

Management of idiopathic crescentic and diffuse proliferative glomerulonephritis: Evidence-based recommendations

KAILASH K. JINDAL

Division of Nephrology, Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada

Management of idiopathic crescentic and diffuse proliferative glomerulonephritis: Evidence-based recommendations. Idiopathic crescentic glomerulonephritis (GN) often presents with a rapid loss of renal function and pathology showing extensive crescent formation. The disease is caused by different immunopathogenetic mechanisms, pauci-immune, often antineutrophil cytoplasmic antibody (ANCA)-positive microvasculitis, anti-glomerular basement membrane (GBM) antibody disease, and immune complex formation. Historical reviews reveal poor renal prognosis, even after treatment with oral steroids and cytotoxic drugs. Prognosis has improved in the last decade. In this article, evidence-based recommendations for management are presented. Because of the high risk of end-stage renal disease (ESRD), early aggressive therapy is recommended, despite weak supporting evidence. Treatment for anti-GBM antibody-induced crescentic GN should be initiated early and should include pulse methylprednisolone, a two-week course of plasmapheresis and two months of treatment with corticosteroids and cyclophosphamide (grade B and C). Treatment for pauci-immune crescentic GN should be pulse methylprednisolone, followed by oral corticosteroids and cyclophosphamide for 6 to 12 months (grade B). Recurrences can be managed similarly (grade B), along with appropriate supportive therapy. In patients who develop ESRD, successful transplantation can be performed. Diffuse endocapillary proliferative GN is classically postinfectious. It generally has a good prognosis when no crescent formation occurs. Adult patients with persistent proteinuria, hypertension, and renal function impairment need careful follow-up and management to modify progressive hemodynamic injury.

This article deals with the evidence-based management of two conditions: crescentic glomerulonephritis (GN), a disease generally characterized by progressive deterioration in renal function, and diffuse endocapillary proliferative GN without crescent formation, a condition in which patients initially have severe renal dysfunction but most often recover and have an excellent long-term prognosis. Patients with crescentic GN and diffuse endocapillary proliferation without crescent formation may have a similar initial clinical presentation. Although there

may also be some overlap in etiology, the major causes of necrotizing crescentic GN may now be separated from those of diffuse endocapillary proliferative GN. The natural history and management of these two entities are also quite different.

Rapidly progressive GN (RPGN) is discussed in detail because of the poor prognosis of untreated patients and recent advances in treatment. Idiopathic diffuse proliferative GN is described more briefly. For both conditions, first the definition is outlined, and then the classification, diagnosis, and pathology. Then, recommendations are offered for management, based on evidence from published studies. The studies were obtained from a comprehensive literature search, followed by secondary searches as needed.

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Rapidly progressive GN is a clinicopathological entity characterized by a rapid loss of renal function (usually a 50% decline in glomerular filtration rate) within three months, with the principal histological finding of extensive crescent formation (usually involving over 50% of the glomeruli) [1].

This disorder is usually due to one of three different mechanisms of glomerular injury [2]. Anti-glomerular basement membrane (anti-GBM) antibody disease is responsible for 10 to 20% of all patients with RPGN. When associated with pulmonary hemorrhage, it is called Goodpasture's syndrome.

A second mechanistic form of RPGN is immune complex RPGN. This entity, which is responsible for approximately 40% of all cases of RPGN, can be due to one of a number of systemic diseases. These include postinfectious GN, IgA nephropathy, Henoch-Schönlein purpura, lupus nephritis, membranous nephropathy, and membranoproliferative GN. A few cases of idiopathic immune complex RPGN have been reported, but they seem to follow a clinical course very similar to patients with RPGN lacking immune deposits. It is possible that non-

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specific immunoglobulin trapping may occur in some of these cases.

The final form of RPGN is pauci-immune RPGN, in which glomerular inflammation and necrosis are present with few or no immune deposits. A large majority of patients with this disorder have antineutrophil cytoplasmic antibodies (ANCA), and many have systemic symptoms of vasculitis. With the advent of ANCA testing, true idiopathic RPGN may be a rare entity.

Clinical features common to the three forms of RPGN include hematuria, proteinuria, decreased urine output, edema, and hypertension. Patients with anti-GBM antibody disease may also have pulmonary hemorrhage with hemoptysis due to antibodies directed against the alveolar basement membrane. Similar clinical findings can also occur in microscopic polyarteritis and Wegener's granulomatosis because of involvement of the vessels by the vasculitic process.

Patients with pauci-immune RPGN often have an insidious onset with initial symptoms being fatigue, fever, night sweats, and arthralgias, features similar to those in patients with systemic vasculitis. The urinalysis typically reveals hematuria, with dysmorphic red blood cells (RBC), RBC casts, and variable degrees of proteinuria. Renal insufficiency is common.

The first step in the management of RPGN is a rapid diagnosis. This requires distinguishing RPGN from other causes of renal failure with acute onset and similar urinary findings. These include acute interstitial nephritis, thrombotic microangiopathies (including hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, acute postpartum renal failure, progressive systemic sclerosis, and malignant hypertension), acute atherosclerotic renal failure, and diffuse proliferative GN [2].

If clinical features point toward GN as a cause of rapidly progressive renal failure, the specific form of GN must be identified in order to provide optimal therapy. Clinical and laboratory features may be helpful in the differential diagnosis, but histological analysis of tissue obtained by renal biopsy is the most important method for categorizing and staging this type of GN.

The purpose of laboratory tests is to help distinguish glomerular causes of acute renal failure, as well as the differential diagnosis among various causes of RPGN. Suggested tests include a complete blood count (CBC) with total and differential white blood cell (WBC) count, peripheral smear, chest x-ray, blood cultures in selected cases, C₃, C₄ and total complement, ANA and anti-DNA antibodies, hepatitis B and C serology, cryoglobulins, anti-GBM antibodies, and ANCA testing.

Although clinical presentation and laboratory studies may be helpful in the differential diagnosis of suspected RPGN, the final diagnosis is established on a detailed analysis of renal pathology by light, immunofluorescence, and electron microscopy. A detailed discussion of renal

pathology in various forms of RPGN is beyond the scope of this article. Only the pathological findings that are helpful in the differential diagnosis of RPGN are discussed.

Immunohistology is most useful in categorizing different types of RPGN. Linear GBM localization of immunoglobulin is indicative of anti-GBM antibody-mediated disease. Ten to 20% of the patients presenting as RPGN have this pattern. Granular glomerular localization of immunoglobulins and complement is indicative of immune complex-mediated diseases, and 30 to 40% of patients presenting as RPGN have this pattern. No or scanty glomerular immunoglobulin localization occurs in pauci-immune necrotizing crescentic GN. This pattern is seen in 40 to 50% of all patients presenting as RPGN, whether clinically limited to renal involvement or part of a systemic vasculitis.

Although breaks in GBMs may be observed on electron microscopy in patients with RPGN, the major role of electron microscopy is in distinguishing the different forms of immune complex-induced RPGN. Scattered large subepithelial dense deposits are typical for post-streptococcal GN. Large subendothelial dense deposits are seen in severe proliferative lupus nephritis. Large mesangial deposits are more characteristic of IgA nephropathy and Henoch-Schönlein purpura-associated nephritis.

Management of rapidly progressive glomerulonephritis

The treatment of RPGN can be divided into two parts: the specific treatment against the inflammatory renal injury and the management of pathophysiological consequences of glomerular disease, such as fluid retention, hypertension, hyperkalemia, and uremia.

Specific therapy against renal inflammatory injury. Few prospective controlled studies exist with sufficient number of patients to allow strong conclusions regarding therapeutic benefits. Most available reports have used historical controls for comparison. The demonstrated benefit in more recent series may be related to several factors other than the effect of the specific treatment, such as earlier diagnosis, recognition of milder cases, and improved management of related complications such as fluid retention, hypertension, uremia, and infections. There is also a possibility of a publication bias for successful reports. Unfortunately, RPGN is an uncommon condition with extremely poor prognosis, and these two factors make it very difficult to perform prospective controlled trials with an adequate number of patients. Assigning patients to a no-treatment arm may not be deemed ethical because of the rapid development of renal failure. The treatment recommendations for this reason will be made on the basis of available data, even though this evidence (level 3 evidence) is not always based on prospective controlled studies.

Treatment of anti-glomerular basement membrane antibody-induced rapidly progressive glomerulonephritis

Recommendation 1. Early diagnosis should be established.

Recommendation 2. Methylprednisolone 7 to 15 mg/kg per day to a maximum of 1 g/day for three days, then prednisone 60 mg daily for seven days, and thereafter 45, 30, 20, 15, 10, 5 mg for one week each is recommended.

Recommendation 3. A daily 4-liter plasma exchange for albumin for 14 days or until anti-GBM antibody disappears is recommended. No plasmapheresis should be given in patients with anuria and crescents involving more than 85% of the glomeruli, unless there is pulmonary hemorrhage.

Recommendation 4. For patients under 55 years old, 3 mg/kg (down to nearest 50 mg) of cyclophosphamide should be given for eight weeks. For patients over 55 years old, 2 mg/kg (down to nearest 50 mg) should be given for eight weeks.

Recommendation 5. Treatment may be prolonged if the anti-GBM antibody is still detectable (grade B and C recommendations; Fig. 1).

Evidence. Before 1975, anti-GBM-induced RPGN was associated with very poor prognosis. In 1973, Wilson and Dixon studied 81 patients with anti-GBM nephritis and reported that 89% progressed to end-stage renal disease (ESRD) or death within five years [3]. Most of those patients had received various combinations of oral steroids and cytotoxic drugs. In a small, randomized, controlled 1985 trial (17 patients) Johnson et al compared the effect of plasma exchange (4 liters every three days) plus immunosuppression (prednisone and cyclophosphamide) to immunosuppression alone on the clinical course and rate of disappearance of antibodies [4]. Patients treated with plasma exchange had a more rapid disappearance of anti-GBM antibodies and mean serum creatinine value that was less than 50% that of patients receiving immunosuppression alone at the end of the study. Similar results were reported by Simpson et al in a non-randomized, controlled study [5]. Couser reviewed 22 published uncontrolled studies involving 186 patients with anti-GBM nephritis who received plasma exchange [1]. His summary suggested a favorable effect of plasmapheresis on pulmonary disease in approximately 90% and renal disease in about 40% of patients.

The largest published series come from the Hammer-smith Hospital [6]. They reported outcome at two months on 59 patients treated with plasma exchange and immunosuppression. When using a daily 4-liter plasma exchange for at least 14 days, 85% of patients were alive after two months of follow-up. Forty-one percent progressed to ESRD, and 44% retained independent renal function. The response to treatment was different according to the

degree of renal function impairment and requirement of dialysis at presentation. Of 30 dialysis-dependent patients with anti-GBM disease treated with plasma exchange and immunosuppression, only four (13%) regained a useful renal function despite a fall in anti-GBM antibodies. Among eight patients with serum creatinine levels greater than 600 $\mu\text{mol/liter}$ at the start of treatment but not needing dialysis, four improved. In contrast, renal function improved in 18 of 21 patients with plasma creatinine of less than 600 $\mu\text{mol/liter}$.

Walker et al, in an uncontrolled study of plasmapheresis, also reported anuria and a high percentage (more than 85%) of glomeruli showing crescents were bad prognostic signs. However, some patients with advanced renal failure improved if they were not anuric [7].

Table 1 provides the summary of studies with level of evidence for treatment of anti-GBM antibody disease. It seems reasonable to conclude that plasma exchange, when used along with immunosuppressive drugs, accelerates the disappearance of anti-GBM antibodies from the circulation and probably improves renal function if instituted promptly in patients with milder forms of anti-GBM nephritis. Some patients with more advanced renal function may also respond provided they are not anuric and have favorable features on biopsy. The recommended replacement fluid with plasmapheresis is albumin because of a lower incidence of complications associated with the use of albumin as compared with plasma [8].

This treatment regimen should not be used in anuric patients with anti-GBM nephritis unless they have pulmonary hemorrhage. The anti-GBM antibody levels are often spontaneously reduced over time in a large majority of such patients.

These recommendations are made despite only levels 3 to 5 evidence in support of the use of plasma pheresis in anti-GBM antibody-mediated RPGN. As recently stated by Bolton, the major emphasis is on early diagnosis and therapy and use of plasmapheresis can be justified because of the poor prognosis of untreated cases [9].

An algorithmic approach to the management of anti-GBM mediated RPGN is shown in Figure 1.

Treatment of pauci-immune crescentic rapidly progressive glomerulonephritis

Recommendation 6. Initial steroid treatment is methylprednisolone 7 to 15 mg/kg/day to a maximum of 1 g/day \times three days, then prednisone 1 mg/kg/day for one month, gradually tapered over the next 6 to 12 months.

Recommendation 7. Cyclophosphamide should be given either orally at a dose of 2 mg/kg/day adjusted to maintain the leukocyte count between 3 and 5 thousand/ml or intravenously starting at 0.5 g/m²/month and increased monthly by 0.25 g to a maximum of 1 g/m² per month. The dose should be adjusted to maintain a nadir of leukocyte count two weeks post-treatment between 3 and 5 thou-

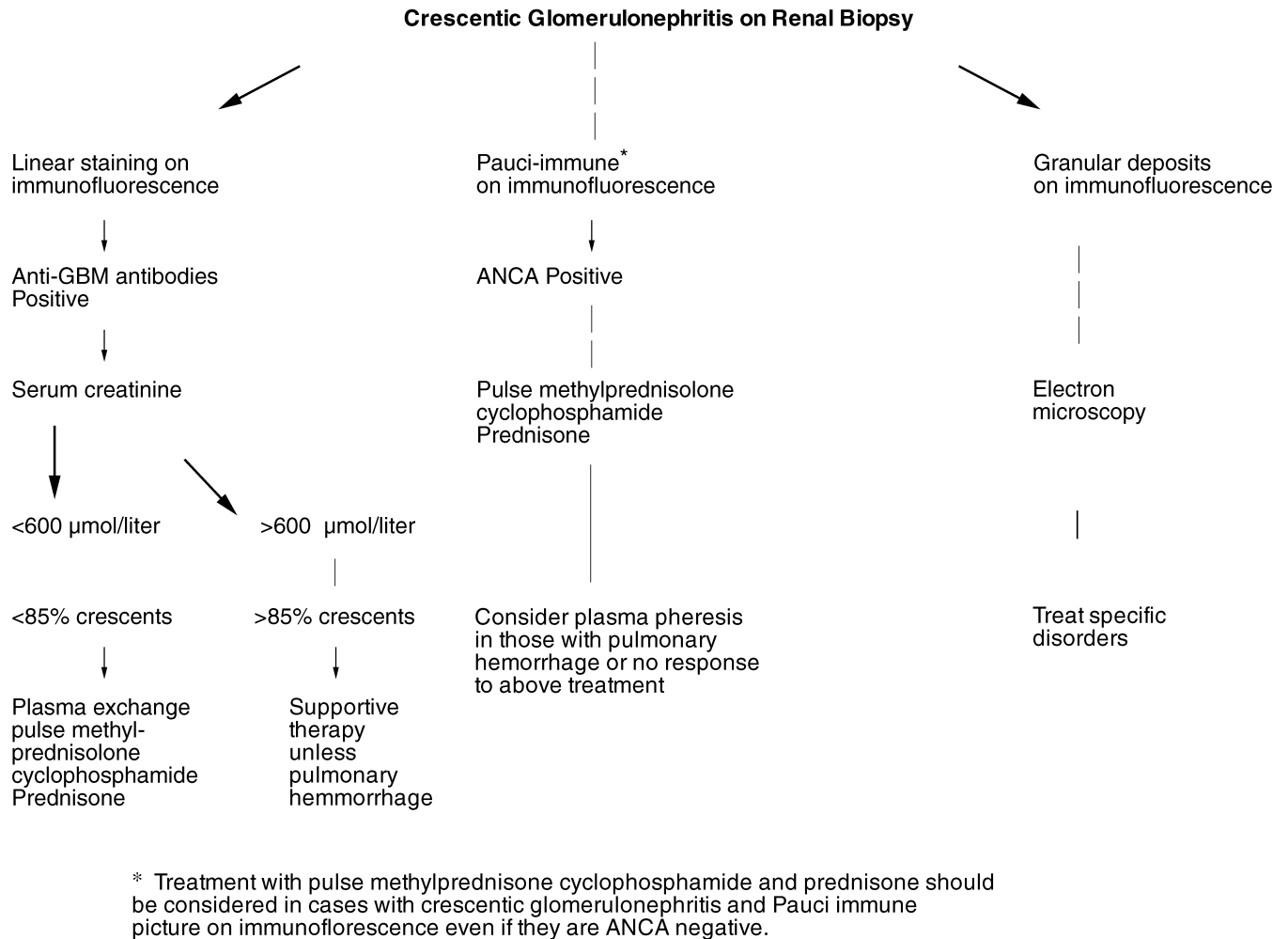


Fig. 1. Decision tree for crescentic glomerulonephritis on renal biopsy. Treatment with pulse methylprednisolone cyclophosphamide and prednisone should be considered in those cases with crescentic glomerulonephritis and a pauci-immune picture upon immunofluorescence, even if they are ANCA negative.

sand/ml. Cyclophosphamide should be continued for 6 to 12 months. Treatment should be given even in advanced patients.

Recommendation 8. Consider plasmapheresis in patients with lung hemorrhage and those with severe disease and no response to conventional therapy.

Recommendation 9. Monitoring for relapse with clinical follow-up, renal function tests, and ANCA is recommended.

Recommendation 10. Treatment of relapses should be similar to original treatment (grade B, recommendations; Fig. 1).

Evidence. In 1988 Couser reviewed the results of treatment in patients with idiopathic RPGN managed in the 1960s and 1970s. Although these patients may have included some patients with immune complex RPGN, patients with postinfectious and anti-GBM antibody-mediated RPGN were excluded. He described 78 patients

treated with various combinations of oral steroids, cytotoxic drugs, and anticoagulants. Only 20% demonstrated significant clinical improvement, and 80% developed ESRD [1]. Thus, similar to anti-GBM antibody-mediated RPGN, review of historical controls suggests a poor prognosis in pauci-immune idiopathic RPGN.

Following the successful use of pulse steroids in eight patients with proliferative GN, Bolton treated patients with idiopathic RPGN with pulse methylprednisolone. In 1992, they reported on a total of 21 patients with idiopathic RPGN treated with methylprednisolone at 30 mg/kg body wt on alternate days for total of three doses [10]. This was followed by oral prednisone starting at 2 mg/kg on alternate days and gradual tapering over 12 months. A few patients also received cyclophosphamide at approximately 100 mg/day and dipyridamole at 200 mg/day. Sixteen of the 21 patients (76%) receiving pulse therapy showed an improvement in renal function. Ten

Table 1. Studies on the treatment of anti-glomerular basement membrane (GBM) antibody induced rapidly progressive glomerulonephritis (RPGN)

Level of evidence	Author [Reference]	Study design	N	Treatment	Result
2	Johnson [4]	Randomized control	17	Steroids, cyclo vs. plasma exchange, steroids, cyclo	Better renal survival with plasmapheresis
3-4	Simpson [5]	Nonrandomized control	20	Steroids, Cyclo, Aza vs. Steroids, Cyclo, Aza and plasmapheresis	Better renal survival with plasmapheresis
4	Hammersmith [6]	Uncontrolled case series	59	Steroids, Cyclo plasmapheresis	44% improved renal function
5	Wilson [3]	Uncontrolled case series	81	Steroids + Cytotoxic agents	ESRD 85%

Abbreviations are: Cyclo, cyclophosphamide, Aza, azathioprine.

of the 15 patients who received pulse therapy and were receiving dialysis were able to discontinue dialysis. Seventy-five percent of patients with 60% or more crescents improved with pulse therapy.

With the realization that many cases with pauci-immune RPGN may, in fact, be cases of renal-limited vasculitis, cytotoxic drugs have increasingly been used in such patients. Testing for ANCA has further strengthened the association of necrotizing crescentic GN and vasculitis.

Nachman et al have recently reported on their experience with the treatment of 97 patients with ANCA-associated microscopic vasculitis with RPGN or ANCA-associated necrotizing crescentic nephritis [11]. Most patients received methylprednisolone pulse at 7 mg/kg for three consecutive days. Prednisone was then given at 1 mg/kg for one month and tapered over several months. Twenty-five patients received treatment with prednisone alone and 72 patients received cyclophosphamide and prednisone following pulse methyl prednisolone. Cyclophosphamide was given orally at 2 mg/kg, adjusted for the WBC count, and given for 6 to 12 months. Intravenous cyclophosphamide was given at an initial dose of 0.5 g/m² once a month and was increased to a maximum of 1.0 g/m² once a month and adjusted according to the two-week leukocyte nadir. Because this was not a randomized controlled trial, multivariate analysis was performed to assess treatment response and relapses. Overall, 75 of the 97 patients (77%) went into remission. Of the 75 responders, 32 patients (43%) remained in long-term remission for a mean follow-up of 44 ± 29 months. Twenty-two of the 75 patients who initially responded to treatment (29%) suffered a relapse that generally occurred within 18 months from the end of therapy. There was a significant difference in the remission rate between corticosteroid-treated patients and cyclophosphamide-treated patients (56 vs. 89%, *P* = 0.003), and furthermore, cyclophosphamide-treated patients had three times less risk of experiencing a relapse than did corticosteroid-treated patients (0.32; 95% CI = 0.12 to 0.84).

A total of 23 patients in this study required dialysis

at the time of their initial presentation, and their average serum creatinine concentration was 801 ± 294 mol/liter. Of these 23 patients, 17 received treatment, 13 with cyclophosphamide (6 oral and 7 intravenous) and 4 with corticosteroids alone. Nine patients (53%) responded, and eight (47%) were treatment resistant. There was no significant difference in the ages, serum creatinine concentrations, or chronicity or activity indices between the respondent and resistant groups.

In the same set of patients, prognostic markers for patient and renal survival were analyzed by the Cox proportional hazard model [12]. The important variables for patient death were presentation with pulmonary hemorrhage and presence of C ANCA (compared with P ANCA) and treatment with steroids alone (5.56 time higher versus combined treatment). The predictors for renal survival were entry serum creatinine value, race (African Americans having a worse outcome compared with Caucasians), and presence of arteriosclerosis on renal biopsy.

Such data support the use of a combination of cyclophosphamide and prednisone following initial pulse methylprednisolone in patients with pauci-immune necrotizing RPGN. Such therapy is indicated even in patients presenting with advanced disease and dialysis dependence. The published studies on treatment of idiopathic or pauci-immune RPGN with level of evidence are summarized in Table 2.

Role of plasmapheresis in pauci-immune rapidly progressive glomerulonephritis

Madore et al have recently reviewed the literature on the role of plasma pheresis in patients with pauci-immune RPGN [13]. In 26 patients with RPGN, Glöckner et al showed no statistical difference in renal outcome of those treated with plasma exchange and immunosuppressive treatment compared with immunosuppressive therapy alone [14]. Cole et al similarly showed no benefit of plasmapheresis over immunosuppressive therapy at

Table 2. Studies on the treatment of pauci-immune crescentic rapidly progressive glomerulonephritis

Level of evidence	Author [Reference]	Study design	N	Treatment	Result
3	Nachman [11]	Nonrandomized control study	97	Pulse steroids followed by oral prednisone vs. Pulse steroids, oral prednisone and cyclophosphamide	Better renal and patient survival with cyclophosphamide
5	Lobo [10]	Uncontrolled case series	21	Pulse steroids, oral prednisone, cyclophosphamide	76% improvement in renal function

Table 3. Studies on plasma exchange (PE) in idiopathic rapidly progressive glomerulonephritis (RPGN)

Level of evidence	Author [Reference]	Study design	N	Treatment	Result
2	Glockner [14]	RCT	26	PE + cytotoxic vs. cytotoxic alone	No benefit of PE
2	Cole [15]	RCT	32	PE + steroids + Aza vs. steroids + Aza	No benefit of PE
2-3	Pusey [16]	RCT	48	PE + Aza + steroids + Cyclo vs. Aza + steroids + Cyclo	No benefit for entire group. For dialysis-dependent patients discontinuation of dialysis more on PE 91% vs. 37%
2	Rifle [17]	RCT	14	Steroids + Cyclo + heparin vs. steroids + Cyclo + heparin	For dialysis-dependent patients discontinuation of dialysis 75%, on PE vs. 0 for controls
2	Mauri [18]	RCT	22	Steroids + Cyclo vs. steroids + Cyclo + PE	No benefit of PE

Abbreviations are: RCT, randomized control trial; Aza, azathioprine; Cyclo, cyclophosphamide.

1, 3, 6, and 12 months following randomization in 32 patients with idiopathic RPGN [15].

Pusey et al provided evidence based on subgroup analysis of a larger study suggesting a benefit in patients who presented with severe (dialysis-dependent) disease [16]. Of the 11 dialysis-dependent patients who were treated with plasma exchange, 10 recovered sufficient renal function to stop dialysis (mean follow-up 4 months) compared with only three of the eight conventionally treated patients. Similar trends were noted in other trials [17, 18].

Madore, Lazarus and Brady concluded that the results of five randomized trials argue against a role for plasma exchange in milder forms of pauci-immune RPGN, but suggested that there was a potential benefit when the technique was used as an adjunct to conventional immunosuppressive therapy in patients with severe disease [13]. However, the data are not convincing enough to provide firm recommendations. Table 3 provides a summary of studies on plasmapheresis in idiopathic RPGN along with the level of evidence.

Management of immune complex rapidly progressive glomerulonephritis

Patients with immune complex RPGN should be treated according to their specific underlying condition. The therapy of crescentic phase of IgA nephropathy, membranoproliferative GN, and membranous GN is discussed elsewhere in this issue and is not repeated. The

postinfectious form of RPGN with crescents seems to have a better prognosis. A review by Couser of 13 series included 76 patients with postinfectious RPGN. Fifty percent recovered spontaneously without disease-specific therapy, 18% underwent partial recovery, and 32% developed ESRD [1]. Zent et al reported a relatively poorer prognosis for crescentic postinfectious GN in South Africa [19]. In this small series, they suggested some benefit of immunosuppressive treatment. However, the number of patients treated is too small to make strong recommendations. A few patients with true idiopathic immune complex crescentic RPGN should be treated similarly to those with pauci-immune RPGN.

Management of pathophysiologic consequences of glomerular disease

Hypertension is very common in patients with acute glomerular disease. This may be caused by intravascular volume expansion. The management therefore involves measures to reduce intravascular volume. These include salt and water restriction and diuretic therapy. If these are not able to reduce the volume effectively, especially in the face of severe oliguria, dialysis and ultrafiltration are required. Peripheral and pulmonary edema will also benefit from these measures. A variety of vasodilators are also effective in reducing blood pressure. Angiotensin-converting enzyme inhibitors may be less effective because of renin-angiotensin system suppression.

Early dialysis may also be indicated for hyperkalemia that does not respond to conservative therapy, metabolic acidosis, and uremic syndrome.

Follow-up and management for renal insufficiency

Adequate follow-up should be performed with clinical assessment of disease activity as well as renal function. The role of ANCA testing in follow-up of patients with pauci-immune RPGN is not clear. Although negative ANCA is useful, a positive ANCA test without clinical evidence of recurrent disease may not be a definite indication for starting therapy. This may trigger the need for a closer follow-up [11, 20]. Treatment for renal insufficiency with appropriate diet and blood pressure control, including the use of angiotensin-converting enzyme inhibitors, would be indicated as in other patients with chronic renal insufficiency. Details of such therapy are discussed in the article on conservative therapy for chronic GN in this issue. Similar to the experience in transplantation, patients on immunosuppressive drugs may benefit from Septra prophylaxis to prevent *Pneumocystis carinii* pneumonia [21]. Calcium supplements of 1 g daily along with 800 IU vitamin D should be used to prevent negative calcium balance. Consideration for bisphosphonates should be given to high-risk patients (postmenopausal women) [22–24].

DIFFUSE PROLIFERATIVE GLOMERULONEPHRITIS

There is some difficulty in the definition of this entity. In the literature, different observers may talk about different disease entities, that is, some cases of idiopathic membranoproliferative glomerulonephritis (GN) could be included.

Cameron has defined this as a clinical presentation of acute nephritic syndrome with histopathology showing endocapillary pattern of proliferation without extensive crescent formation [25]. In its most classic form, poststreptococcal GN presents in this fashion. However, in the temperate climates, cases of poststreptococcal GN are now uncommon. Known causes of diffuse proliferative GN include postinfectious, diffuse proliferative lupus nephritis, Henoch-Schönlein purpura, and IgA nephropathy.

The diagnostic work-up should follow as outlined with RPGN, including a clinical search for infections, clinical and serological investigations for lupus, and a kidney biopsy.

What is known of the natural history of this disease is mostly limited to the natural history of poststreptococcal GN. Although there is controversy, the prognosis of epidemic poststreptococcal GN in childhood is generally good. If the biopsy reveals endocapillary changes only, then healing within five years is the rule. Even in adults, where there is no crescent formation and disease is lim-

ited to endocapillary proliferation, the prognosis is good. There is a slightly higher incidence of crescent formation and mesangiocapillary and glomerulosclerotic changes in the adult cases. Because of these changes, the incidence of chronic renal damage may increase with increasing age.

Treatment with immunosuppressive therapy, including steroids, azathioprine, or cyclophosphamide, has been shown to have no benefit in patients with diffuse proliferative GN. The best available data come from the Medical Research Council Working party reported in 1971. They evaluated treatment of proliferative GN with azathioprine and prednisone. Fifty-one adults with proliferative GN were in the treatment group, and 52 were in the control group. Minimum treatment was for eight weeks, but in over two thirds of the patients, the treatment was continued for six months. After a minimum follow-up of six months, there was no benefit with immunosuppressive therapy [26]. Similar results have been reported by Booth et al [27].

During acute presentations, patients should receive symptomatic treatment for hypertension and fluid overload with salt and fluid restriction, diuretics, and vasodilators.

During follow-up, hypertension, proteinuria, and renal function should be assessed. Patients with significant proteinuria, hypertension, and/or renal function impairment should receive appropriate nonspecific therapy to slow down the progressive hemodynamic renal function impairment.

Reprint requests to Kailash K. Jindal, M.D., Division of Nephrology, Queen Elizabeth II Health Sciences Center, Room 5078, Dickson Building, Victoria General Hospital Site, 1278 Tower Road, Halifax, Nova Scotia B3H 2Y9, Canada.

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