21] but most cases occur sporadically suggesting an important role of other as yet unknown environmental factors.

SLE presenting as alveolar haemorrhage in the context of lupus nephritis is extremely rare and carries a grave prognosis with mortality figures between 30% and 50% though interestingly these figures do not seem to be affected by the presence or absence of renal failure at presentation.[22—24]

Immunology and pathogenesis

ANCA-positive vasculitides

Anti-neutrophil cytoplasmic antibody (ANCA) is an anti-neutrophil antibody directed against its constituents on a subcellular level. Although there are a large variety of ANCA directed against numerous components of the neutrophil, only two forms of ANCA, specific for proteinase 3 (PR3) and myeloperoxidase (MPO) are thought relevant to small vessel vasculitis. PR3 and MPO are present in the azurophilic primary granules of neutrophils and can be expressed on the cell surface in stimulated polymorphonuclear cells. Binding of ANCA to neutrophil membranes activates the cell leading to the release of lytic enzymes, chemoattractant interleukin-8 and oxygen free radicals. Neutrophils subsequently aggregate on endothelium causing inflammation and damage to the vasculature. The strongest evidence for a pathogenic role of ANCA in vasculitis comes from a case of a newborn child developing

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PRS 48 h following delivery from a mother with active MPO-ANCA MPA via transplacental transfer.[25] Despite this it remains unclear in many diseases whether or not ANCAs are simply playing a bystander role in the inflammatory cascade or directly driving vasculitic inflammation.

Characterisation of the precise stimulus for ANCA production by B cells is the subject of much ongoing research. It is well known that chronic inflammatory disorders such as rheumatoid arthritis, inflammatory bowel disease and autoimmune hepatitis have a strong association with ANCA positivity, particularly MPO.[26] Hypotheses rooted in the theory of molecular mimicry have suggested that chronic infection may act as an immunological trigger by bacterial antigens morphologically imitating neutrophilic peptides leading to ANCA production.[27] *Staphylococcus aureus* colonisation of the nasal cavity is an established risk factor for disease relapse in GPA which is thought to result from CpG repeats within Staphylococcal DNA acting as the antigenic stimulus.[28] Elsewhere within the respiratory field, chronic suppurative lung diseases such as cystic fibrosis and bronchiectasis expose patients to high bacterial burdens for prolonged periods and there is increasing interest in non-classical target ANCA-antigen reactivity which may have a pathogenic role in these diseases. This is perhaps best illustrated by the weak association between bactericidal permeability increasing (BPI)-antigen and pseudomonas colonised cystic fibrosis populations where the presence of BPI-ANCA confers an increased risk of faster decline in lung function and poorer outcomes.[29] Further clarification of the pathogenicity of these autoantigens may be important to improving our understanding of these complex multisystem diseases.

Anti-glomerular basement membrane disease: Goodpasture's syndrome

Goodpasture's disease is an antibody mediated (usually IgG) destruction of the carboxyl terminal of the α-3 chain of Type IV collagen. This takes place via antibody binding to peptides in the non-collagenous domain of this chain which is expressed on numerous vascular beds including renal glomeruli and tubules, pulmonary alveoli and retinal capillaries. Variable manifestation of pulmonary haemorrhage in patients with anti-GBM antibodies may be due to impaired access of the autoantibody to alveolar capillary membranes.[30,31] Thus patients who have sustained prior lung injury through smoking, infection or pneumotoxin inhalation, such as cocaine inhalation, are usually those most at risk of developing pulmonary haemorrhage or 'full-blown' Goodpasture's syndrome.[31,32] Downstream activation of complement and proteases destroy the capillary basement membrane subsequently leading to formation of crescents in the glomerulus and necrosis of pulmonary alveolar walls.

Immune-complex mediated disease

The most common cause of immune-complex mediated PRS is SLE. This is an autoimmune disease characterised by pathogenic autoantibody production to double stranded DNA through cognate interactions between B cells and helper T cells.[33] DNA-anti-DNA immune complexes form within the glomerulus and activate glomerular complement leading to cascade production of damaging inflammatory cytokines and chemoattractants. Persistent inflammation disrupts the regulated production of damaging transforming growth factor-beta (TGF-β) leading to pathogenic extracellular matrix deposition in the renal mesangium.[34]

Essential mixed cryoglobulinaemia (Type II) is another rare cause of PRS related to immune-complex deposition. It is thought to be triggered in most cases by chronic Hepatitis C virus infection.[35] Viral antigen stimulates monoclonal antibody production by B cells leading to an immune-complex mediated vasculitis resulting in a triad of arthralgias, purpura and neurological weakness and in severe cases alveolar haemorrhage. Henoch Schonlein Purpura, though more common in younger age groups, can also cause a pulmonary capillaritis through deposition of IgA immune complexes within alveoli. Drug-induced vasculitides are usually ANCA positive (predominantly MPO) and come about by small molecules forming immune complexes within capillaries of the pulmonary and renal vasculature. Certain drugs may act as haptens meaning they elicit immune responses only when attached to a carrier protein. Common culprits include hydralazine and propylthiouracil,[36] the former of these exhibiting a dose dependant risk.[37]

Patient evaluation and clinical features

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 PRS 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. Similarities exist with presentation of pneumonia or severe cardiac failure with pulmonary oedema but the presence of some of the abnormalities listed in Table 2 should prompt consideration of PRS to the attending physician.

Clinically apparent haemoptysis secondary to diffuse alveolar haemorrhage (DAH) occurs in about 55% of cases.[38] In one-third of cases of DAH however, haemoptysis does not manifest clinically.[39] Haemoptysis is usually of small volume (<200 ml/24 h) and may be accompanied by a low

Table 2 Characteristic clinical findings in PRS.

Purpuric rash
Active urinary sediment on dipstick testing accompanying biochemical renal impairment
Arthralgia
Cerebral ischaemia
Mononeuritis multiplex
Pericarditis/myocarditis
Sinusitis
Fall in Hb levels

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grade fever, breathlessness and cough. Constitutional symptoms of anorexia and weight loss may be present if there has been a protracted disease course. Table 3 outlines other clinicopathological features of the most common disorders.

Acute kidney injury may be apparent from admission serum biochemistry which carries greater diagnostic significance in the presence of an active urinary sediment. Proteinuria is more common than haematuria but when both are present on urinalysis, this is indicative of glomerular membrane damage due to glomerulonephritis. Proteinuria rarely extends to the nephrotic range and an active urinary sediment in the setting of normal renal biochemistry does not exclude renal involvement.[40] Urine microscopy may show red cell casts or red cell dysmorphia.

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 (Figs. 1 and 2). In 25% of cases, chest radiography may be normal in which event pulmonary thromboembolic disease should be considered. Cavitating disease is most common in GPA though diagnostic overlap exists with cavitating pneumonia, mycobacterial or malignant disease which in the acute setting may be difficult to distinguish. Persistence of interstitial shadowing on plain chest radiograph may suggest alveolar fluid accumulation secondary to underlying mitral stenosis, pulmonary veno-occlusive disease or cardiogenic pulmonary oedema. A rare but important cause of DAH is idiopathic pulmonary haemosiderosis which may result in prolonged DAH but renal impairment is not a feature of this disorder.

Blood test abnormalities may include a normochromic, normocytic anaemia with elevation of blood nitrogen urea and creatinine levels. Evidence of haemolysis with fragmented red blood cells on film may suggest underlying thrombotic thrombocytopaenic purpura (TTP). Serum antibody detection of anti-GBM, ANA and/or ANCA is key to diagnostic work-up if a PRS is suspected where the value of a positive result depends chiefly on the pre-test probability of disease. However the level of ANCA titre is not considered part of the diagnostic criteria in systemic vasculitis in the International Consensus Statement of ANCA testing.[41] Whilst the presence of a positive cytoplasmic ANCA (cANCA) (directed against PR3 antigen) correlates with underlying GPA (present in 85% of cases), perinuclear ANCA (pANCA) (directed against MPO) has cross reactivity with a number of other inflammatory and autoimmune conditions, making clinical interpretation more relevant.

Anti-GBM antibodies detected using different immunoassays including immunoperoxidase labelling have a sensitivity of 95–100% with a specificity of 90–100% for Goodpasture's disease.[31] Anti-GBM disease can exist in the absence of anti-GBM circulating antibody though its identification may require testing of patient's serum with positive and negative controls to demonstrate reactivity. Only 35–70% of patients with CSS have a positive cANCA with 10% being positive for PR3. In fact CSS is more often ANCA negative than positive, and where positive, usually it is associated with cANCA or pANCA.

Table 3 Clinicopathological features of the common diffuse alveolar haemorrhage (DAH) syndromes.

	Granulomatosis with polyangiitis (Wegener's)	Microscopic Polyangiitis	Churg–Strauss syndrome	Anti-GBM disease
Renal pathology	Granulomatous inflammation with extensive necrosis rarely accompanied by necrotising vasculitis	Necrotising vasculitis with few or no immune deposits on immunofluorescence (pauci-immune)	Eosinophil-rich granulomatous infiltration. Vasculitis histologically indistinguishable from WG and MPA	Segmental to global fibrinoid necrosis with crescent formation in 90% progressing to fibrous crescents. Linear IgG staining of GBM on immunofluorescence
Clinical features	ENT necrosis/collapse of nasal bridge cartilage Conduction deafness – Eustachian tube damage Orbital scleritis, proptosis	Pleurisy Asthma Haemoptysis	Late onset asthma Sinusitis, rhinitis Eosinophilia GI disturbance – mesenteric eosinophilic infiltration Myositis (Cardiac failure) Skin nodules/purpura	50% present with rapidly progressive glomerulonephritis 50% present with a pulmonary-renal syndrome (Goodpasture's syndrome)
Immunology	PR3 ANCA positive 75–90%	MPO-ANCA positive 45%	MPO-ANCA positive in 35–70%	Anti-GBM antibody positive in 85–90%
Prognosis	Mortality correlated to cANCA titre. High relapse rate	Mortality highest in first year of diagnosis	Multisystem (renal, GI, Cardiac) carries worst prognosis	Serum Creatinine at time of treatment most valuable prognostically

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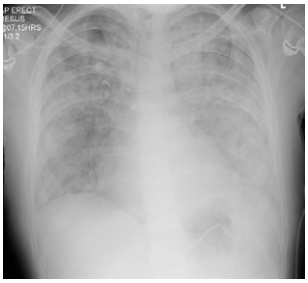

Figure 1 Chest radiograph showing acute pulmonary haemorrhage.

Lung function tests performed within 48 h of symptom onset may show elevation of the gas transfer factor (DLCO). This is significant if raised by greater than 30%. However this investigation requires breath-holding on an air, carbon monoxide and helium mixture for about 10 s. This may not be possible in those with marked dyspnoea.

Flexible bronchoscopy is generally used in the exclusion of infection and confirmation of DAH. Classically serial bronchial washings show increasingly blood stained lavage fluid and cytology may show haemosiderin-laden macrophages adding weight to the diagnosis.

Prior to immunosuppression, confirmation with tissue diagnosis is often advisable and the kidney and lung represent the most accessible biopsy sites. In diffuse pulmonary involvement, thoracoscopic lung biopsy is preferable to transbronchial lung biopsy but this procedure carries considerable risk. In general, lung biopsy should only be used as a last resort if the diagnosis cannot be established in another way.

Percutaneous renal biopsies are often more accessible and are sent for standard histopathology and immunohistochemistry. GPA classically shows necrotising granulomata, vascular wall inflammation and geographic necrosis. CSS in contrast shows extravascular granuloma with eosinophilic tissue infiltration. Histological confirmation of Goodpasture's disease requires immunoflourescence studies with anti-GBM antibody deposition along alveolar and glomerular basement membrane.

PRS in intensive care

A significant number of patients with PRS deteriorate rapidly and present with life threatening respiratory and renal failure requiring admission to ICU. Their management represents a major challenge as mortality is of the order of 25—50%. If left untreated, PRS can follow a fulminant course and is often fatal.[42] As with more indolent presentations, outcome depends on prompt recognition, exclusion of infection and rapid aggressive treatment. Transfer to a specialist centre may be needed.

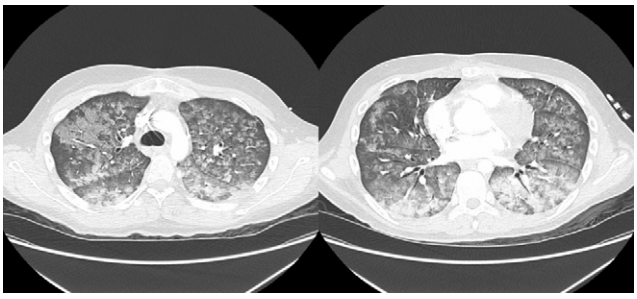

Figure 2 CT chest (2 slices) showing diffuse pulmonary haemorrhage. Both Figs. 1 and 2 reproduced with permission.

Diagnosis in the ICU

In the majority of patients admitted to ICU the diagnosis is already known.[42] Acute deterioration may be due to a flare of the underlying disease causing diffuse alveolar haemorrhage (DAH) and respiratory failure or more commonly severe infection or drug toxicity caused by immunosuppressive treatment. In some patients, the diagnosis is made only after admission to ICU. In a series of 26 patients admitted to ICU with systemic necrotising vasculitis, a surprising high number (42%) were diagnosed in the ICU.[43]

Diagnosis of pulmonary-renal syndrome in the ICU can be challenging. There is no single test and premorbid symptoms and signs are often non-specific. There is considerable overlap with other common ICU presentations such as sepsis and cardiorespiratory compromise. A history of breathlessness and cough with low grade fever should be sought which has subsequently developed into clinical respiratory failure with non-specific changes on the chest radiograph. Even in severely unwell patients haemoptysis is frequently absent despite radiological suggestion of DAH.

Pointers to vasculitis in critically ill patients are as previously discussed. Worsening pulmonary infiltrates with persistent low grade fever in the face of falling haemoglobin and renal failure requiring haemofiltration is suggestive of PRS. The presence of blood and protein in the urine rather than leukocytes and nitrites may have led to treatment for urosepsis rather than prompting a search for glomerulonephritis. New onset hypertension can herald undiagnosed renal involvement and unexplained hypoxia may indicate subclinical pulmonary haemorrhage especially in the context of progressive coalescing alveolar shadowing on chest radiography.

Distinguishing vasculitis from infection in the ICU setting is essential. Persistently negative microbiological samples, in the context of an inflammatory illness, make the presence of vasculitis more likely. When safe to do so, bronchoscopy should be performed to exclude infection and look for evidence of DAH.

Intensive care unit specific management

In the ICU the management of pulmonary-renal syndromes centres on immunosuppression therapy (outlined later) and supportive care. Some important aspects of supportive care are listed below:

Minimizing the risk of sepsis

Patients with vasculitis frequently die of sepsis.[43] In a series of 26 patients with necrotising vasculitis admitted to ICU, 75% died of sepsis.[44] The risk of nosocomial infection in

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these patients is very high due to immune-suppression. Severe infection due to cyclophosphamide occurs in about 10% of cases and has a high mortality.[42] Careful monitoring for bone marrow suppression and superadded infection is indicated. Septrin prophylaxis against PCP infection is often used.

Respiratory and airway management

In GPA there may be subglottic stenosis which can result in difficult intubation. Smaller endo-tracheal tubes or tracheostomy may be needed.[42] In acute lung injury due to diffuse alveolar haemorrhage large tidal volumes or pressure changes may exacerbate damage to pulmonary microvasculature. Lung protective ventilation, as used in the management of ARDS, with tidal volumes of 6 ml/kg and inspiratory plateau pressures below 30 cmH_2O with permissive hypercapnia may reduce lung injury.[42]

Cardiovascular and renal

Patients with pulmonary-renal syndrome may be hypotensive because of a combination of dehydration, haemorrhage and systemic inflammatory response and may require inotropic support. Many patients develop severe acute renal failure and require haemodialysis in ICU. Of these the majority will eventually progress to end stage renal failure and require long term renal replacement therapy.

Treatments

ANCA associated PRS: remission induction

Treatment outcomes for systemic vasculitis prior to the introduction of glucocorticoids were dismal with survival at 1 year from diagnosis in the region of 20–30%.[45] This benefit disappeared at 3 years most probably secondary to complications from long term steroids. The introduction of cyclophosphamide in conjunction with steroids in the 1970s heralded a new age in vasculitis management in that 5-year mortality was lowered from 50% with glucocorticoid treatment alone to 12% with combination therapy.[46]

Cyclophosphamide is an alkylating agent that brings about cell apoptosis through DNA and RNA synthesis inhibition. Its side effect profile depends on cumulative dose. Acutely it predisposes to haemorrhagic cystitis and myelosuppression. Chronically it increases the lifetime risk of bladder cancer, lymphoproliferative disorders and gonadal toxicity. Despite this advance, treatment toxicities and secondary complications remain relatively frequent and survival curves are still attenuated compared to the normal population. Age and serum creatinine at presentation remain the strongest predictors of both survival and renal outcome.[47]

Induction of remission is most commonly achieved with high dose intravenous methyprednisolone (0.5 g–1 g/day) for 3–5 days for which there is no substantial evidence base. This is coupled with pulsed intravenous cyclophosphamide administered every 2–3 weeks (15 mg/kg/pulse) on 6–9 occasions or as a daily oral regime (1–2 mg/kg/day). In the presence of severe renal disease defined as a serum creatinine >500 μmol/L, there is additional short term benefit from plasmapheresis in terms of renal recovery in the first 18 months.

Debate continues over the long term benefit of plasma exchange (PE) in the acute setting. The mechanism of action of PE is largely unknown. PE is likely to dilute down ANCA titres and removes a large fraction of pro-inflammatory cytokines, complement and coagulation factors from the systemic circulation. It most likely decreases progression to end stage renal disease in those with severe renal failure at presentation.[48] There is no proven long term survival benefit from its use and furthermore little evidence for its role in the treatment of less severe disease. Other agents used less frequently for induction of remission include methotrexate and mycophenolate mofetil (MMF). Whilst methotrexate is contraindicated in severe renal disease, MMF has shown superiority to cyclophosphamide in maintaining normal renal function at 6 months from diagnosis.[49] A recent trial of rituximab for induction of remission in ANCA associated disease was not superior to standard intravenous cyclophosphamide. Sustained-remission rates were high in both groups however.[50]

Maintenance of remission

The most effective method of maintenance of remission is also the subject of ongoing trials and there is considerable inter-practitioner variability over both choice of immunosuppression and duration of treatment. Currently, glucocorticoids are continued at low dose for a minimum of 18 months alongside a steroid sparing agent. This is usually extended to 2 years total in those with PR3 positive ANCA in view of their higher rate of relapse.[51] The most widespread European practice is switching from cyclophosphamide to azathioprine at the 3–6 month interval from diagnosis.

Studies looking at maintenance therapy with methotrexate, leflunomide and MMF have not shown any advantage over azathioprine to date.[52–54] Biological therapies studied include the TNF-α inhibitor Infliximab and the TNF-α 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-α agents tested however resulted in unacceptably high infection complication rates.[55,56] Rituximab has however recently been demonstrated to be as effective as cyclophosphamide in two randomised controlled trials.[50,57]

Anti-glomerular basement membrane disease – Goodpasture's

Urgent plasma exchange is initiated when this diagnosis is suspected to deplete plasma of circulating anti-GBM antibody. There is evidence to suggest earlier commencement has beneficial effect on long term renal recovery.[58] On average a 14-day course of plasma exchange is completed which is usually adequate to return anti-GBM antibody to normal titres. Immunosuppression is started alongside this

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therapy usually consisting of oral prednisolone (1 mg/kg) and oral cyclophosphamide (2–3 mg/kg/day). Available evidence suggests completely anuric patients respond poorly to this regime going on to require long term renal replacement therapy with consequent poor survival in the region of 50% at 2 years.[58]

Systemic lupus erythematosus

Pulmonary haemorrhage in the context of lupus nephritis carries a poor prognosis. Urgent immunosuppression should be given with high dose methylprednisolone and cyclophosphamide. New therapies such as Rituximab and MMF are in trial stages which bring about successful remission in 80% of cases.[59,60] Relapse rates are high however despite the improved toxicity profile.[60] Recent studies looking at rituximab as add-on therapy in SLE have failed to show significant benefit but this is most likely due to poor trial design.[61,62]

Conclusion

Our rationale for review of these rare disorders is their frequent first presentation to respiratory physicians and disproportionate lack of involvement in subsequent care. Clinical vigilance is key as the symptom complex of PRS is often non-specific. The diversity of conditions encompassed by this group of disorders lends itself to a wide range of severity of presentation from the general outpatient clinic to the ICU setting. Often multidisciplinary input is required. Although traditionally the domain of our rheumatology and renal colleagues, an updated working knowledge of PRS including the disease pathogenesis and complications is central to the practice of a general respiratory physician especially in such a rapidly advancing field with increasingly targeted treatment strategies.

Conflict of interest

No conflicts of interest declared.

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