Longterm Followup of Childhood Lupus Nephritis

STEFAN HAGELBERG, YUNA LEE, JOANNE BARGMAN, GORDON MAH, RAYFEL SCHNEIDER, CARL LASKIN, ALLISON EDDY, DAFNA GLADMAN, MURRAY UROWITZ, DIANE HEBERT, and EARL SILVERMAN

ABSTRACT. ***Objective***. To determine the longterm outcome in children with onset of lupus nephritis before 18 years of age.

Methods. Sixty-seven patients with onset of lupus nephritis prior to age 18 were identified. The mean followup time was 11 years (range 5–19). The mean age at diagnosis was 13.2 years (range 4–17). The male:female ratio was 1:3.8. Renal biopsies were classified using the WHO classification. Fifteen patients had Class II, 8 patients Class III, 32 patients Class IV, and 11 patients Class V and one patient refused biopsy. The cohort consists of the 66 patients who had a renal biopsy. Five patients received cyclophosphamide (CYC) and 17 received azathioprine (AZA) as part of the initial treatment of Class IV nephritis. Eight additional patients received CYC because of a flare of disease while receiving AZA, and 8 other patients received AZA because of a flare of disease while taking prednisone therapy.

Results. Four patients died; 6 developed endstage renal disease (ESRD); all but one of the patients who died and/or had ESRD had WHO Class IV [diffuse proliferative glomerulonephritis (DPGN)]; only 2 Caucasians developed ESRD, although 16 out of 36 Caucasians had DPGN; serum creatinine at followup was normal in 84% of the survivors; presently 70% of the patients take less than 7.5 mg prednisone/day and 62% do not take cytotoxic drugs. No patient is currently treated with CYC. All 8 patients with Class III nephritis were taking medication at last followup.

Conclusion. The longterm outcome in this group of children with lupus nephritis, in whom AZA was the most commonly used immunosuppressive agent, was excellent, with 94% patient survival at a mean followup of 11 years. Our results suggest that non-Caucasian patients with pediatric onset lupus nephritis may be at increased risk for renal failure compared to Caucasians. (J Rheumatol 2002;29:2635–42)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS NEPHRITIS CHILDHOOD
OUTCOME CYCLOPHOSPHAMIDE

Systemic lupus erythematosus (SLE) in childhood accounts for roughly 10–20% of all cases of SLE, and the clinical features and outcome may differ from that seen in adult onset SLE[1]. It has been suggested that both nephritis and central nervous system (CNS) involvement are more common in pediatric onset SLE[2]. Although studies have suggested that pediatric patients with nephritis have a poor longterm outcome compared to adults, followup studies from the last decades have shown that the outcome for both renal and patient survival in pediatric SLE is likely similar to that seen in adult SLE[1-5]. The leading cause of morbidity and mortality worldwide in adult and pediatric onset SLE is now infection, often secondary to immunosuppression[6-8]. In addition, cardiovascular disease has become increasingly recognized as a cause of late morbidity[9].

There is some controversy about the optimal treatment of pediatric SLE nephritis, particularly with regard to the choice of cytotoxic agents[10-14]. Although most investigators advocate the use of immunosuppressive agents for patients with the more severe forms of nephritis, many of these agents may be associated with significant toxicity and, in particular, severe infections, infertility, and malignancies. The latter 2 toxicities are particularly important in pediatric SLE, as most patients are girls who have only recently entered child-bearing years. The choice of cytotoxic agents must take into account the risk:benefit ratio balancing efficacy with longterm toxicity.

We describe the longterm followup of 67 patients with pediatric SLE with nephritis. There was a 94% patient survival after an average of 11 years of followup.

From the Divisions of Rheumatology and Nephrology, Department of Paediatrics, The Hospital for Sick Children; and the Divisions of Nephrology and Rheumatology, University Health Network, Department of Medicine, University of Toronto, Toronto, Ontario, Canada.

S. Hagelberg, MD, PhD; G. Mah, MD; R. Schneider, MB, BCh, FRCPC; E. Silverman, MD, FRCPC, Division of Rheumatology, Department of Paediatrics, The Hospital for Sick Children; Y. Lee, MD, FRCPC; J. Bargman, MD, FRCPC, Division of Nephrology, University Health Network, Department of Medicine, University of Toronto; A. Eddy, MD, current address: Division of Nephrology, Children's Hospital and Regional Medical Center, University of Washington, Seattle, WA, USA; D. Hebert, MD, FRCPC, Division of Nephrology, Department of Paediatrics, The Hospital for Sick Children; C. Laskin, MD; D. Gladman, MD, FRCPC; M. Urowitz, MD, FRCPC, Division of Rheumatology, University Health Network, Department of Medicine, University of Toronto.

Address reprint requests to Dr. E. Silverman, Division of Rheumatology, Hospital for Sick Children, Toronto, Ontario M5G 1X8.
E-mail: earl.silverman@sickkids.on.ca

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MATERIALS AND METHODS

All patients seen between the years 1984 to 1991 at the Lupus Clinic at the Hospital for Sick Children, Toronto, Canada, were eligible for inclusion into the study. Patients were excluded if they had been seen only in consultation and/or were not routinely followed on a regular basis at the Lupus Clinic or had followup < 5 years. Eighty-nine patients were identified who met the inclusion criteria and 67 (75%) had had at least one episode of nephritis a minimum of 5 years before the study. Sixty-six of the 67 patients had a renal biopsy performed within 4 weeks of initiating treatment for renal disease; one patient refused a biopsy. The cohort consists of the 66 patients in whom a renal biopsy was performed. The male:female ratio was 1:3.8.

Data at the time of followup were available from the medical records of patients actively followed at the Hospital for Sick Children or University Health Network (Table 1). When a patient was not actively followed at one of the 2 hospitals, patient information was then obtained with informed consent from the medical records of their current physician and/or by a telephone interview of the patient. Full laboratory investigation and medication data were available for all patients.

Cyclophosphamide (CYC) was given as intravenous bolus therapy. The CYC was given monthly for 7 doses, every 3rd month for 4 doses, and then every 6 months for 2 doses. The dose was initiated at 500 g/m^2 and increased by 250 mg/m^2 on successive months to a maximum of 1 g/m^2. The dose was adjusted to maintain an absolute neutrophil count > 500 cells/ml at the nadir of the count. Patients received the full course unless there was a disease flare during therapy. Azathioprine (AZA) was given daily orally. The dose was 2–3 mg/kg per day with a maximum of 150 mg. The dose was titrated to maintain a total white blood cell count between 3 and 4 × 10^3 cells/ml.

RESULTS

Renal outcome. Sixty-six of 67 patients had a renal biopsy and the 66 patients make up our cohort. The most common lesion seen was Class IV nephritis in 48% of patients, followed by Class II in 23%, Class III in 12%, and Class V nephritis in 17% (Table 2). At mean followup of 11 years (range 5–19) only 6/66 (9%) of patients had developed endstage renal disease (ESRD), while an additional 3 patients had died of sepsis that complicated acute renal failure. Therefore 9/66 (14%) patients developed ESRD or had acute renal failure at the time of death. Eight of these 9 patients had Class IV nephritis while the other patient, who died, had Class V-C (membranous nephritis with focal proliferative changes). Four of the 6 surviving patients received a kidney transplant, of whom 2 patients had functioning transplants at last followup. Of the failed transplants, one patient was undergoing hemodialysis and one continuous ambulatory peritoneal dialysis (CAPD). The other 2 patients are currently undergoing hemodialysis.

Table 1. Followup (yrs) of patients with pediatric SLE nephritis.

	Mean	Range	Median
Age at diagnosis, yrs	13.2	4–17	14
Age at followup, yrs	24.2	9–34	23
Followup time, yrs	11.0	5–21	10

Table 2. World Health Organization classifications of kidney biopsies.

Classification	Number
Mesangial (Class II)	15
Focal Proliferative (Class III)	8
Diffuse Proliferative (Class IV)	32
Membranous (Class V)	11
No biopsy	1
Total	67

Of the other 58 patients, only 4 patients had an elevated serum creatinine level. All 4 patients with mildly abnormal renal function had Class IV nephritis, while all 15 patients with Class II, all 8 patients with Class III, and 10/11 patients with Class V nephritis (one patient died) had normal renal function at followup. Therefore at last followup 81% (54/67) of all patients had normal serum creatinine levels.

Using Kaplan-Meier survival analysis, renal survival rates for all patients were 93% at 5 years, 85% at 10 years, and 80% at 15 years and 19 years (Figure 1A). Kaplan-Meier survival for renal survival for Class IV nephritis was 87% at 5 years, 72% at 10 years, and 65% at 15 and 19 years (Figure 1B).

Mortality. Four of 67 patients died, for a 6% overall mortality. Two of the deaths occurred within the first year of diagnosis. Both these patients had Class IV nephritis and were in renal failure at the time of presentation and death. Sepsis was the immediate cause of death, and both these patients had received high dose corticosteroid and CYC as the initial therapy for their nephritis with renal failure. The 3rd patient had Class V nephritis and associated focal proliferative nephritis and developed ESRD 8 years after diagnosis. This patient died shortly after the development of ESRD. The 4th patient who died had Class IV nephritis and died at age 31, 15 years after the diagnosis of nephritis. The cause of death was acute myocardial infarction following vigorous activity. He had normal renal function without a history of heart disease. His only cardiac risk factors were a history of prednisone use and borderline, untreated, hypertension.

No patient with Class II or Class III died. By Kaplan-Meier survival analysis for all patients, the 5 year survival rate was 97%, 10 year survival rate was 95%, and 15 and 19 year survival rates were both 90% (Figure 2A). Using Kaplan-Meier survival analysis for patients with diffuse proliferative glomerulonephritis (DPGN), the 5 year survival rate was 94%, 10 year survival rate was 91%, and 15 and 19 year survival rates were 88% (Figure 2B).

Therapy. All patients received treatment with corticosteroids for nephritis and 42 also received treatment with antimalarials during the course of their illness. Immunosuppressive agents were not used routinely for all patients, and the frequency of use and choice of agent varied during different time periods and was dependent on the type of nephritis. Most patients (94%; 30/32) with Class IV nephritis received AZA and/or CYC and 73% (22/30) received these medica-

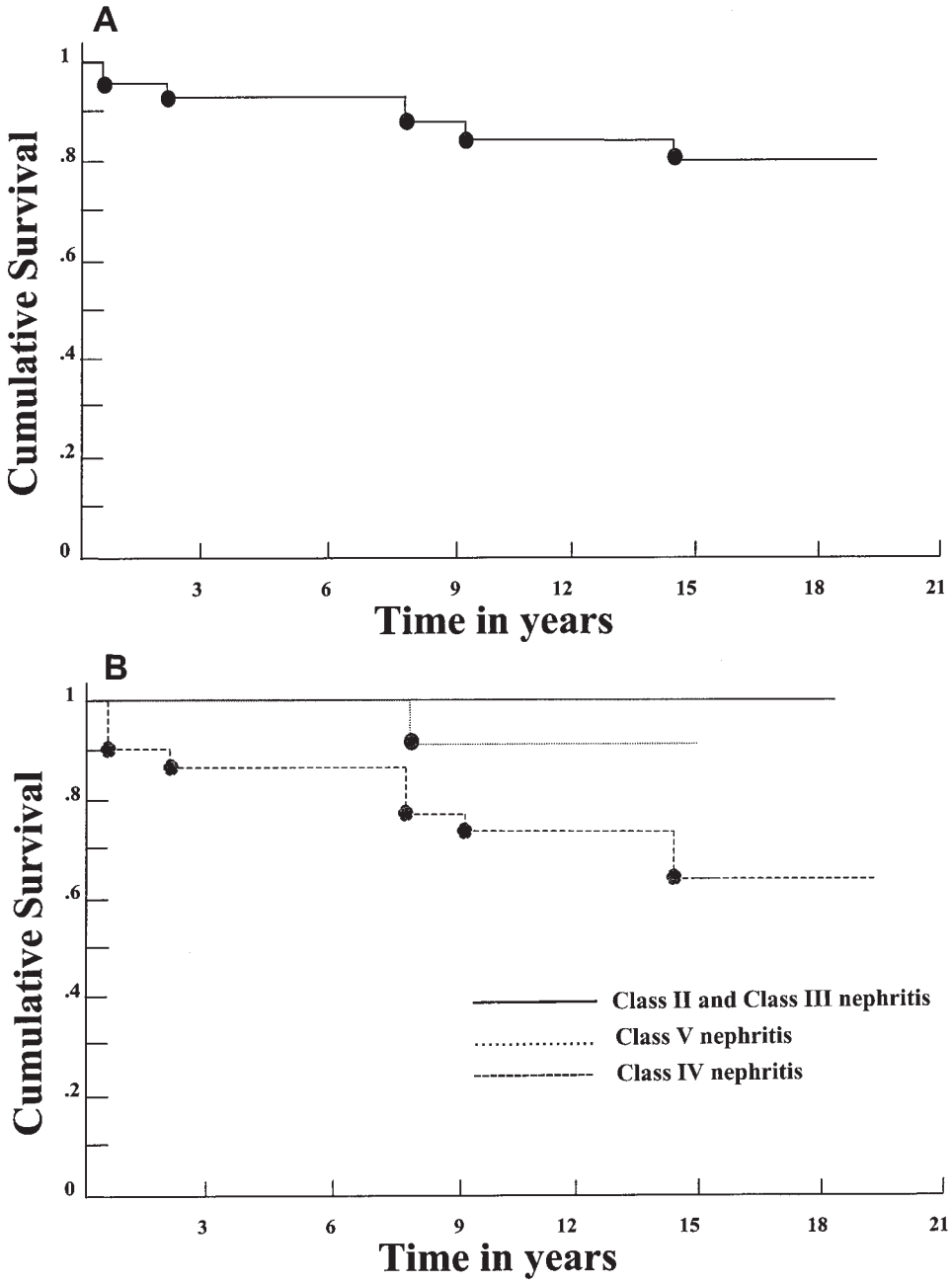

Figure 1. A. Kaplan-Meier survival analysis of renal survival for all 66 patients with pediatric onset lupus nephritis. Circles designate times of renal death or patient death. B. Kaplan-Meier survival analysis of renal survival for all 66 patients with pediatric onset lupus nephritis divided into the WHO classification. Patients with Class II and Class III nephritis are shown as the solid line along the top. The outcome of these 2 groups was 100% overlapping. Patients with Class V nephritis are shown as the dotted line and Class IV nephritis as the broken line with small circles. Circles designate times of renal death or patient death.

tions within 4 weeks of the time of diagnosis of Class IV nephritis. Seventeen patients received AZA as their initial immunosuppressive agent in addition to corticosteroid therapy. Only 5 patients received CYC as the initial immunosuppressive agent and this was given as monthly pulse intravenous infusions (in one patient it was given for CNS disease and not nephritis) (Table 3). A further 5 patients with Class IV nephritis subsequently received pulse CYC during the course of their illness. In 4 of these 5 patients, CYC was given following a flare of renal disease (flare occurred during the period the patient took AZA), while in the other patient it was given for persistent CNS disease and not for nephritis. Thirty-one percent of patients with Class IV nephritis received CYC therapy. Twenty-two

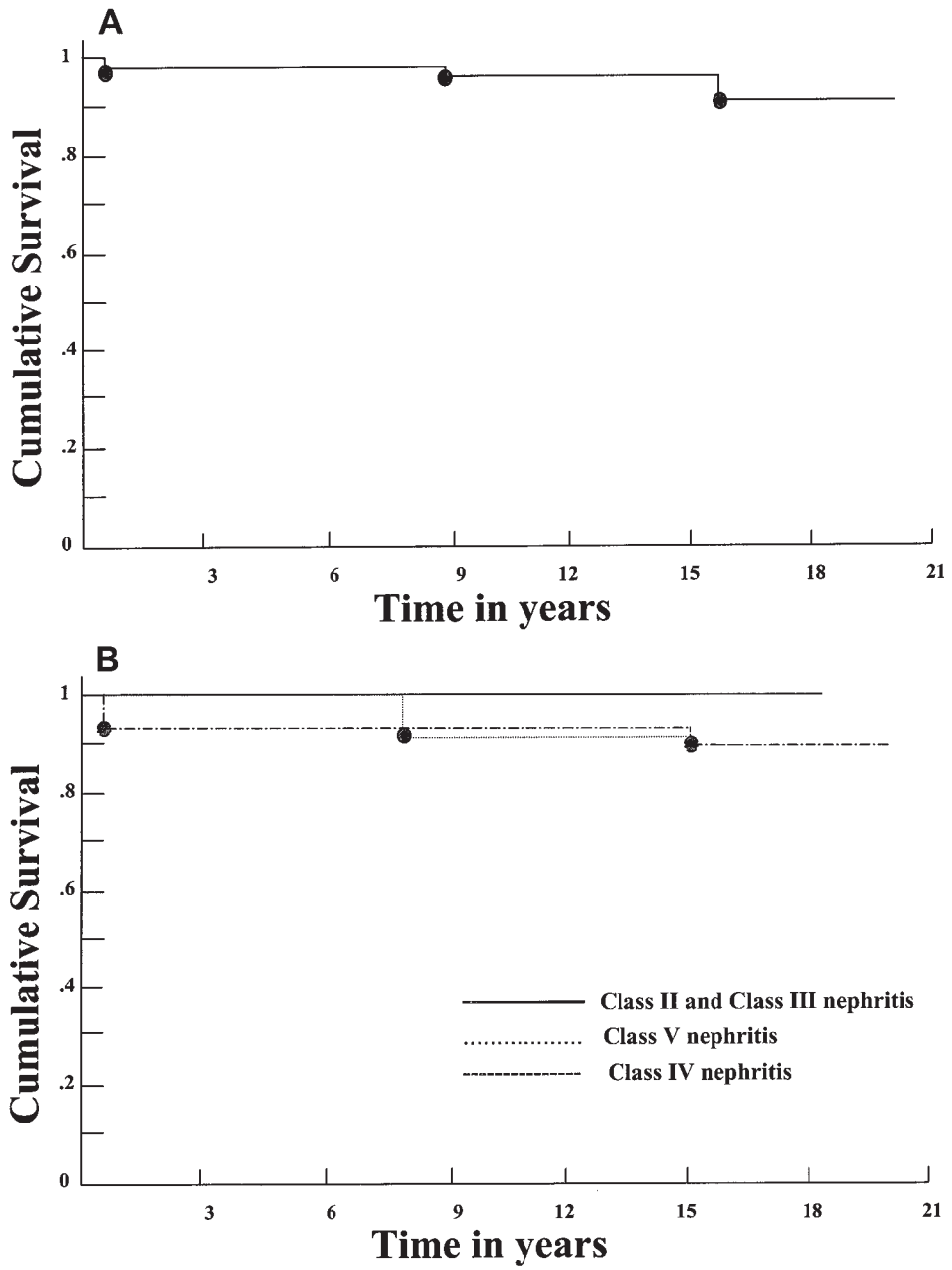

Figure 2. A. Kaplan-Meier survival for all 66 patients with pediatric onset lupus nephritis. Circles designate times of death. B. Kaplan-Meier survival for all 66 patients with pediatric onset lupus nephritis divided into the WHO classification. Patients with Class II and Class III nephritis are shown as the solid line along the top. The outcome of these 2 groups of patients was 100% overlapping. Patients with Class V nephritis are shown as the dotted line and Class IV nephritis as broken line with small circles. Circles designate times of death.

patients with Class IV nephritis were treated with either prednisone alone (2 patients) or prednisone plus AZA. Serum creatinine was normal at mean followup of 10 years in all of these 22 patients.

Only one of 8 patients with Class III nephritis received CYC (after relapse while taking AZA), 6 received AZA, and one methotrexate (MTX). Four of the 6 patients treated with AZA received AZA within 6 weeks of diagnosis of SLE nephritis. All patients with Class III nephritis had normal renal function at mean followup of 10 years. None of 15 patients with Class II nephritis received CYC, and, similarly to the patients with Class III nephritis, all patients had normal renal function at mean followup of 10 years (range 5–17). Five patients with Class II received AZA and one received MTX. Of the 11 patients with Class V nephritis, only 2 received CYC. In both patients, the CYC therapy was

Table 3. Use of cyclophosphamide treatment in 13 patients with pediatric SLE nephritis.

WHO Classification of Renal Biopsy	At Time of Biopsy	After Failure of AZA Therapy
Class IV	5*	5*
Class V	0	2
Class III	0	1
Total	5	8

* One of the 5 patients, one at diagnosis and one following failure of azathioprine therapy, was treated with cyclophosphamide as a result of severe central nervous system rather than their renal disease. AZA: azathioprine.

given following failure of therapy with AZA. A further 7 patients received azathioprine. No patient was treated with any other immunosuppressive agent. Serum creatinine was normal in 10 of the 11 surviving patients at a mean followup of 9 years (range 5–14). One patient died 8 years after diagnosis of Class V nephritis with focal proliferative nephritis (the course was complicated by sclerodermatous changes of her intestines and significant malnutrition). No patient received cyclosporine.

Therapy at last followup. At mean followup of 11 years (range 5–21), 62% of patients were receiving prednisone but only 30% (19/63) of patients were taking > 7.5 mg prednisone per day (Table 4). Of note, only 14% of patients with Class IV nephritis were taking > 7.5 mg prednisone, compared to 62% of patients with Class III nephritis, 27% with Class II, and 50% with Class V. The percentage of patients with Class IV nephritis (59%) who were taking any prednisone was lower than the percentage of patients with Class III (100%) and patients with Class V nephritis (70%). None of the 63 patients were receiving CYC at the time of the last visit, while 19 were receiving AZA and 5 MTX. All patients receiving AZA or MTX were also taking prednisone.

Hypertension. At the time of the followup visit, 16/63 (25%) patients were treated with antihypertensive medication. Ten of the 16 patients had Class IV nephritis, 3 patients Class V nephritis, and 2 patients Class II. Only 3 patients had an increased serum creatinine level. Half of the hypertensive group were Caucasian.

Effect of ethnic background on outcome. Thirty-six (54%) of the 67 patients were Caucasian (Table 5). There was a similar percentage of Caucasian patients (44%; 16/36) with Class IV nephritis compared to non-Caucasian patients (52%; 16/31). Interestingly, there was a statistically significant difference between the number of Caucasian patients who were alive without ESRD (34/36) compared the number of non-Caucasian patients who were alive without ESRD (23/31) ($p = 0.02$ by chi-square). In addition, there was a statistically significant difference in the outcome of patients with Class IV nephritis depending on racial background. Fourteen of 16 Caucasian patients with Class IV nephritis were alive without ESRD, as compared to 9/16 who were non-Caucasian ($p = 0.05$, chi-square). The one Caucasian patient who died, died of myocardial infarction with a normal serum creatinine. The only patient without Class IV nephritis who died (Class V with features of focal proliferative nephritis) also was non-Caucasian.

DISCUSSION

SLE is a multiorgan system disease that affects patients of all ages. Young age of onset and renal involvement have been associated with significant morbidity and mortality[1,9,15-24]. This study was undertaken to determine the longterm outcome of nephritis in pediatric onset SLE followed at a single center. We found that at a mean followup of 11 years there was an excellent overall survival rate of 94% for all patients with nephritis, and a 91% survival rate for patients with Class IV nephritis (DPGN). The renal survival was 93%, with a patient survival of 97% at 5 years. The corresponding rates for patients with DPGN were 87% and 94%. These rates are higher than reported in previous pediatric studies, where overall patient survival ranged from 44 to 91%[11,15-17,25-29] and are at the higher end of the survival described in studies of adults (which have ranged from 70 to 95%[22,23,30-34]).

The outcome of nephritis is dependent on the severity of the lesion on renal biopsy. Patients with Class II nephritis generally have an excellent prognosis and require no specific therapy. Our study confirms the excellent longterm outcome of Class II, as all patients had normal renal function at followup and only a minority of patients were taking

Table 4. Immunosuppressive therapy at last followup based on WHO classification of lupus nephritis.

	Class II, n = 15	Class III, n = 8	Class IV, n = 29	Class V, n = 10
No medication	9	0	12	3
No prednisone	9	0	12	3
Prednisone, ≤ 7.5 mg/day	2	3	13	2
Prednisone, ≥ 7.5 mg/day	4	5	4	5
No immunosuppressive	12	0	21	5
Azathioprine	2	6	7	4
Methotrexate	1	2	1	1
Cyclophosphamide	0	0	0	0

Table 5. Demographics of patients with pediatric SLE: ethnic background.

	Number of patients
Caucasian	36
Asian	15
Black	7
East Indian	7
Native Canadian	1
Total	66

medication at followup. Patients with focal proliferative nephritis (Class III) have a more variable outcome — the outcome may depend on the percentage of each glomerulus involved and presence or absence of fibrinoid necrosis and subendothelial deposits, and the number of glomeruli involved[35,36]. All patients in our study with Class III nephritis were alive without ESRD, although interestingly, all patients were still taking corticosteroids and the majority of patients were also using a cytotoxic agent. A similar outcome of Class III nephritis has recently been reported in adults[37]. The risk of progression to ESRD is greatest in patients with DPGN (Class IV) and is dependent on the severity of the lesion. In our study, death or the development of ESRD was almost exclusively restricted to patients with Class IV nephritis, wherein 25% of patients with Class IV nephritis developed ESRD.

Previous comparisons of adult SLE to pediatric onset SLE have reported a worse prognosis, a more severe onset, and a requirement for higher doses of prednisone in pediatric SLE[1-5]. Most investigators have suggested that CYC plus corticosteroid is the therapy of choice in the treatment of Class IV nephritis and for some patients with Class III nephritis[11-14,38-43]. Most of our patients were treated with corticosteroids and AZA and did not receive CYC. With this therapy we have observed an excellent 5 year and a good longterm outcome. The percentage of patients within each WHO classification was similar to previous studies in childhood SLE and therefore could not account for the more favorable outcome seen in our study.

Based on the US National Institutes of Health (NIH) study in adults, since 1986 the "gold standard" of care for patients with significant renal involvement has been intravenous CYC[39]. Subsequent studies have shown good short term response to pulse intravenous CYC[40,41,43-46], but longer term studies have shown that 20–50% of patients with Class IV nephritis will develop ESRD at a mean followup of 5 years[38,47-50]. Similar to what has been seen in adults, short term followup studies in pediatric SLE have shown that intravenous CYC is of benefit for severe nephritis[12,13,42]. A larger pediatric study from Thailand failed to show as good a response to CYC therapy as reported in the US study, with only a 39% complete remission rate[14]. A large pediatric study and a review article of therapy of pediatric SLE nephritis failed to discern any difference in the outcome of children treated with intravenous CYC compared to AZA[11,51]. Our data suggest that treatment of Class IV nephritis in pediatric SLE with corticosteroids and AZA, at the time of diagnosis of renal involvement, was associated with a similar, if not better, longterm survival than has been reported with CYC, including the data from the NIH in 2001[52].

The first reported study of AZA in SLE nephritis was in 1968, and in 1977 there was a report of the efficacy of AZA in childhood SLE[53,54]. A recent review of more than 100 patients from a single center suggested that longterm outcome (minimum followup of 10 years) of patients with DPGN treated with AZA was at least as good as, if not superior to, that of patients treated with CYC[10]. Metaanalyses of therapy of lupus nephritis have failed to show that CYC plus corticosteroid was superior to AZA plus corticosteroids for either total mortality or ESRD[55,56].

The other major issue is toxicity of therapy. Adult studies of CYC therapy have revealed a significant risk of amenorrhea, an increased incidence of cervical dysplasia, and an increased risk of infection. Similar toxicities have not been seen with the use of AZA[57]. Age at the start of CYC therapy and the cumulative dose are the major determinants for the development of these complications of CYC therapy[58,59]. Severe infection and treatment associated death have been associated with CYC in pediatric patients with SLE nephritis treated in Thailand, but were not reported in a US study[13,14]. These complications were not seen in our patients treated with CYC or AZA.

Similarly to previous studies in adults, we found that non-Caucasian pediatric patients with nephritis had a poorer renal outcome compared to Caucasian patients. This finding could not be explained by the higher incidence of severe nephritis in non-Caucasian patients, as the incidence of DPGN was similar in both groups. It has been suggested that the association of racial background with poor renal outcome may be confounded by socioeconomic factors, although this is controversial[60-65]. In the Canadian healthcare system there is universal, free, ready access to medical care. In our study there was no difference in time to referral between Caucasian and non-Caucasian patients. Similarly to studies in adults, we could not explain the poorer outcome in non-Caucasian patients based on time to diagnosis, the presence of hypertension, access to treatment, or age at diagnosis[66,67].

In this report we have described excellent longterm survival of patients with pediatric SLE nephritis. The survival rate of our patients exceeded the previous survival of pediatric SLE nephritis[15-17,68,69]. Similarly to previous studies, the major causes of death in our study were sepsis and renal failure[15-17,70]. We have confirmed the suggestion that poor renal outcome in both adult onset and pediatric onset SLE nephritis is associated with non-Caucasian races. The majority of patients with either Class III or Class IV nephritis responded well to early therapy with high dose corticosteroids and AZA and had an excellent longterm outcome with few side effects. In a pilot study in pediatric patients with SLE nephritis refractory to prednisone, AZA, and/or CYC therapy, Buratti, *et al* reported that mycophenolate mofetil may have a steroid-sparing effect[71]. In our study, a higher percentage of patients with Class III than Class IV nephritis were still undergoing therapy at last followup. This may reflect a reluctance to treat these patients with AZA early in the course of their illness, or that

patients with Class III nephritis have a different longterm course of their disease. We suggest that patients with Class III and Class IV pediatric onset SLE nephritis should receive high dose corticosteroid and AZA therapy at the time of diagnosis of their nephritis. CYC therapy should be considered for patients who fail or who are noncompliant with AZA therapy. The use of mycophenolate mofetil and cyclosporin A should be further investigated in pediatric SLE nephritis.

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