

# Three Decades of Progress in Treating Childhood-Onset Lupus Nephritis

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## Summary

**Background and objectives** Childhood-onset lupus nephritis (LN) carries a worse renal prognosis compared with adults. Controlled treatment trials in children are lacking. We compared renal and patient survival in a cohort of pediatric patients followed over 3 decades.

**Design, settings, participants, & measurements** A retrospective analysis was conducted on 138 patients with childhood-onset systemic lupus erythematosus from 1980 to 2010. The core cohort included 95 with severe LN: 28 progressed to end-stage renal disease (ESRD group) whereas 67 did not (no-ESRD group). Patients were stratified into four “eras” according to the introduction of the primary immuno-suppressive drug: era 1: triple oral therapy with corticosteroids (CS), cyclophosphamide (CYC), and azathioprine (AZA); era 2: intravenous CYC; era 3: mycophenolate mofetil (MMF) ± CYC; era 4: rituximab (RTX) ± CYC ± MMF.

**Results** Mean age at diagnosis was  $12.3 \pm 2.9$  years with median follow-up of 5 years. Poor renal function (estimated GFR < 60 ml/min per 1.73 m<sup>2</sup>) and nephrotic proteinuria at diagnosis imparted a poor prognosis. Increasing proteinuria correlated with progression of kidney disease. The addition of MMF in era 3 improved 5-year renal survival from 52% to 91% and overall patient survival from 83% to 97%. African-American ethnicity was associated with significant risk for progression to ESRD whereas Hispanic ethnicity conferred an advantage. Infection and cardiovascular disease were the primary causes of patient demise.

**Conclusions** Renal and patient survival in childhood-onset LN has improved during the past 3 decades with progressive treatment regimens. Future trials in children are very much warranted.

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## Introduction

Childhood-onset lupus nephritis (LN) is more severe and carries a worse prognosis than in adults (1). Improved renal outcome over the last few decades has been demonstrated in adults, first with the introduction of intravenous cyclophosphamide (CYC) in the 1980s (2–4) and later with mycophenolate mofetil (MMF) in the 1990s (5,6). However, the superiority of one immunosuppressant over the other has not been clearly established (7). Pediatric treatment regimens have been derived from adult protocols with a paucity of information in the medical literature on the long-term outcome of pediatric LN based on the treatment regimens used (8,9).

Historically, high-dose corticosteroids (CS) were the mainstay of therapy from the outset and have continued to be a major component throughout the decades (2,10–12). In the 1980s, intravenous CYC was introduced as the standard of care for severe LN despite its significant toxicities inclusive of malignancy and gonadal dysfunction (9,13). Oral azathioprine (AZA) and oral CYC with oral CS were used as primary treatment for LN at our institution until 1985,

at which time the transition was made to intravenous “pulse” methylprednisolone (MP) and intravenous CYC as the basic immunosuppressant for LN (2–4). During recent years, MMF has emerged as a potential alternative to more toxic regimens for induction and maintenance therapy (5–8,14). We and others began using B cell depletion with rituximab (RTX) around the year 2003 (15,16).

The main purpose of our study was to compare renal and patient survival in a pediatric cohort over 3 decades with the successive introduction of new treatment regimens that included CS, CYC, MMF, and RTX. Additional objectives were to evaluate determinants underlying the progression of LN to ESRD in childhood.

## Patients and Methods

A retrospective analysis was performed on a cohort of 138 patients diagnosed with systemic lupus erythematosus (SLE) who received their care at Holtz Children’s Hospital at the University of Miami Miller School of Medicine between January 1980 and December 2010. The study was approved by the institutional

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review board with waiver of consent authorization. Children were considered eligible for inclusion in the analysis if they fulfilled the American College of Rheumatology criteria for the diagnosis of SLE at an age <18 years at the time of disease onset. Patients with drug-induced lupus, discoid lupus, or mixed connective tissue disease were excluded.

Of the initial cohort, 95 patients had biopsy-proven severe LN, World Health Organization (WHO) class III or higher (17). Twenty-eight patients (29%) went on to develop ESRD and were categorized as the “ESRD group,” whereas the 67 patients (71%) that maintained kidney function were designated the “no-ESRD group.” The medical records were reviewed for demographic characteristics, age at diagnosis, medical treatment received, period of follow-up, and type of LN by initial and iterative biopsies. Renal function was assessed by estimated GFR (eGFR) calculated from the traditional Schwartz equation using serum creatinine, age, gender, and height (18). Proteinuria was documented at initial presentation and at the time of last follow-up.

**Clinical Protocols**

Patients were further stratified into four eras of treatment according to the introduction of a primary immunosuppressive drug regimen as shown in Table 1. We have not designated the calendar years of treatment because there was considerable overlap in treatment regimens during the last 2 decades of observation.

Era 1 encompassed patients with severe LN (WHO class III or higher) who were treated at our institution before 1985 with “triple oral therapy” that included CS (prednisone; 1 mg/kg per day), AZA (1 mg/kg per day), and CYC (1 mg/kg per day). Patients were maintained on this triple therapy throughout their clinical course, with tapering and eventual discontinuation of medication only with signs of drug toxicity or recovery on the basis of several papers published at the time (19,20).

Era 2 included those patients who received intravenous pulse MP (15 to 30 mg/kg per dose × 3, maximum of 1 g) used at the onset of nephritis plus intravenous CYC (500 mg/m<sup>2</sup> per dose, maximum of 1 g) for 6 consecutive months as primary treatment for LN from 1985 to the late 1990s on the basis of the landmark National Institutes of Health trials that heralded the era of intravenous CYC as the mainstay of treatment for LN (2–4). During this de-

cade, we abandoned the use of oral AZA and oral CYC and treated all patients with severe LN with intravenous CYC without the use of concomitant oral maintenance therapy. Patients who subsequently experienced disease recurrence or progression were treated with additional pulses of intravenous MP and/or intravenous CYC. Four of the 24 patients included in this era had received prior treatment with oral triple therapy, which was discontinued once intravenous CYC therapy was instituted. The remaining 20 of 24 received only intravenous CYC and steroids as immunosuppressive therapy. This era serves to illustrate the effect of intravenous CYC on renal and patient survival when used in isolation without concomitant maintenance therapy.

In era 3, from the late 1990s onward, we incorporated daily oral MMF as maintenance therapy (300 to 600 mg/m<sup>2</sup> per day) for LN in 31 patients (5–9). This was used after induction regimens of intravenous CYC for 17 of 31 patients. The remaining 14 patients were treated with MMF alone. This era serves to demonstrate the effect of the addition of MMF to the treatment regimen.

In era 4, 23 patients were treated with RTX (187.5 mg/m<sup>2</sup> for one dose, followed by 375 mg/m<sup>2</sup> for three weekly doses) in combination with intravenous CYC and/or oral MMF. Initially, 16 patients were treated for refractory disease after failed treatments with intravenous CYC and MMF (16). More recently, seven patients have received RTX and MMF as induction therapy followed by MMF as maintenance.

Patients in all four eras received low-dose daily maintenance oral CS (0.25 mg/kg per day). After era 1, all patients received pulse intravenous MP at induction and with relapses. After 1996, from the middle of era 2, most patients also received adjuvant therapy with angiotensin blockade in the form of angiotensin converting enzyme inhibitors or angiotensin receptor blockers as well as hydroxychloroquine. An analysis of the role of these adjuvant therapies was not undertaken.

**LN and Renal Disease Activity**

Renal biopsies were classified according to the new proposed modifications of the WHO classification (17): class I, mesangial immune deposits without mesangial hypercellularity; class II, mesangial immune deposits with mesangial hypercellularity; class III, focal proliferative glomerulonephritis; class IV, diffuse proliferative glomerulonephritis; and

**Table 1. Patient and renal survival on the basis of era of initial treatment regimen**

Era	n	WHO Classification (n)			Treatment	Renal Survival (%)		5-Year Patient Survival (%)
		III	IV	V		2-Year	5-Year	
1	17	3	12	2	Triple oral therapy: CS + AZA + CYC	82	52	83
2	24	1	19	4	iv-CYC	62	51	87
3	31	4	20	6	MMF ± iv CYC	96	91	97
4	23	1	18	4	RTX ± iv CYC ± MMF	95	88	91

Low-dose maintenance CS was used in all eras. Pulse intravenous methylprednisolone was used in eras 2 to 4. WHO, World Health Organization; AZA, azathioprine; CYC, cyclophosphamide; CS, corticosteroids; iv, intravenous; MMF, mycophenolate mofetil; RTX, rituximab.

class V, membranous nephropathy. Only those patients with class III or greater were included in the analysis. For those patients who underwent renal biopsy more than once or had a "mixed" histology, the biopsy with the most severe features was used for the designation. One patient was morbidly obese and never had a tissue diagnosis. However, her clinical course was similar to her sister who had class IV.

Renal function as assessed by eGFR was stratified over time by stages of chronic kidney disease (CKD) according to the Kidney Disease Outcomes Quality Initiative classifications: stage 1  $\geq 90$  ml/min per 1.73 m<sup>2</sup>, stage 2  $< 90$  to 60 ml/min per 1.73 m<sup>2</sup>, stage 3  $< 60$  to 30 ml/min per 1.73 m<sup>2</sup>, stage 4  $< 30$  to 15 ml/min per 1.73 m<sup>2</sup>, and stage 5  $< 15$  ml/min per 1.73 m<sup>2</sup> equivalent to ESRD (21). Progression to stage 3 CKD or higher was considered significant renal damage and was used to define response to treatment in both groups. ESRD was defined as the progression to CKD stage 5, necessitating the institution of chronic renal replacement therapy via dialysis or kidney transplantation.

Degree of proteinuria was determined by the random urine protein to creatinine ratio (UPr/Cr, in mg/mg) with normal ( $< 0.2$ ) and nephrotic ( $> 1.0$ ) range (22). By protocol, the first morning void was attempted but was not consistently available. Serum albumin was assayed as an indirect measure of the nephrotic syndrome. All serum and urine chemistries and immunoassays were performed in the central hospital clinical laboratory or the Quest referral laboratories.

Socioeconomic status (SES) data were not available for the cases in this cohort. As a proxy for individual-level

data, we used neighborhood-based measures of SES extracted from the 2000 U.S. census data by zip code (23). High poverty was defined as  $> 10\%$  of neighborhood residents living below the federal poverty line. Low median household income was defined as a median household income  $< \$25,000$ . This method of using neighborhood-based SES measurements as a proxy for individual measures of SES has been validated in previous studies (23).

### Statistical Methods

Data were analyzed using the *t* test for parametric datasets and the chi-squared test for categorical variables with univariate analysis. Odds ratios (ORs) with the 95% confidence intervals (95% CIs) were given. Progression to stage 3 CKD and renal survival were calculated by the Kaplan-Meier method followed by the log-rank test (Mantel-Haenszel test) and the log-rank test for trend. Multiple regression analysis was performed using ESRD as the dependent variable compared with initial eGFR, gender, initial UPr/Cr, treatment era, race/ethnicity, SES, and WHO renal histology class. Median values with interquartile range were reported for non-normally distributed data. All other results were expressed as the mean  $\pm$  SD.  $P < 0.05$  was considered statistically significant.

### Results

Table 2 displays the patient characteristics for the core cohort, no-ESRD, and ESRD groups. The ratio of female to male children with severe LN was 4:1. The progression to ESRD was not significantly different between boys and

**Table 2. Patient demographic and clinical characteristics for core cohort, no-ESRD, and ESRD groups**

Characteristic <i>n</i> (%)	All Patients 95 (100%)	No-ESRD 67 (71%)	ESRD 28 (29%)	No-ESRD <i>versus</i> ESRD <i>P</i> Value
Gender				0.79
female	76 (80%)	54 (81%)	22 (79%)	
male	19 (20%)	13 (19%)	6 (21%)	
Race				
African American	53 (56%)	32 (48%)	21 (75%)	$< 0.03$
Hispanic	28 (29%)	24 (36%)	4 (14%)	$< 0.05$
Caucasian	10 (11%)	9 (13%)	1 (4%)	0.27
Asian	4 (4%)	2 (3%)	2 (7%)	0.58
SES				0.99
median household income \$ $\times 10^3$	$\$35.4 \pm 13.0$	$\$36.0 \pm 14.3$	$\$34.0 \pm 10.0$	
SES $> 10\%$ poverty by zip code	66 (75%)	44 (72%)	23 (82%)	0.14
WHO class				
III	9 (10%)	8 (12%)	1 (4%)	0.27
IV	69 (73%)	46 (70%)	23 (82%)	0.30
V	16 (17%)	12 (18%)	4 (14%)	0.77
Age of onset (years)	$12.3 \pm 2.9$	$12.9 \pm 2.7$	$11.9 \pm 3.1$	0.12
Median time to progression: stage 3 CKD or higher	$8.0$ (0.2 to 10.0)	Undefined (2.5 to 8.0)	$3.2$ (0.2 to 10.0)	$< 0.01$
Mean follow-up (years)	$6.0 \pm 4.0$	$5.1 \pm 3.6$	$7.7 \pm 4.2$	$< 0.01$
Initial eGFR (ml/min per 1.73 m <sup>2</sup> )	$107 \pm 49$	$117 \pm 49$	$83 \pm 41$	$< 0.01$
Final eGFR (ml/min per 1.73 m <sup>2</sup> )	$87 \pm 60$	$117 \pm 42$	$12 \pm 5$	$< 0.01$
Initial UPr/Cr (mg/mg)	$2.7 \pm 2.6$	$2.6 \pm 2.8$	$2.9 \pm 2.1$	0.61
Final UPr/Cr (mg/mg)	$2.5 \pm 4.9$	$1.3 \pm 2.3$	$7.5 \pm 8.2$	$< 0.01$

SES, socioeconomic status; eGFR, estimated GFR in ml/min per 1.73 m<sup>2</sup>; CKD, chronic kidney disease; UPr/Cr, urine protein-to-creatinine ratio (normal  $< 0.2$ ).

girls. Nearly 90% of the study group was of nonwhite ethnicity with 56% African American (AA), 29% Hispanic, and 4% Asian. AA ethnicity was significantly associated with more rapid progression to ESRD (OR 3.3,  $P < 0.03$ ; 95% CI 1.2 to 8.7) whereas Hispanic ethnicity conferred an advantage to renal survival (OR 0.3,  $P < 0.05$ ; 95% CI 0.09 to 0.9). SES derived from median household income on the basis of zip code area of residence was not significantly different between the ESRD and no-ESRD groups (Table 2).

Diffuse proliferative nephritis was the most common histology in 73% of the study patients. Renal biopsy classification was not significantly different between the groups that progressed to ESRD compared with those that maintained kidney function ( $P = 0.35$ ). The mean age of onset among all patients with severe LN was  $12.3 \pm 2.9$  years (median age 13, range 6 to 18 years). The children in the ESRD group were slightly younger at presentation ( $11.9 \pm 3.1$  years) than those in the no-ESRD group ( $12.9 \pm 2.7$  years), although this was not statistically significant. The median duration of follow-up for the entire cohort was 5 years (interquartile range 6 years). Although the ESRD group had a longer period of follow up ( $7.7 \pm 4.2$  years) compared with the no-ESRD group ( $5.1 \pm 3.6$  years), the time to progression to ESRD was  $4.0 \pm 3.4$  years (median 3.2, range 0.5 to 12 years), which was similar to the no-ESRD group follow-up.

eGFR at the time of diagnosis was significantly less in the ESRD group as compared with the no-ESRD group ( $83 \pm 41$  ml/min per  $1.73 \text{ m}^2$  versus  $117 \pm 49$  ml/min per  $1.73 \text{ m}^2$ , respectively;  $P < 0.01$ ). Patients with an initial eGFR  $< 60$  ml/min per  $1.73 \text{ m}^2$  had an OR of 3.6 (95% CI 1.3 to 10;  $P = 0.02$ ) to progress to ESRD. Similarly, nephrotic-range proteinuria (UPr/Cr  $> 1.0$ ) at the time of diagnosis predicted progression to ESRD (OR 4.1; 95% CI 1.1 to 15.4;  $P = 0.04$ ). There was a significant correlation between decline in renal function and worsening proteinuria as shown in Figure 1.

### Progression to CKD Stage 3 or Higher

Progression to stage 3 CKD or higher for the entire cohort and for the two subgroups (ESRD and no-ESRD) is shown in Figure 2. Median time to progression to stage 3 CKD or higher for the entire cohort ( $n = 95$ ) was 8 years. Those with ESRD progressed to stage 3 CKD or higher at

a median of 3.2 years (range 0.5 to 12 years) whereas those in the no-ESRD group have had a slower progression that remains undefined.

### Renal Outcomes by Treatment Eras

The Kaplan–Meier renal survival curves to ESRD of each of the treatment eras are shown in Figure 3. Not shown is the renal survival for the entire cohort ( $n = 95$ ), which was 10 years. The median renal survival decreased from 8 to 6 years between eras 1 (triple therapy) and 2 (intravenous CYC), although not significantly ( $P = 0.23$ ). With the addition of MMF in era 3, the median renal survival between era 2 (intravenous CYC) and 3 (MMF  $\pm$  CYC) increased significantly from 6 to 12 years ( $P < 0.01$ ). The 5-year absolute renal survival increased from 52% to 91% ( $P < 0.01$ ), as shown in Table 1. With the addition of RTX in era 4, no demonstrable improvement in renal survival occurred. However, a subset of patients treated solely with RTX and MMF ( $n = 7$ ) has experienced no renal demise with a median follow-up of 3.3 years (range 1 to 16 years).

By multiple regression analysis, only race/ethnicity and treatment era maintained a significant association with progression to ESRD ( $P = 0.01$ ).

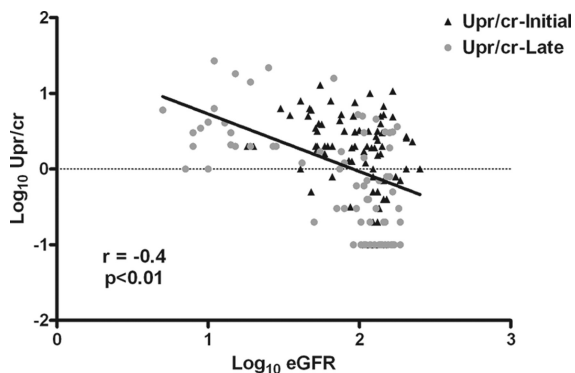
### Patient Outcome

Ten patients with severe LN died during the period of observation. Five deaths occurred in the ESRD and no-ESRD groups (Table 3). Three patients in the no-ESRD group manifested acute kidney injury at the time of death, one patient died with stable renal function, and one experienced sudden death of unknown cause. Infection was the most common cause of death (70%), followed by cardiovascular disease (20%). The absolute 5-year patient survival increased from 83% in era 1 to 97% in era 3 and 91% in era 4 ( $P < 0.05$ ).

### Discussion

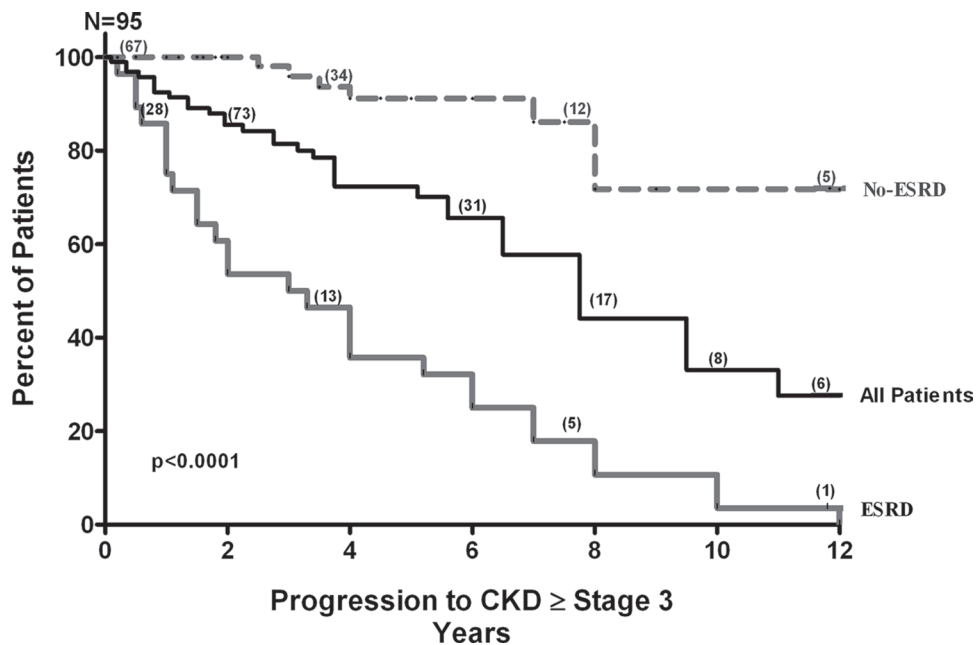
In this retrospective cohort study of childhood-onset SLE and severe LN, we have shown improved patient and renal survival with the application of accepted treatment regimens derived from those developed for adults. This experience has spanned 3 decades and represents the largest North American cohort of pediatric patients with severe LN to be reported to date. The major predictors of poor renal outcome were AA ethnicity, low eGFR ( $< 60$  ml/min per  $1.73 \text{ m}^2$ ), and nephrotic-range proteinuria (UPr/Cr  $> 1.0$ ) at the time of diagnosis.

Race/ethnicity has been strongly implicated in the severity of disease presentation and the ultimate prognosis of SLE. Patients of AA heritage have a more aggressive course compared with Caucasians, particularly relative to renal disease (24–26). However, Hispanics are not clearly characterized, possibly because of the complex racial mixture of Hispanic communities (27). The South Florida ethnic demographic offers an opportunity to examine disease activity relative to race/ethnicity. Although the ethnic distribution in South Florida is  $> 57\%$  Hispanic, the occurrence of SLE and LN is predominantly in the AA population. In the report presented here, we show that AA pediatric patients with LN were more likely to progress to ESRD; whereas, the Hispanics showed an advantage in

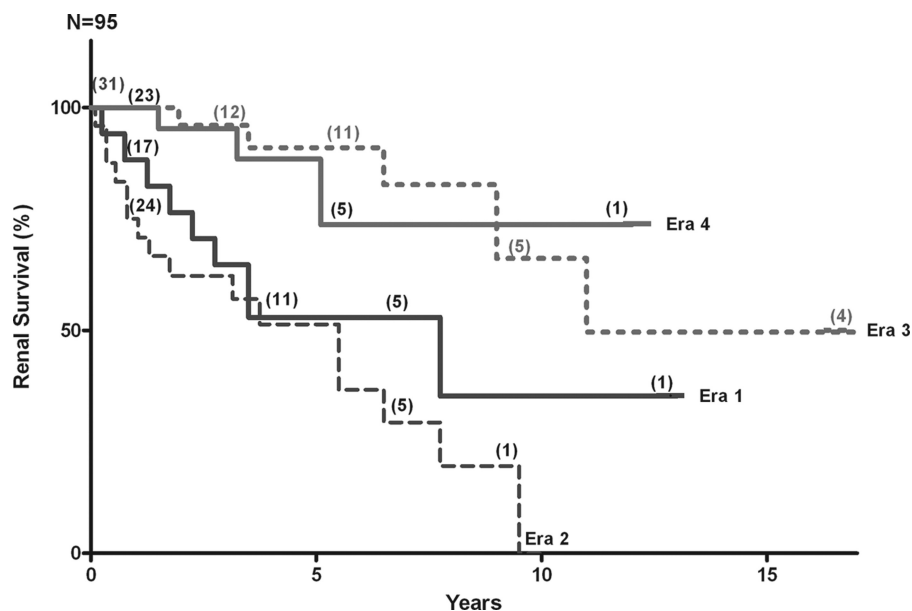


**Figure 1.** | Regression correlation of increasing proteinuria with decline in estimated GFR (eGFR) ( $r = -0.4$ ;  $P < 0.01$ ). UPr/cr, urine protein to creatinine ratio.





**Figure 2.** | Kaplan–Meier curves showing progression of chronic kidney disease (CKD) beyond stage 3 or higher (estimated GFR <math><60</math> ml/min per 2) in patients with childhood-onset severe lupus nephritis divided according to their outcome group of ESRD and non-ESRD within the period of observation. Those with ESRD developed CKD stage 3 at a median of 3.2 years after diagnosis; whereas, those in the non-ESRD group had a slower and as yet undefined rate of progression to CKD. Overall time to progression to stage 3 CKD or higher for the entire cohort ( $n = 95$ ) was 8 years.



**Figure 3.** | Kaplan–Meier survival curves comparing renal survival during four eras of progressive treatment regimens: Era 1 ( $n = 17$ ), triple oral therapy with corticosteroids, cyclophosphamide (CYC), and azathioprine; era 2 ( $n = 24$ ), intravenous CYC; era 3 ( $n = 31$ ), mycophenolate mofetil (MMF) was added  $\pm$  intravenous CYC; era 4 ( $n = 23$ ), rituximab (RTX) was added  $\pm$  MMF  $\pm$  CYC. Eras 1 and 2 were not different from each other. With the introduction of MMF (era 3), the 5-year renal survival increased from 51% to 91% ( $P < 0.01$ ) compared with eras 1 and 2. The addition of RTX (era 4) to the treatment regimens improved renal survival compared with eras 1 and 2 ( $P < 0.01$ ) but has not been better than the addition of MMF in era 3.

preservation of renal function. The high incidence of genetic variants in AAs as well as the high prevalence of mixed race, particularly in the Caribbean Hispanics, may

be important contributors to this phenomenon (28,29). Importantly, SES, as assessed by neighborhood median household income and percent poverty level, did not in-

**Table 3. Clinical features of patients with lupus nephritis who died**

Patient	Gender	Race/Ethnicity	Age at Diagnosis (Years)	Time to Death (Years)	Treatment Era	ESRD	Cause of Death
1	F	Caucasian	13	4.0	1	No	Portal hypertension
2	F	AA	10	2.0	1	No	Sepsis
3	M	AA	14	2.5	1	No	Sepsis
4	F	Asian	14	7.0	1	Yes	Sepsis
5	F	Hispanic	12	0.5	2	No	Unknown sudden death
6	M	AA	15	3.5	2	Yes	Anasarca; heart failure
7	F	AA	13	1.5	2	Yes	Sepsis
8	F	AA	13	3.5	3	No	Sepsis
9	F	AA	11	9.5	4	Yes	Peritonitis
10	F	Hispanic	6	13.0	4	Yes	Pulmonary hypertension

M, male; F, female; AA, African American.

fluence the renal outcomes of the ethnic populations in South Florida. This may be because most of our patients were located in high-poverty neighborhoods and were not clearly stratified by these methods.

Another issue regarding our unique patient population and the observed improved response to MMF may also be related to race/ethnicity. Our data show that, with the introduction of MMF, renal survival improved significantly from 52% to 91% in contrast to a poorer response with the addition of intravenous CYC in era 2. Although these results substantiate other published experiences in adults (30), they merit further scrutiny in children. The recent Aspreva Lupus Management Study suggests that patients of AA and Hispanic ethnicity demonstrate a better response to MMF than CYC (31). This may account for the better-than-expected response to MMF in our primarily nonwhite patient population. Although the reasons for such a response remain obscure, the emerging field of pharmacogenetics may yield some insight.

The use of B cell depletion with RTX as adjuvant therapy for severe drug-resistant cases of SLE began at our institution in the early 2000s (18). Recently, RTX has been used in a select group of patients as induction therapy in combination with MMF (32). Thus far, only seven patients at our institution have been treated in this manner, and although follow-up is <5 years, none has experienced loss of renal function. There is a component of selection bias in that the sicker patients were treated with intravenous CYC in eras 3 and 4. The remarkable observation is that, despite this bias in era 3, MMF achieved improved survival. In era 4, the sicker patients who received RTX did not fair better than those that received MMF so RTX had no “salvage” effect. However, those few patients treated only with MMF and RTX early in their disease have had 100% renal survival. It is impossible at this point to know the true benefit of RTX therapy. Nevertheless, the apparent safety and efficacy of RTX as an adjuvant treatment in pediatric patients with LN should serve as impetus for further randomized trials.

Proteinuria was an important indicator of renal disease activity. Heavy proteinuria at the time of initial diagnosis as well as persistent proteinuria that was unresponsive to treatment interventions were important correlates of dis-

ease progression. This confirms that proteinuria can be used to monitor the response to medical interventions. Also, during recent years, adjuvant therapies such as angiotensin antagonists may have offered an advantage regarding antifibrotic effects and modulation of proteinuria (33).

In this young cohort, histologic class did not determine the progression to ESRD. This may be attributed to the lack of protocol biopsies after a course of intravenous CYC as advocated by Askenazi *et al.* (34). Rather, as a function of the retrospective nature of our study, initial biopsies were performed early in the disease for classification purposes and subsequent biopsies were performed because of worsening clinical symptoms. Hence, follow-up biopsies tended to show progression of disease. Class V, membranous nephropathy, was as likely to be associated with progression as was class IV, and these patients were treated similarly. The clinical distinction of these two LN classes remains controversial, and our experience is consistent with other reports from nonwhite pediatric populations (35,36).

A major limitation of the study is that it is a retrospective analysis in a disproportionately ethnic minority population of pediatric patients. The bias is that this is a select cohort of patients who traditionally carry a poorer prognosis when compared with previously reported adult, primarily Caucasian, cohorts. Although the long-term experience spans 3 decades, the earlier eras of treatment are encumbered with dosing regimens of oral immunosuppressants that lacked consistent monitoring of immune status and serum drug levels to follow compliance. Nevertheless, consistency in treatment was one of the strengths of this study because of center protocol adherence.

Although our data show improved 5-year patient survival from the early 1980s to late 2010, the cause of death continues to be attributable to infection, and presumably overimmune suppression, in >70% of the patients. This reflects a continued misplaced emphasis on disease control in deference to patient safety. Cardiovascular disease constituted the second leading cause of mortality in our study, which is consistent with the data of Sule *et al.* (37) and emphasizes the need for close cardiac surveillance of these

children. Moreover, our data did not adequately examine long-term consequences of the treatment regimens, particularly related to chronic CS and CYC treatments in the very young. Clinical and immune surveillance are needed to provide adequate and safe treatment of LN in the very young patient.

## Conclusions

The long-term study presented here has provided unique insight into the treatment of severe LN in a large pediatric cohort spanning 3 decades of progressive treatment regimens. We have shown a significant improvement in patient and renal survival with the addition of MMF to the treatment regimen. Adjuvant therapies including angiotensin blockade and RTX remain to be validated for efficacy and safety. An overriding caution prevails for closer monitoring of drug toxicity with the predominant cause of death being infection and extreme immunosuppression in this vulnerable population. Finally, the role of racial, ethnic, and socioeconomic disparities in the response to therapies and the ultimate prognosis of young patients with SLE require much focus and research for the future.

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## Disclosures

None.

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