Abstract In children, systemic lupus erythematosus (SLE) is often more severe than in adults. Renal disease is very common in SLE, with clinical symptoms of renal involvement occurring in 30%–70% of patients. In the absence of appropriate treatment the child may die from the disease or progress rapidly to renal failure. However, aggressive treatment regimens, in particular corticosteroids, carry the risk of growth retardation, accelerated atherosclerosis, and severe infectious complications. Lupus nephritis is classified into six groups depending on the severity of the histological lesions. The most-appropriate treatment for optimal efficacy with minimal side-effects depends on the disease severity. Mild lesions (class I or II) require only careful follow-up to identify any disease progression. Patients with class III nephropathy (focal and segmental glomerulonephritis) may have mild clinical symptoms, in which case no specific therapy is indicated, or more-severe symptoms of the nephrotic syndrome, hypertension, and sometimes moderate renal insufficiency. These patients require the same aggressive therapy as those with class IV disease (diffuse proliferative glomerulonephritis). Our current protocol starts with three methylprednisolone pulses followed by 1.5 mg/kg per day oral prednisone and six monthly pulses of cyclophosphamide. After a second renal biopsy the patient may be maintained on azathioprine while the prednisone dosage is slowly tapered. In children with milder disease we use lower doses of oral prednisone (1–1.5 mg/kg per day). Patients with membranous glomerulonephritis (class V) require no specific therapy if they have pure membranous nephropathy, but require aggressive therapy if they have the nephrotic syndrome. In those patients who progress to end-stage renal disease, clinical and serological remission is common and renal transplantation can be performed, as recurrence in the transplant is very rare.

Key words Lupus nephritis · Pulse methylprednisolone · Oral prednisone · Cyclophosphamide · Azathioprine

Introduction

Most children with systemic lupus erythematosus (SLE) are diagnosed during adolescence and the disease is exceptional before the age of 5 years. In children, the disease is often more severe than in adults, with multisystem involvement [1]. Pediatricians are faced with difficult problems related to the impact of a chronic disease on the child and his family and the side-effects of the treatment. In the absence of aggressive treatment, the child may die or progress to renal failure. Such treatments may be responsible for severe infectious complications, and the side-effects of long-term corticosteroid treatment, in particular growth retardation and accelerated atherosclerosis, are of particular concern [2]. Renal disease is very frequent in patients with SLE. Clinical symptoms of renal involvement occur in 30%–70% of patients, according to the series. Immunofluorescence of renal biopsies has shown immunoglobulin and complement deposition in as many as 90% of patients; ultrastructural abnormalities are found in almost all patients. Renal disease and its treatment remain a major cause of morbidity and mortality. There is no doubt that the use of high-dose corticosteroids has improved the prognosis of severe lupus nephritis. During the past 20 years, new therapeutic approaches, including the use of cytotoxic agents, have further improved renal survival rates, which have reached 80% at 10 years. However, there is still some controversy regarding the best treatment, mainly due to the lack of well-designed prospective therapeutic trials with adequate numbers of patients. Most publications report uncontrolled trials and retrospective analyses, which do not allow definitive conclusions to be drawn.
Indications for renal biopsy

Renal involvement in SLE is extremely variable, with some patients showing minimal urinary anomalies and others rapidly progressive renal failure with nephrotic syndrome. The clinical picture is related to the severity of histological abnormalities on renal biopsy. Most patients with acute rapidly progressive renal insufficiency, heavy proteinuria, and red and white cell casts have diffuse proliferative glomerulonephritis. In these patients, clinical and biological data are sufficient for the diagnosis of SLE. In contrast, patients with nephrotic syndrome and minimal hematuria with little serological activity of the disease often have membranous nephropathy. However, those patients with hematuria, proteinuria with or without nephrotic syndrome, and a normal or subnormal glomerular filtration rate may have any class of glomerular lesions (focal or diffuse proliferative glomerulonephritis with varying degrees of severity or membranous glomerulonephritis). The prognosis is different and knowledge of the underlying histological lesions is most important to decide the best therapy [3]. A renal biopsy may also be indicated in a patient with glomerular disease in whom there are no extra-renal manifestations of SLE. The need for a renal biopsy in patients with no clinical evidence of renal disease is more problematic. Glomerular lesions may be found in this setting (usually mesangial deposits and mild mesangial proliferation). However, some patients with the so-called silent lupus nephritis present with more-severe histological lesions, such as focal and segmental glomerulonephritis or very rarely diffuse proliferative glomerulonephritis [4].

Classification of lupus nephritis

The World Health Organization classification for lupus nephritis, which uses light microscopy, immunofluorescence, and electron microscopy, is widely accepted [5]. This classification into six histological groups (Table 1) has recently been modified [6] and constitutes the first step before deciding on any therapy [7, 8]. Austin et al. [9] introduced the activity and the chronicity indices, which may further contribute to the prognosis. Active histological lesions include cellular crescents, endocapillary proliferation, fibrinoid necrosis, karyorrhexis, thrombi, wire loops with subendothelial immune deposits, glomerular leukocyte infiltration, and interstitial mononuclear cell infiltration. These active lesions are each graded 0–3 (with both necrosis and cellular crescents graded 0–6) to give an activity index graded 0–24. Active lesions are potentially reversible with treatment. It should be noted that extra-membranous deposits are not considered active lesions. Conversely, irreversible lesions allow the definition of the chronicity index and include glomerular sclerosis, fibrous crescents, tubular fibrosis, and interstitial fibrosis. These lesions do not respond to treatment. Although the activity and the chronicity indices are important to decide on the best therapy for individual patients, their prognostic significance is still debatable. The National Institutes of Health (NIH) group found that an activity index >12/24 or an elevated chronicity index were indicative of a poor renal prognosis [9]. A chronicity index ≤2 was associated with a 10-year renal survival rate of 100%, whereas when the chronicity index was between 2 and 4 the renal survival rate was only 70%. The renal survival rate at 10 years was only 35% in patients with a chronicity index >4. However, a study including unselected patients with lupus nephritis found that activity and chronicity indices did not accurately predict renal outcome [10].

<table>
<thead>
<tr>
<th>Table 1 World Health Organization histological classification of lupus nephritis</th>
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<tr>
<td>Class I: normal</td>
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<tr>
<td>A – normal by all techniques</td>
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<tr>
<td>B – normal by light microscopy but deposits seen by immunofluorescence or electron microscopy</td>
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<tr>
<td>Class II: mesangial glomerulonephritis</td>
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<tr>
<td>A – mesangial widening and/or mild hypercellularity</td>
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<tr>
<td>B – moderate hypercellularity</td>
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<tr>
<td>Class III: focal and segmental glomerulonephritis</td>
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<tr>
<td>A – with active necrotizing lesions</td>
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<tr>
<td>B – with active and sclerosing lesions</td>
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<tr>
<td>C – with sclerosing lesions</td>
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<tr>
<td>Class IV: diffuse proliferative glomerulonephritis</td>
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<tr>
<td>A – without segmental lesions</td>
</tr>
<tr>
<td>B – with active necrotizing lesions</td>
</tr>
<tr>
<td>C – with active and sclerosing lesions</td>
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<td>D – with sclerosing lesions</td>
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<tr>
<td>Class V: membranous glomerulonephritis</td>
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<tr>
<td>A – pure</td>
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<tr>
<td>B – associated with class II lesions (A or B)</td>
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<tr>
<td>Class VI: chronic sclerosing glomerulonephritis</td>
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Therapy of patients with mild renal lesions

Class I, which is rarely observed, is represented by normal renal biopsies when examined by light microscopy, immunofluorescence, and electron microscopy. This is a rare situation and patients have no renal symptoms. Class II is defined by mesangial glomerulonephritis with mesangial deposits and hypercellularity. Patients may have mild proteinuria and microscopic hematuria, but the glomerular filtration rate is usually normal. Renal disease in these patients does not need specific therapy, as there is little probability of progression [11]. Nevertheless, careful follow-up of the patient is necessary, as progression to a more-severe renal disease is possible.
Therapy of patients with focal and segmental glomerulonephritis

Patients with class III nephropathy have focal and segmental glomerulonephritis. The lesions involve less than 50% of the glomerular surface area and less than 50% of glomeruli present on the biopsy sample are affected. Lesions include cellular proliferation, leukocyte infiltration, karyorrhexis, and fibrin deposits. The natural course of the disease depends upon the extent of renal lesions. When less than 20% of glomeruli are affected by small segmental lesions, the long-term prognosis is favorable, with probably less than 5% risk of progression to end-stage renal failure after 5 years [12]. Patients usually have mild renal symptoms, with low-grade proteinuria without nephrotic syndrome and a normal glomerular filtration rate. In this setting, there is no indication for specific therapy, which may however be required for extra-renal symptoms. However, the situation is different when cellular proliferation, necrosis, and large subendothelial deposits involve more than 40% of the glomeruli present on the biopsy sample [7, 12]. The clinical symptoms are often more severe, with an active urine sediment, nephrotic syndrome, hypertension, and, in some patients, moderate renal insufficiency. The course of the disease is similar to that of diffuse proliferative glomerulonephritis, and the same aggressive therapy is needed. It is important that the biopsy sample contains a large number of glomeruli so that the severity of the renal disease is not underestimated.

Therapy of patients with diffuse proliferative glomerulonephritis

Class IV corresponds to diffuse proliferative glomerulonephritis, where cellular proliferation involves more than 50% of the glomeruli. Extra-capillary proliferation with crescent formation, wire loops, and necrosis are often observed on the biopsy. The clinical symptoms are more severe: hematuria with casts, nephrotic syndrome, hypertension, and moderate or severe renal insufficiency. Patients with class IV glomerulonephritis are at high risk of progression to end-stage renal disease if adequate therapy is not instituted.

Prognostic factors in patients with severe lupus nephritis

Some patients with diffuse proliferative glomerulonephritis are at higher risk of progression, particularly those with extensive crescent formation and necrotizing glomerular lesions [13–18]. These patients may require more-aggressive therapy than those whose biopsy shows a lower activity index [19]. Many studies have also shown that other factors may be of prognostic significance, including age, gender, race, hypertension, initial serum creatinine concentration, the delay between onset of renal disease and treatment, exacerbations of the nephropathy, and the response to therapy after the 1st year [9, 16, 20–25]. This may explain why, despite numerous uncontrolled and controlled therapeutic studies, there is no general agreement on the best therapy in these patients.

An analysis of these prognostic factors is important in order to identify the most-effective and safest therapy for individual patients. Several studies have shown that lupus nephritis has a worse prognosis in men than women. Dooley et al. [25] found a poor renal survival in black Americans with diffuse proliferative glomerulonephritis compared with white patients. The renal survival rate in black patients was 58% at 5 years compared with 95% in white patients following pulse cyclophosphamide therapy. The significance of race in the poorer prognosis of lupus nephritis is not clear. Several possible reasons have been proposed: socioeconomic factors, different HLA phenotypes, and inherited susceptibility for progression to renal failure. However, these findings do not necessarily imply that black people should receive more-aggressive treatments.

Levey et al. [26] identified several risk factors for progression to renal failure in 86 patients with severe class III or class IV lupus glomerulonephritis treated with prednisone and oral cyclophosphamide. An elevation of serum creatinine was the only initial feature predictive of progression to renal failure. The risk of renal failure was higher in patients with initial serum creatinine >106 μmol/l. Interestingly, the same authors found that the subsequent clinical course in response to therapy refined the prognosis based on initial serum creatinine. The risk of progression to renal failure was higher in those patients who did not show resolution of renal abnormalities within 48 weeks of follow-up. Patients with normal initial serum creatinine and patients with resolution of elevated initial serum creatinine had a similar and much lower risk of progression to renal failure. Other authors [9, 16, 21, 27, 28] have also reported the prognostic significance of elevated serum creatinine at presentation. However, these findings were not confirmed in several studies with longer periods of follow-up [24, 29–31].

Esdaile et al. [32] studied the impact of the delay between the onset of renal disease, the renal biopsy, and initiation of therapy and found that the duration of renal disease prior to renal biopsy was a statistically significant predictor for renal failure or death due to renal disease. The most likely explanation for these findings is that early treatment of renal disease is associated with better outcome. There was a significant increase in serum creatinine, urinary protein excretion, and activity and chronicity indexes on renal biopsy in patients in whom the treatment was delayed.

Moroni et al. [24] retrospectively studied the prognostic significance of renal flares, defined as a rapid increase of serum creatinine and/or in proteinuria, in 70 patients with lupus nephritis. Patients with renal flares were more likely to have a persistent doubling of serum creatinine than those who had no renal flares. The
relative risk of a persistent doubling of serum creatinine was 27 times higher in patients with rapid increases in serum creatinine. This outcome was more frequent in patients who did not respond rapidly to therapy. These data support the need for aggressive treatment of exacerbations of lupus nephritis.

A few reports in recent years have identified risk factors for renal failure or mortality in children with lupus nephritis. Yang et al. [33] retrospectively evaluated the clinical course, histopathology, and prognosis of 167 children. Those with persistent hypertension, anemia, increased serum creatinine concentration at the time of biopsy, and a low CH50 were more prone to develop renal failure. The overall renal and patient 5-year survival rates were 87.7% and 91.1%, respectively. McCurdy et al. [34] found that persistent hypertension, anemia, abnormalities of urinalysis, and elevated serum creatinine levels were significantly associated with progression to renal failure in a group of 71 children, 22% of whom progressed to end-stage renal failure. Diffuse proliferative glomerulonephritis, active and chronic lesions were also associated with progression to renal failure. Baqi et al. [35] analyzed the risk factors for renal failure in 56 children with lupus nephritis. Univariate analysis revealed a significant association between progression to renal failure and an elevated serum creatinine level, a decreased C3 complement level, hypertension, and class IV lupus nephritis. Multivariate analysis showed that progression to renal failure was independently associated with class IV lupus nephritis, hypertension at presentation, and a low C3 complement level in association with elevated serum creatinine levels. These three reports, as well as other studies of adults, found that hypertension was a significant risk factor for renal failure. Therefore, children with hypertension should be treated appropriately with antihypertensive drugs, as control of blood pressure may be as important as anti-inflammatory treatment.

Therapeutic regimen

The therapeutic regimen for class IV lupus nephritis has changed over the years. Although there are a large number of reports, there are few randomized studies, and these few include limited numbers of patients and, more importantly, do not indicate the long-term outcome after 10 years of follow-up. Pollak et al. [36], 38 years ago, showed that high doses of corticosteroids could improve the course of diffuse proliferative glomerulonephritis, whereas low doses were ineffective. Most nephrologists treat these patients with 1–2 mg/kg per day prednisone alone for several months, followed by a slow dose reduction when the disease is under control. However, high doses of oral prednisone alone not only give poor results in the long term but also are often associated with serious side-effects. Many authors have proposed initiation of therapy with intravenous methylprednisolone pulses, which have potent and rapid anti-inflammatory and immunosuppressive effects [37–41]. Following methylprednisolone pulses, extra-renal symptoms disappear rapidly, and serum creatinine returns more rapidly to normal. Furthermore, this allows oral prednisone to be started at a lower dose, thus reducing the complications of this treatment.

Some patients with diffuse proliferative glomerulonephritis are well controlled with corticosteroids alone. However, several studies have shown that renal survival is significantly better when cyclophosphamide or azathioprine is added to corticosteroids [42–46]. A meta-analysis performed by Felson and Anderson [47] analyzed eight trials published between 1971 and 1983 and compared the outcome of 113 patients treated with corticosteroids alone with that of 137 other patients who received cyclophosphamide and/or azathioprine in addition to corticosteroids, with a follow-up of 2–82 months. Only two-thirds of the patients had biopsy-proven class IV nephropathy. The addition of cyclophosphamide and/or azathioprine lowered the incidence of progression to renal failure by 40% compared with treatment with corticosteroids alone. There was no difference in terms of mortality between the groups. The meta-analysis did not indicate that cyclophosphamide was superior to azathioprine.

In the studies performed at the NIH, 111 patients with lupus nephritis were randomized in five groups and received either high-dose prednisone alone, moderate doses of prednisone in association with azathioprine, with oral cyclophosphamide, with azathioprine and oral cyclophosphamide, or with cyclophosphamide given as intravenous boluses [48]. There was no difference in the outcome during the first 5 years, but after 5 years the incidence of renal failure was significantly higher in the group receiving prednisone alone compared with patients given intravenous cyclophosphamide. There was a trend for a better outcome in patients who received intravenous cyclophosphamide compared with those given oral cyclophosphamide alone or in combination with azathioprine, although the differences were not statistically significant. Patients receiving azathioprine did better during the 1st decade than those treated with prednisone alone, but the incidence of renal failure was not statistically different after 10 years in these two groups. The results of these studies have greatly influenced nephrologists in their therapeutic decisions. Many use intravenous cyclophosphamide for the treatment of diffuse proliferative glomerulonephritis [49, 50]. However, the interpretation of the results of the NIH trials should take into account several points. Firstly, among the 111 patients enrolled in the studies, 6 had no renal biopsy, 7 had a mesangiocapillary glomerulonephritis, and 16 a pure membranous glomerulonephritis. Secondly, some of the patients in the prednisone group were from a historical group. Thirdly, the number of at-risk patients after 10 years was only 8–12 in each group. If the beneficial effect of cyclophosphamide is clearly demonstrated in high-risk patients, there is no indication from the NIH trials that patients with less-severe nephritis treated early during the course of...
the disease with steroids alone may not have an excellent outcome.

Cyclophosphamide given as monthly boluses at a starting dose of 750 mg/m² may be less toxic than given orally every day at a dose of 2 mg/kg. The dose of cyclophosphamide given in bolus form is increased to 1,000 mg/m² if the white blood cell count remains above 3,000/mm³ [51]. The optimal duration of cyclophosphamide pulse therapy has not been determined. Another trial was performed at the NIH in 65 patients with severe lupus nephritis, defined by an impairment of renal function and/or a high activity index on renal biopsy [45]. Three regimens were compared: (1) six monthly pulses of cyclophosphamide, (2) the same regimen followed cyclophosphamide pulses every 3 months for 2 additional years, and (3) six monthly pulses of methylprednisolone without cyclophosphamide. Oral prednisone was given to all patients at a starting dose of 0.5 mg/kg per day and then tapered. The probability of doubling serum creatinine after 5 years of follow-up was higher in patients treated with methylprednisolone pulses than in those receiving cyclophosphamide (48% versus 25%). The probability of relapse of lupus nephritis was significantly higher in patients receiving cyclophosphamide pulses for 6 months compared with those receiving the long-course cyclophosphamide regimen (55% versus 10% after 5 years of observation). The conclusions of the investigators were that cyclophosphamide pulses are more effective than methylprednisolone pulses in preserving renal function and that maintenance cyclophosphamide pulses reduce the risk of relapse.

In children with active lupus nephritis, the data on the efficacy of cyclophosphamide pulses remain scant. Lehman et al. [52] treated 16 children with cyclophosphamide monthly for 6 months and then every 3 months. They reported a significant improvement at 1 year in urine protein excretion, hemoglobin levels, C3, C4, and creatinine clearance, despite a significant reduction in prednisone dosage. Baqi et al. [35] compared two treatment modalities in children with class II and class IV lupus nephritis: high-dose pulse methylprednisolone for 10 days, followed by oral prednisone (20 patients) or intravenous cyclophosphamide given monthly for 6 months and then every 3 months for a period of 3 years with oral prednisone (30 patients). The authors found no difference in outcome for the two treatment modalities.

Other authors have reported the possibility of controlling the disease with a shorter course of therapy. Levey et al. [26] reported the results of the Lupus Nephritis Collaborative Study where patients with severe lupus nephritis were treated with oral prednisone at a starting dose of 60–80 mg/day and oral cyclophosphamide for 8 weeks. Exacerbations were treated with increased doses of corticosteroids. Only 16% of the 31 patients who had a normal serum creatinine concentration at the start of the treatment had a rise in serum creatinine at the latest follow-up, after a mean follow-up of 144 weeks, and only 2 (6.5%) progressed to renal failure. Conversely, 16 of the 55 patients (29%) with elevated initial serum creatinine levels progressed to renal failure during the follow-up period. These patients may have benefited from a more-aggressive regimen. Patients with severe lupus nephritis and normal initial serum creatinine may thus have an excellent outcome without cyclophosphamide pulses, although the duration of follow-up in this study was rather short.

Our current protocol for patients with severe lupus nephritis comprises three methylprednisolone pulses followed by 1.5 mg/kg per day oral prednisone and six monthly pulses of cyclophosphamide. A second renal biopsy is then performed and, when the disease is under control, the patient may be maintained on azathioprine while the prednisone dosage is slowly tapered. In children with milder disease, we often propose starting treatment with intravenous methylprednisolone pulses, followed by oral prednisone at moderate doses, 1–1.5 mg/kg per day. We do not routinely prescribe cytotoxic agents in this situation.

Complications of pulse cyclophosphamide

The incidence of hemorrhagic cystitis is very low provided adequate intravenous hydration is provided for at least 24 h [51]. In order to minimize the risk of hemorrhagic cystitis, we also administer mesna, which binds to cyclophosphamide metabolites in the urine. Nausea and vomiting are frequent during intravenous cyclophosphamide therapy. This may be in part prevented by the concomitant use of antiemetic agents, such as ondansetron (Zofren). Cyclophosphamide pulses often result in neutropenia, with a serious risk of infection, which may be life-threatening [53]. Herpes zoster infections are frequent in these patients. Children and their families should be aware of the risk of transient alopecia. Ovarian toxicity is another serious complication. The risk of amenorrhea depends on the age of the patient at the start of the treatment and the total number of pulses [54]. When treatment is given for 6 months, the risk of amenorrhea is very low if the patient is less than 25 years of age, while 25% of patients over 30 years will develop this complication. When the total number of pulses exceeds 15, the likelihood of developing amenorrhea is 17% for patients less than 25 years of age and nearly 100% for those over 30 years. There are no published data on the long-term gonadal toxicity of cyclophosphamide pulses given to prepubertal girls. The gonadal toxicity of pulse cyclophosphamide in men has not been studied. However, studies in children with idiopathic nephrotic syndrome indicate that toxicity may occur if the cumulative dosage is higher than 200 mg/kg. No disseminated malignancies have been reported in patients treated with cyclophosphamide pulses, although longer follow-up periods are needed before any definite conclusions can be drawn.

Sepsis is a major complication in children with SLE and may be responsible for death. The increased risk of
bacterial and opportunistic infections can be explained by hypocomplementemia, decreased neutrophil function, neutropenia, and the use of corticosteroids and cyclophosphamide. There is no consensus on the use of prophylaxis in these patients.

Treatment of relapses

Relapse of the disease may be defined as a worsening of renal symptoms. Some patients may present with an increase in serum creatinine associated with an active urinary sediment and often increased proteinuria [55]. The presence of red cell and/or white cell casts is predictive of a renal relapse. In other patients, an increase in proteinuria is the only renal symptom. In such cases, serological abnormalities may be important. An elevation of the anti-DNA antibody titer and a decrease in the complement levels (C4 and C3) are most often associated with renal flares. These serological parameters should be checked regularly, as changes often precede a clinical relapse [56, 57]. However, many relapses do not involve the kidney. Patients with an increase in anti-DNA antibody titer and/or a reduction in C3 levels should be monitored closely for the next few months, but not treated solely on the basis of these serological changes. In patients with worsening of renal symptoms, repeat renal biopsy may also be helpful before deciding upon a change in therapy. Patients who show active lesions on repeat renal biopsy may need aggressive treatment. Other patients with increased serum creatinine may have extensive tubulointerstitial lesions with mild glomerular lesions, which do not require any therapy. In such cases, the renal biopsy shows interstitial fibrosis with some accumulation of monocytes and plasma cells. Tubulointerstitial lesions with lymphocyte infiltrates and granular peritubular deposition of immunoglobulins are seen in patients with active class III or class IV disease and require therapy. Some patients treated initially for diffuse proliferative glomerulonephritis who respond well to therapy may have an increased proteinuria several months later. A repeat renal biopsy is useful in this situation, as it may show active lesions or pure membranous nephropathy, which pose different therapeutic decisions. We believe that a repeat renal biopsy is often needed in patients with renal relapses in order to decide the best therapy and avoid unnecessary aggressive treatments which may be more harmful than a renal biopsy. Many authors now treat diffuse proliferative glomerulonephritis and renal exacerbations with methylprednisolone pulses, followed by oral prednisone with tapering doses.

Treatment of patients with membranous nephropathy

Membranous lupus glomerulonephritis (class V) may precede other manifestations of lupus. It is characterized by mild mesangial hypercellularity, diffuse thickening of the capillary walls, and peripheral, granular deposition of immunoglobulins and complement fractions. In some patients, the membranous lesions are associated with mesangial proliferation. This category resembles diffuse proliferative glomerulonephritis. In other patients, the histological findings are similar to idiopathic membranous glomerulonephritis. Moderate proteinuria is accompanied in 50% of patients by hematuria. A nephrotic syndrome often develops. Moderate renal failure and hypertension are observed in 25% of patients. Anti-DNA antibody titers are usually moderately elevated.

Patients with pure membranous nephropathy, mild proteinuria, and normal renal function have a good prognosis, with a 5-year renal survival close to 85% [58, 59]. There is general agreement that no specific treatment is needed. The treatment of patients with nephrotic syndrome is controversial. These patients are at risk of thrombotic complications. Moroni et al. [60] randomly assigned patients to receive either a 6-month regimen consisting of corticosteroids (3 methylprednisolone pulses followed by oral prednisone 0.5 mg/kg per day during months 1, 3, and 5) and chlorambucil (0.2 mg/kg per day during months 2, 4, and 6) or symptomatic treatment. The probability of surviving without developing renal failure at 10 years was 92% in the treated group compared with 60% in the control group. Complete or partial remissions were significantly more frequent in the treated group. Radhakrishnan et al. [61] treated ten nephrotic patients with cyclosporine for periods of up to 43 months. Proteinuria decreased to less than 1 g/day in six patients and between 1 and 2 g/day in two patients. Repeat renal biopsies in five patients showed a decrease in the histological activity index but a rise in the chronicity index. Serum creatinine levels were not significantly increased at the end of the study.

Sloan et al. [59] recently reported that patients with membranous nephropathy and proliferative lesions have a worse prognosis. Therefore, patients with endocapillary proliferation and/or necrosis in >50% of glomeruli should be treated as patients with class IV nephropathy. Patients with a worsening of renal function should have a repeat renal biopsy in order to detect superimposed proliferative lesions and rapidly institute aggressive treatment.

Other therapeutic approaches

Plasma exchanges have been proposed with the aim of removing immune complexes that may be involved in the pathogenesis of lupus nephritis. A randomized controlled trial compared a standard therapy with prednisone and oral cyclophosphamide with the same treatment plus plasma exchanges, three times a week for 4 weeks, in 86 patients with severe lupus nephritis [62]. The mean follow-up was 136 weeks. There were no differences between the groups in terms of patient survival, renal survival, clinical activity of the disease, and complications. However, this does not mean that plasma exchanges are
not of help in individual patients [63, 64]. A multicenter trial of the effects of synchronized plasma exchanges and cyclophosphamide pulses in very severe lupus patients is currently in progress.

Intravenous immunoglobulins have been reported to be effective in individual patients, including patients with nephritis [65, 66]. Cyclosporine has been given to patients who were not well controlled by standard therapy. A decrease of proteinuria and an improvement of renal function followed the treatment, while the dose of prednisone could be tapered [67]. These results show that cyclosporine may be used in some patients as a steroid-sparing agent.

**End-stage renal disease**

The incidence of end-stage renal disease in lupus nephritis is approximately 20%, this complication developing after a mean period of 5 years [68, 69]. Patients with a slow progression to renal failure often have a decrease in clinical and serological activity. Dialysis, either hemodialysis or peritoneal dialysis, can be started, and these patients do as well as non-lupus patients with end-stage renal disease. Other patients have a rapid course to renal failure, maintaining clinical and serological signs of activity. Therapeutic decisions are difficult, as aggressive treatments may allow a recovery of renal function and discontinuation of dialysis. However, these patients are at higher risk of iatrogenic complications, particularly infection, which may be life-threatening [70, 71].

Clinical and biological symptoms of the disease most often improve in patients on chronic dialysis, thus allowing discontinuation of corticosteroids and immunosuppressive therapy. However, clinical manifestations can persist or even appear at this stage.

Renal transplantation is the treatment of choice for those who progress to renal failure. The outcome after renal transplantation in these patients is similar to that of patients with other diseases [72–74]. However, it may be advisable to wait for a few months before proposing transplantation, until the clinical and serological activity of lupus have decreased. Moreover, a period without corticosteroids and immunosuppressive agents may be beneficial to the child. After renal transplantation, the activity of the disease declines and recurrence in the graft is exceptional.

**Conclusions**

The initial treatment of diffuse proliferative glomerulonephritis should be vigorous. Corticosteroids alone would require excessively high doses that would lead to serious complications. Therefore, immunosuppressive agents, either oral or intravenous, are given, but there are still some questions on the duration of treatment, given the possible long-term complications. When deciding on the treatment, the physician should bear in mind that aggressive treatment of mild renal lesions exposes the patients to infectious complications and that inadequate treatment of severe nephritis exposes the patient to the risk of progression to renal failure. In all cases, careful follow-up is necessary to avoid these complications, and good compliance with the treatment is also important [2]. In those patients who progress to end-stage renal disease, clinical and serological remission is common, and renal transplantation can be performed, as recurrence in the transplant is very uncommon.

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A controlled trial of combined therapy for newly diagnosed severe childhood IgA nephropathy


The most appropriate treatment for patients with IgA nephropathy is controversial. Treatment with prednisolone, azathioprine, heparin-warfarin, and dipyridamole for 2 yr (group 1) or heparin-warfarin and dipyridamole for 2 yr (group 2). All of the 40 patients in group 1 and 34 of the 38 patients in group 2 completed the trial. The mean urinary protein excretion fell in group 1 patients ($P < 0.0001$), but remained unchanged in group 2 patients. The mean serum IgA concentration was reduced in group 1 patients ($P = 0.0002$), but was unchanged in group 2 patients. BP and creatinine clearance were normal at the end of the trial in all but one group 2 patient, who developed chronic renal insufficiency. The percentage of glomeruli showing sclerosis was unchanged in group 1 patients, but increased in group 2 patients ($P = 0.006$). The intensity of mesangial IgA deposits decreased in group 1 patients ($P = 0.02$), but remained unchanged in group 2 patients. In conclusion, the present study shows that treatment of children with severe IgA nephropathy with prednisolone, azathioprine, heparin-warfarin, and dipyridamole for 2 yr early in the course of disease reduces immunologic renal injury and prevents increase of sclerosed glomeruli.