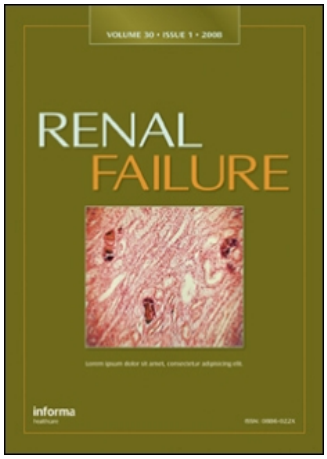

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Long-Term Efficacy and Safety of Quadruple Therapy in Childhood Diffuse Proliferative Lupus Nephritis

Gülay Demircin [a]; Ayşe Öner [b]; Özlem Erdoğan [a]; Ali Delibaş [c]; Şahika Baysun [a]; Mehmet Bülbül [a]; Kenan Bek [d]; Ayşegül Oksal [e]
[a] Department of Pediatric Nephrology, Dr. Sami Ulus Children's Hospital, Ankara, Turkey
[b] Department of Pediatric Nephrology, Ufuk University, Medical School, Ankara, Turkey
[c] Department of Pediatric Nephrology, Mersin University, Medical School, Mersin, Turkey
[d] Department of Pediatric Nephrology, 19 Mayıs University, Medical School, Samsun, Turkey
[e] Department of Pathology, Dr. Sami Ulus Children's Hospital, Ankara, Turkey

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CLINICAL STUDY

Long-Term Efficacy and Safety of Quadruple Therapy in Childhood Diffuse Proliferative Lupus Nephritis

Gülay Demircin
Dr. Sami Ulus Children's Hospital, Department of Pediatric Nephrology, Ankara, Turkey

Ayşe Öner
Ufuk University, Medical School, Department of Pediatric Nephrology, Ankara, Turkey

Özlem Erdoğan
Dr. Sami Ulus Children's Hospital, Department of Pediatric Nephrology, Ankara, Turkey

Ali Delibaş
Mersin University, Medical School, Department of Pediatric Nephrology, Mersin, Turkey

Şahika Baysun
Dr. Sami Ulus Children's Hospital, Department of Pediatric Nephrology, Ankara, Turkey

Mehmet Bülbül
Dr. Sami Ulus Children's Hospital, Department of Pediatric Nephrology, Ankara, Turkey

Kenan Bek
19 Mayıs University, Medical School, Department of Pediatric Nephrology, Samsun, Turkey

Ayşegül Oksal
Dr. Sami Ulus Children's Hospital, Department of Pathology, Ankara, Turkey

In this study, we evaluated the frequency, clinical presentation, treatment protocols, prognostic factors, and outcome in children with diffuse proliferative lupus nephritis (DPLN). Between June 1990 and December 2004, 46 patients were diagnosed to have systemic lupus erythematosus (SLE), and 26 of them (56.5%) were found to have DPLN. Renal manifestations were present in 25 patients, and the majority of them presented with severe renal findings, such as nephrotic syndrome and renal failure. All patients were given a quadruple therapy protocol including 6–12 monthly courses of methyl prednisolone pulse therapy combined with oral prednisolone, oral cyclophosphamide, azathioprine, and dipyridamole. Nineteen of these patients were regularly followed up with a mean follow-up period of 5.9 years. Complete remission was achieved in 15 of 19 patients, and chronic renal failure developed in four patients. Renal survival rate was calculated to be 78.9% at the end of 5, 10, and 14 years. Although nephrotic range proteinuria, hypoalbuminemia, renal failure, and activity index above 12/24 at presentation seemed to be associated with poor prognosis, no significant difference could be found. Hypertension and chronicity index greater than 6/12 were found to be bad prognostic predictors. We concluded that satisfactory results were achieved with our quadruple therapy protocol; thus, more aggressive and expensive therapies can be avoided and preserved for more serious and persistent diseases.

Address correspondence to Dr. Gülay Demircin, Dr Sami Ulus Children's Hospital, Pediatric Nephrology Department, Ümitkent Sitesi, A8 Blok, No:10, Ümitköy, Ankara, Turkey; Tel.: 090-312-2357799; Fax: 090-312-3170353; E-mail: gulaydemircin@hotmail.com

Keywords diffuse proliferative lupus nephritis, childhood, clinical findings, quadruple therapy, prognosis

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, autoimmune, episodic multisystem disease characterized by widespread inflammation of the blood vessels and connective tissues affecting virtually every organ and the system of the body.[1,2] Renal involvement is one of the main clinical presentations determining the course and outcome of the disease in children with SLE, and patients with diffuse proliferative (Class IV) lupus nephritis (DPLN) are at higher risk of progression to end-stage renal disease if adequate therapy is not instituted.[3,4] Survival in patients with SLE has been significantly improved after the 1980s by the use of immunosuppressive drugs even in severe lupus nephritis. However, despite decades of investigation, no general agreement exists on the optimal treatment for these patients.[5,6]

In this study, we evaluated the frequency, clinical presentation, treatment protocols, and prognosis of children with DPLN followed up in our clinics for nearly 15 years in order to discuss the efficacy and duration of therapy in these high-risk patients.

PATIENTS AND METHOD

Between June 1990 and December 2004, 46 patients (39 girls, 7 boys) with a mean age of 11.3 years (range: 3.5–18 years) were diagnosed with SLE in the Department of Nephrology of a Children's Hospital in Ankara, Turkey, according to the revised criteria of American College of Rheumatology for SLE.[7] All patients underwent renal biopsy. Histopathological findings were classified according to the classification of World Health Organization (WHO) as: minimal change or normal (Class I), mesangial proliferative lupus glomerulonephritis (Class II), focal proliferative lupus glomerulonephritis (Class III), diffuse proliferative lupus glomerulonephritis (Class IV), membranous lupus glomerulonephritis (Class V), and advanced sclerosing lupus glomerulonephritis (Class VI).[3,8] Sixteen of our patients were found to have Class II, 1 with Class III, 26 with Class IV, and 3 with Class V lupus glomerulonephritis.

Patients with Class IV lupus glomerulonephritis (DPLN) were selected and investigated for clinical findings at presentation, renal manifestations, histopathological findings, efficacy and safety of treatment protocols, outcome, and clinical and laboratory findings affecting the prognosis.

Histopathological findings were evaluated for activity and chronicity indices according to the scoring system of Austin et al.[9] proposed for lupus nephritis. Activity index included cellular proliferation, fibrinoid necrosis/karyorrhexis, cellular crescents, hyaline thrombi/wire loops, leucocyte infiltration, and tubulointerstitial abnormalities like mononuclear cell infiltration. Chronicity index included glomerular sclerosis, fibrous crescents, interstitial fibrosis, and tubular atrophy. Each factor was scored from 0 to 3, but fibrinoid necrosis and cellular crescents were weighted by a factor of 2. The maximum score was 24 for the activity index and 12 for the chronicity index.

All patients with DPLN were given a quadruple therapy protocol including 6–12 monthly courses of methyl prednisolone pulse therapy (30 mg/kg/day with a maximum dose of 1 gram) given three days consecutively, followed by an oral prednisolone, oral cyclophosphamide (2 mg/kg/day) for 2–3 months, followed by azathioprine (0.2 mg/kg/day) and dipyridamole (5 mg/kg/day) as an induction therapy. The maintenance therapy of these patients included low dose oral prednisolone, dipyridamole, and azathioprine for at least five years. Mycophenolate mofetil (MMF) was used in maintenance therapy in exceptional cases. The patients were investigated for the complications of therapy by ophthalmological examination and bone mineral densitometry with six-month intervals. Four patients with normal or mild urinary findings (transient proteinuria and/or hematuria) at presentation were biopsied for the second time after induction therapy in order to see the effect of the therapy, and all improved to Class II nephritis.

The patients were defined to have complete remission (CR) if renal functions and urinalysis are normal, partial remission (PR) if persistent hematuria and/or proteinuria exist with normal or near-normal renal functions, chronic renal failure (CRF) if deteriorated renal functions persist, and end stage renal disease (ESRD) if continuous renal replacement therapy is necessary.

Clinical findings and renal manifestations of patients were documented. The effects of time of initiation of therapy, presence of hypertension, nephrotic range of proteinuria and hypoalbuminemia, renal failure at presentation, and activity and chronicity indices at histopathological evaluations were investigated on the prognosis of patients.

Chi-square test and Fisher's exact test were used for statistical comparisons. A p value less than 0.05 was considered to be significant. Renal survival was calculated by the method of Kaplan and Meier.

RESULTS

There were 26 patients (22 girls, 4 boys) with DPLN, which made up 56.5% of all SLE patients. Their ages ranged from 5 to 17 years, with a mean age of 12.4 years.

Most of the patients had renal and hematological findings, arthritis, and malar rash at presentation (see Table 1). Renal manifestations were present in 25 patients (96.2%), and a majority of them presented with severe renal findings like nephrotic syndrome and renal failure (see Table 2). However 15.4% of patients had minor manifestations like transient

Table 1
Clinical findings of patients with DPLN at presentation

Clinical findings	Number of patients (%)
Renal	25 (96.2)
Hematologic	20 (76.9)
Arthritis	15 (57.7)
Malar rush	13 (50.0)
Neurologic	9 (34.6)
Serositis	9 (34.6)
Cutaneous	6 (23.1)
Oral ulcers	5 (19.2)
Photosensitivity	3 (11.5)

Table 2
Renal findings of patients with DPLN at presentation (26 patients)

Renal findings	Number of patients (%)
Proteinuria	22 (84.6)
<40 mg/m2/hr	5 (19.2)
>40 mg/m2/hr	17 (65.4)
Hematuria	19 (73)
Microscopic	11 (42.3)
Macroscopic	8 (30.8)
Hypoalbuminemia	17 (65.4)
Renal failure	16 (61.5)
Transient proteinuria and/or hematuria	3 (11.5)
Normal findings	1 (3.8)

hematuria and/or proteinuria or normal clinical renal findings. Serum creatinine levels of the patients ranged between 0.6 mg/dL and 4.5 mg/dL, with a mean value of 1.6 mg/dL.

The mean follow-up period of the patients was 3.5 years (1 month–14 years). Four patients were lost to follow-up within 1–6 months (mean three months) after the initial therapy was given. Two patients under dialysis therapy died in one month at the beginning of initial therapy. One patient developed Wegener Granulomatosis (WG) after remission from SLE and died because of infection during the course of therapy for WG 10 months later.[10] The overall mortality rate was 11.5%. The other 19 patients were regularly followed-up with a mean follow up period of 5.9 years (2–14 years). The efficacy of treatment and outcome were evaluated in these regularly followed-up 19 patients.

The most frequent complications of therapy were cushingoid feature (18 patients) and osteopenia (10 patients), all of which recovered after the reduction of corticosteroid dose and calcium and vitamin D supplementation, respectively. One patient developed aseptic necrosis of femur head, and one had pulmonary tuberculosis (Tbc), treated successfully by surgery and anti-Tbc drugs, respectively. Another patient had persistent leukopenia due to azathioprine during maintenance therapy and recovered after the replacement of the drug with MMF.

Complete remission was achieved in 15 (79%) of 19 patients within 2–4 months, and CRF developed in 4 (21%) patients. Two of these patients were incompliant to therapy, and both of them developed ESRD in two years' time. All of the patients with ESRD had renal failure at presentation. However, 60% of patients presented with renal failure achieved CR (see Table 3). Renal survival at the end of 5, 10, and 14 years were calculated to be 78.9% (see Figure 1). All patients achieved clinical and laboratory remission for extrarenal manifestations. Hypertension and chronicity

Table 3
Outcome of 19 regularly followed-up patients according to their renal presentation

Renal presentation	Number of patients	Complete remission	Chronic renal failure
Transient proteinuria and/or hematuria or normal	4	4	—
Persistent proteinuria and/or hematuria	2	2	—
Nephrotic syndrome and/or nephritic syndrome without renal failure	3	3	—
Nephrotic syndrome and/or nephritic syndrome with renal failure	10	6	4

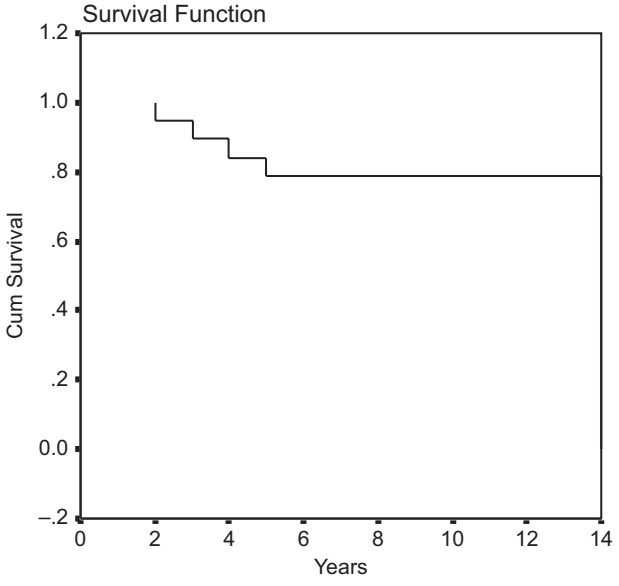

Figure 1. Renal survival of patients with DPLN (Kaplan and Meier).

index greater than 6/12 were found to be bad prognostic predictors. Although nephrotic range proteinuria, hypoalbuminemia, renal failure, and activity index above 12/24 at presentation seemed to be associated with poor prognosis, no significant difference could be found (see Table 4).

Of 15 patients with CR, one patient had relapse after three years of remission as he discontinued therapy, but remission was achieved shortly after the therapy was restarted. Three patients were referred to adult nephrology clinics after a follow up period of 4–6 years at remission. One of these patients had one relapse after referral because of acute stress and healed with MMF therapy, and one maintained her CR without relapse. The data of the third patient could not be retrieved. The therapy of two patients was stopped because of 6 and 7 years of complete remission. Both of these patients had transient proteinuria as the only renal finding at presentation, and their repeat biopsies after induction therapy showed improvement to Class II lupus nephritis. However, they had relapse with renal failure two years after cessation of therapies, and remission was achieved shortly after the therapy was restarted in both patients.

Table 4
Clinical and laboratory findings at presentation affecting the prognosis of 19 regularly followed-up patients

Findings at presentation	Number of patients	Complete remission	End stage renal disease	*p* value
Time of initiation of therapy				
0–3 months	13	10	3	$p = 0.576$
3–6 months	3	3	—	$p > 0.5$
> 6 months	3	2	1	
Hypertension (+)	5	2	3	$p = 0.037$
Hypertension (–)	14	13	1	$p < 0.05$
Nephrotic range proteinuria (+)	11	7	4	$p = 0.103$
Nephrotic range proteinuria (–)	8	8	—	$p > 0.05$
Hypoalbuminemia (+)	11	7	4	$p = 0.103$
Hypoalbuminemia (–)	8	8	—	$p > 0.05$
Renal failure (+)	11	7	4	$p = 0.103$
Renal failure (–)	8	8	—	$p > 0.05$
Activity index				
0–12/24	14	12	2	$p = 0.272$
13–24/24	5	3	2	$p > 0.05$
Chronicity index				
0–6/12	15	15	—	$p = 0.0$
7–12/12	4	—	4	$p < 0.01$

DISCUSSION

Lupus nephritis is one of the main clinical presentations determining the course and outcome in SLE patients, and approximately two-thirds of children and adolescents with SLE develop the manifestations of renal involvement mostly within the first year of diagnosis.[2,3,11] Diffuse proliferative lupus glomerulonephritis is the most common and the most severe histologic type of lupus nephritis, occurring in 40–75% of children with SLE.[11–15] In our study, DPLN was also found to occur in 56.5% of all patients, being the most common type of lupus nephritis.

The clinical picture in SLE is generally related to the severity of histological abnormalities on renal biopsy, but clinical features may not always correlate with histopathology.[5,11,16] As the prognosis and management of SLE depends on the underlying histological lesions, renal biopsy, though controversial, is needed in all children with SLE even with no clinical evidence of renal disease in order to decide the best therapy and predict the prognosis of the disease.[6,16] In our study, though the majority of patients with DPLN presented with serious renal findings like nephrotic syndrome and renal insufficiency, four patients admitted with minor or normal renal findings, confirming the necessity of renal biopsy on all patients with childhood SLE. Moreover, an improvement of the degree of nephritis of these four patients to Class II after induction therapy and relapse of two of them with renal failure years after long-term remission and cessation of therapies also support the need for appropriate therapy according to the histopathological classification.

The use of high dose corticosteroids and various cytotoxic agents has improved the prognosis of DPLN. However, there is still some controversy for the best treatment of the disease.[5] Today, corticosteroids are regarded as the basis for treatment of all types of lupus nephritis, including DPLN.[17] Many authors propose to initiate the induction therapy in DPLN with methyl prednisolone pulses (MPP), which have potent and rapid antiinflammatory and immunosuppressive effects, and to continue with lower doses of oral corticosteroids.[5,6,11,15,17] Although some patients with DPLN are controlled with corticosteroids alone, the addition of cytotoxic immunosuppressive drugs reduces the chance for progression to chronic irreversible lesions and improves short- and long-term prognosis.[6,17] Historically, azathioprine and oral or intravenous cyclophosphamide are the most frequently used immunosuppressive drugs in combination with corticosteroids, together with antiplatelet agents.[15,17] The most widely used intravenous cyclophosphamide regimen consists of monthly infusions with 500–1,000 mg/m^2 doses for six months, followed by 2–4 monthly infusions for 18–24 months.[13,17–21] Compared with daily oral cyclophosphamide

(1–3 mg/kg/day), the intravenous route has been accepted to have the advantage of less severe side effects, like cystitis and bladder cancer, as the cumulative doses are smaller.[17] However, not all investigators encounter such difficulties if the daily oral dose of cyclophosphamide does not exceed 1.5 mg/kg/day and daily treatment does not exceed 4–6 months.[18] Azathioprine is believed to be as effective as cyclophosphamide in SLE, especially in maintenance therapy, and generally well tolerated at 1–2.5 mg/kg/day doses.[5,18] Together with dipyridamole, our quadruple therapy protocol included methyl prednisolone pulses followed by oral prednisolone, oral cyclophosphamide, and azathioprine as induction. Successful results were obtained without severe complications, and a long remission period could be achieved with low dose oral prednisolone and azathioprine as maintenance therapy.

In recent years, methotrexate, cyclosporine, and mycophenolate mofetil (MMF) have been used in therapy-resistant patients, but there are not yet large randomized studies showing their efficacy and superiority to cyclophosphamide and azathioprine.[17,18,22–25] Plasma exchange, intravenous immunoglobulins, tacrolimus, rituximab, fludarabine, cladribine, monoclonal antibodies, and rapamycin are the other therapeutic approaches used in DPLN.[5,6,14,17,22,26,27] There are also experimental therapies, such as gene therapy and stem cell transplantation, in the management of lupus nephritis.[17,22] We used MMF in maintenance therapy in one patient who developed persistent leukopenia with azathioprine, and it was well tolerated. Another patient who was referred to adult clinics was given MMF because of relapse after referral, and she too achieved remission.

Although the use of immunosuppressive agents has improved the prognosis of severe lupus nephritis in the last decades, renal disease and its treatments remain a major cause of morbidity and mortality.[5,28] In the literature, the mortality rate in children with SLE differs according to the different centers. The overall mortality rate in all SLE patients was found to be as high as 32% in India, 22.2% in Egypt, 15.8% in Thailand, 6% in Canada, and 1.9% in Serbia.[1,129–32] In patients with DPLN, these rates increased to 9.8% in Canada and 2.9% in Serbia.[11,32] In a study from Turkey, Emre et al.[33] found the mortality rate to be 9.3% in all children with SLE and 13.8% in DPLN patients. The mortality rate in our patients with DPLN was 11.5%. Two of them died at the very early period of admission before the effect of therapy was started. The third patient achieved remission from SLE with our standard therapy, but he developed WG and died because of infection during the treatment of WG 10 months later.[10] If we exclude this patient, our mortality rate because of SLE was found to be 7.7%. Both of these rates are not higher than other patients in the literature, excepting the study in Serbia.

The incidence of ESRD in lupus nephritis is approximately 10–20%, and it develops after a mean period of five years.[3–5] In the literature, the studies on the prognosis of childhood SLE are limited, and they mostly include all types of SLE nephritis.[11,13,21,30,34,35] Barbano et al.[21] reported the outcome of 33 patients with childhood-onset SLE and compared the effects of treatment of monthly intravenous cyclophosphamide with corticosteroids alone or combined with azathioprine. They found that survival was better and protection of renal function lasted longer in the former group without evident short- or long-term side effects. Dixit et al.[13] assessed the response rates and outcome in 14 children with SLE (9 with DPLN) given six-monthly pulses of intravenous cyclophosphamide followed by longer duration pulses and found that only half of the patients achieved renal remission; of this group, 86% relapsed and 42% had adverse outcomes, including death and chronic renal failure. Bakr et al.[30] reported 52 children with SLE, 42 of whom had nephritis (36% Class IV). More than half of the patients received methyl prednisolone pulse with or without a combination of cyclophosphamide pulses, and complete remission was achieved in 55.6% of patients. Bogdonovic et al.[11] reported 53 children with SLE nephritis treated with corticosteroids alone or combined with azathioprine or with intravenous cyclophosphamide. Renal disease was in remission in 80% of patients, either complete (50%) or partial (30%), and the five-year kidney survival rate was found to be 88.6%, 82.4% in the 34 patients with Class-IV nephritis. In our study, 21% of patients developed ESRD, while 79% had complete remission. Renal survival rate was calculated to be 78.9% at the end of 5, 10, and 14 years. The prognosis of our patients with our quadruple therapy protocol was not worse but in fact better than the other SLE patients treated with other protocols, even though all of our patients had the most severe form of SLE nephritis. The patients who were incompliant and that did not respond to therapy at the first months were more susceptible to develop ESRD.

Some patients with DPLN are at higher risk of progression, particularly those with higher activity index in histopathological examination.[5] Many studies have also shown that other factors, including age, gender, race, socioeconomic status, hypertension, initial renal failure, delay of treatment, exacerbations, absence of remission, and the response to therapy after the first year, may be of prognostic significance.[5,11,34,36–38] Bogdonovic et al.[11] reported that nephritic syndrome and Class IV nephritis at initial biopsy were the only parameters significantly associated with adverse outcome. Hernandez et al.[20] found that a high chronicity index, interstitial fibrosis, persistent hypertension, and hypocomplementemia after treatment were the major variables associated with ESRD. Baqi

et al.[38] reported that the children with Class IV disease, hypertension, and high creatinine and low C3 complement levels at the time of diagnosis were at increased risk for ESRD, and concluded that the initial histopathological classification of lupus nephritis was the most reliable prognostic factor for disease progression. In the study of Emre et al.[33] from Turkey, adverse outcomes were significantly associated with the persistent hypertension, anemia, high serum creatinine level, heavy proteinuria, nephritic syndrome, and Class IV nephritis at presentation. Including only Class IV SLE patients, our study has been already performed on high risk patients for progression and revealed hypertension as the only bad prognostic clinical predictor and high chronicity index as the only bad prognostic histopathological factor. Although nephrotic range proteinuria, hypoalbuminemia, and renal failure at presentation together with the high activity index were also associated with poorer prognosis, no statistical significance could be found.

The goal of long-term management in patients with lupus nephritis is the suppression of disease with minimum side effects of treatment, but there is no consensus on the time when the therapy should be stopped.[34] Although it is often suggested that one stop treatment after five years or more even in patients with very severe lupus nephritis, renal flares are common in up to 37–65% of patients, mostly soon after the initial episode and especially when immunosuppressive therapy is reduced, but it can be prolonged up to 11–25 years after complete remission.[37,39,40] Every renal flare-up leaves a number of sclerosed glomeruli and areas of tubulointerstitial fibrosis, leading to a progression of renal failure, but the effectiveness of long-term maintenance therapy has not yet been investigated in long-term prospective studies.[40] In our study, we discontinued the therapy in two patients after a remission period of six and seven years, and both had relapse two years after cessation of therapy. Another patient relapsed after he stopped receiving his drugs himself after a remission period of three years. Remission was achieved shortly after the therapy was restarted in all patients.

In conclusion, DPLN is the most common and most serious form of nephritis in childhood SLE, but with appropriate management, its prognosis may be improved. Satisfactory results with few and mild complications were achieved with our quadruple therapy protocol with a complete remission of 79%; thus, more aggressive and expensive therapies can be avoided and preserved for more serious and persistent diseases. However, the treatment needs to be continued for a longer period of time, probably lifelong, and patients need to be more compliant to therapy.

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