

# Influence of Non-Complicated Urinary Tract Infection on Renal Relapses in Proliferative Lupus Nephritis

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**Objective:** In patients with proliferative lupus nephritis treated with IV cyclophosphamide, analyze urinary tract infection (UTI) as a cause of treatment delay and renal relapses, compared with lupus nephritis patients without infection.

**Patients and methods:** We studied SLE patients (ACR criteria) with renal biopsy showing nephritis class IV. All patients received monthly intravenous cyclophosphamide (CYC) treatment during 6 months. Thereafter patients were assigned to 2 groups: patients who developed UTI, and those who did not; renal function tests, UTI and renal relapses were bimonthly evaluated during one year (follow-up period). To analyze data, Student *t* test,  $\chi^2$ , Fisher exact (when appropriate), and bivariate analysis, were performed.

**Results:** We studied 50 patients, 25 with UTI (Group I) and 25 without UTI (G-II). The mean age was 30.07  $\pm$  8.15 years, 82% were female. *Escherichia coli* was the pathogen most frequently isolated (73%). UTI (G-I) was the cause for treatment delay in 19 cases (76%), compared with 3 patients (12%) in G-II whose treatment was delayed because of some other causes (severe leucopenya, hypersensitivity, and gastrointestinal side effects) (OR, 23.22; 95% CI, 5.26-105.1; *P* = .001). During the follow-up, 90.9% of patients in G-I reached partial or complete renal remission within 3 months, but only 35% maintained remission after the year of follow-up. Meanwhile, patients in G-II had complete and partial renal remission of 85% and 63%, respectively. In the first group we observed persistent albuminuria (*P* < .05), low

complement levels and high ab-dsDNA titers. Renal flares were present in 18 patients in G-I and 9 in G-II.

**Conclusions:** UTI in lupus nephritis patients has a negative impact. It leads to delayed CYC therapy and to a higher renal flare rate.

**Key words:** Lupus nephritis. Urinary tract infection. Systemic lupus erythematosus. Renal relapse.

## Influencia de la infección de vías urinarias no complicada en la frecuencia de exacerbaciones en pacientes con nefritis proliferativa difusa lúpica

**Objetivo:** Determinar si la infección de vías urinarias (IVU) es un indicador de retraso en el tratamiento inmunodepresor y de recaída renal en pacientes con nefritis lúpica.

**Pacientes y métodos:** Se analizó a pacientes con nefritis lúpica proliferativa difusa que recibieron tratamiento con ciclofosfamida intravenosa durante, al menos, 6 meses. Al cabo de ese tiempo se realizó un seguimiento prospectivo asignando a los pacientes a uno de 2 grupos: grupo I (pacientes que durante el seguimiento desarrollaron IVU), y grupo II (grupo control, pacientes sin infección). Se evaluaron bimestralmente la función renal y el número de recaídas durante un año de seguimiento. Para el análisis estadístico, se emplearon la prueba de la *t* de Student, la prueba de la  $\chi^2$ , el test de Fisher (cuando se requiera) y el análisis bivariado.

**Resultados:** Se incluyó a 50 pacientes, 25 en cada grupo. Los casos del grupo I correspondieron a IVU no complicada. La edad promedio fue de 30,07  $\pm$  8,15, y el 82% eran mujeres. El uropatógeno descrito con más frecuencia fue *Escherichia coli* (73%). La presencia de IVU determinó la interrupción temporal del tratamiento en 19 casos (76%), mientras que en el grupo sin IVU esto ocurrió sólo en 3 pacientes (12%), por otras causas, como leucopenia grave, hipersensibilidad y síntomas gastrointestinales graves (*odds ratio* = 23,22; intervalo de confianza del 95%, 5,26-105,1; *p* = 0,001). Durante el

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año de seguimiento, en el grupo I, el 90,9% alcanzó la remisión parcial en los primeros 3 meses de seguimiento y el 35% logró la remisión completa después de un año; en el grupo II, los porcentajes de remisión fueron del 85 y el 63%, respectivamente. En el grupo I se observó un incremento en la albuminuria ( $p < 0,05$ ), persistencia de hipocomplementemia y títulos elevados de anticuerpos anti-ADN. En este grupo se encontraron 18 exacerbaciones y en el grupo control, 9.

**Conclusiones:** En pacientes con nefritis lúpica proliferativa difusa, la presencia de IVU no complicada se asocia a un retraso en el tratamiento inmunodepresor y a un incremento en las recaídas renales.

**Palabras clave:** Nefritis lúpica. Infección urinaria. Lupus eritematoso sistémico. Recaída renal.

## Introduction

Systemic lupus erythematosus (SLE) is the prototype of systemic autoimmune diseases and for many years has been the classic model of illness resulting from tissue damage caused by the deposit of autoantibodies and immune complexes.<sup>1,2</sup> Its etiology is unknown, but both cellular and humoral immune response dysfunction are the physiopathologic basis for this disease.<sup>3</sup> There are several factors that influence the course and the prognosis of lupus nephritis. In several studies, an elevation of the serum creatinine is a prognostic factor of progression to renal failure. Older age, hypoproteinemia, hypertension, and associated illnesses are also prognostic of kidney failure. Serum creatinine levels are the only parameter that, in an isolated form, has shown an important consistency in the long-term prognosis. On the other hand, some studies have shown that immunologic function markers (complement and anti-DNA antibodies) are predictors of chronic renal failure, though the results of the latter data has not been reproduced in a uniform manner, reflecting perhaps the capacity of the therapies employed to alter such parameters. Some authors have emphasized that patients younger than 23 years have a larger possibility to develop renal damage, as is the case with male patients, but these findings have not been confirmed. In the evaluation of the renal biopsy, some factors have been associated with a poor prognosis, such as diffuse proliferative glomerulonephritis (DPGN), histological criteria of severe activity, and chronic, irreversible changes. Recent studies have identified new factors linked to the development of nephropathy as being potentially modifiable, such as hypertension, cholesterol levels, tobacco use and the presence of antiphospholipid antibodies.<sup>2,4-7</sup>

Complications from immunosuppressant treatment, mainly infections, increase the morbidity and mortality

of this group of patients. Infections are a frequent complication in patients with SLE; up to 50 and 150 episodes per 100 patients/year<sup>4</sup> have been described and some reports have mentioned that they are a frequent cause of hospital admittance and even death in these patients.<sup>8</sup> Urinary tract infection (UTI) is the most frequent cause of infection; the causative agents commonly involved are community acquired (80%-90%) and the most frequent is *Escherichia coli*. Few studies have analyzed their probable influence on the evolution of the disease,<sup>8,9</sup> so we have decided to analyze the influence of UTI on the delay in treatment and the frequency of renal relapses in patients with lupus nephritis that received treatment with immunosuppressants and cyclophosphamide.

## Patients and Methods

Patients who had 4 or more criteria for the classification of SLE as proposed by the ACR.<sup>10</sup> Disease activity was determined according to the SLE disease activity index (SLEDAI)<sup>11</sup> and damage was measured using the systemic lupus international collaboration clinics damage index (SLICC).<sup>12</sup> All patients underwent kidney biopsy and those with class IV lupus nephritis were chosen. All patients had received treatment with pulse intravenous cyclophosphamide therapy for at least 6 months. Patients with these characteristics were separated into 2 groups: patients with UTI and those without UTI. For the group with UTI, these were defined as presenting the following criteria: *a*) complicated UTI: repeated infection in which there are upper urinary tract signs and symptoms, anatomical or functional alterations in patients who are immunocompromised and with antibiotic resistance; *b*) asymptomatic bacteriuria: a case with 2 positive cultures with more than 100 000 colony forming units, without urinary symptoms; *c*) repeated UTI: 3 or more episodes of UTI in 1 year; and *d*) bacteriuria and pyuria: for the present study we considered that uncomplicated UTI was present bacteriuria and pyuria were present and the patient had required antibiotic treatment as considered by the treating physician, even when lacking a urine culture.

Pregnant patients were excluded, as were those with chronic renal failure (creatinine over 2 mg/dL, in 2 different determinations with at least one month between them) or undergoing dialysis. Active nephritis was defined as the presence of proteinuria >1 g in 24 h, the presence of erythrocyturia, urine casts, a diminution of 30% in the 24 creatinine clearance and an increase in the serum creatinine of 30% over the baseline.

The evaluation of renal function (urine test, serum creatinine, creatinine clearance, and 24 hour urine albumin) was done in all patients every month for the

first 6 months (induction period) and every 2 months afterwards until the 18 month follow-up period was complete.

Response to treatment was defined as: *a*) complete (an increase in creatinine that did not exceed 30% of the lowest value seen during treatment, proteinuria <1 g per day, absence of urine casts and less than 10 erythrocytes per field for at least 6 months and without any immunosuppressive treatment, prednisone dose equaling or less than 10 mg per day), and *b*) partial (an increase no greater than 50% in serum creatinine of the lowest value seen during treatment, for at least 6 months, without immunosuppressant treatment, independent of proteinuria or sediment).

Relapses (or flares) were defined as follows:

1. *Relapse after a complete response:* *a*) proteinuric relapse: an increase in proteinuria to > 2 g per day (with a stable serum creatinine and inactive urinary sediment); *b*) slight nephritic relapse: reappearance of cellular casts or >10 erythrocytes per field, an increase in proteinuria of at least 2 g per day and stable creatinine; *c*) moderate nephritic relapse: reappearance of cellular casts or >10 erythrocytes per field, an increase in proteinuria of >2 g per day, and stable creatinine; and *d*) severe nephritic relapse: reappearance of cellular casts or >10 erythrocytes per field, an increase in serum creatinine of >30% of the value during the complete response, independently of the proteinuria.

2. *Relapse after a partial response:* *a*) proteinuric relapse: increase in proteinuria of >2 g per day, with no changes in the urinary sediment and normal creatinine (an increase of <30% of the value at the moment of stabilization), and *b*) slight nephritic relapse: an increase in cellular casts or >10 erythrocytes per field, if the baseline value was <10 erythrocytes per field, or double the erythrocytes per field at baseline, if this was >10 erythrocytes per field.

3. *Moderate nephritic relapse:* increase in cellular casts, an increase in proteinuria to >2 g per day, without an increase in creatinine to more than 30% from baseline.

4. *Severe nephritic relapse:* an increase in the number of cellular casts with an increase in serum creatinine of >30% from baseline, independent of proteinuria.

## Treatment of Nephritis

All patients were treated with cyclophosphamide at a dose of 0.5 to 1 g/m<sup>2</sup> of body surface, monthly, for 6 months and bimonthly for a year. The cumulative dose was determined as was the time of administration of intravenous monthly pulses, and the mean daily dose (during the 6 previous months) of prednisone. For their inclusion, only patients that completed the induction of remission period (6 months) and that, after this had

shown remission of the nephritis, were considered. The study period included the maintenance period (months 6 to 18). Patients who had not attained remission after the induction phase (6 months) were excluded or those who, at the discretion of the treating physician needed to continue with therapy or required another immunosuppressant.

## Clinical Evaluation and Follow-Up

In the initial clinical evaluation, demographic data such as age and gender as well as the obstetric history and comorbidities such as hypertension, dyslipidemia, kidney stones, pelvic anatomy alterations, and obesity, were documented. Each month for 6 months and then bimonthly for 12 months, laboratory testing that included a complete blood count, blood chemistry, renal function, anti-DNA antibodies and serum complement, were carried out. The number and type of renal relapse were determined according to the above described. An delay in treatment with pulse intravenous cyclophosphamide and its cause was also documented. A delay in treatment was defined as the interruption in pulse IV CYC for at least 2 weeks in regard to the proposed date of administration. For the present analysis only the delays attributed to UTI to form group I, and that was compared to patients with demographic, clinical and treatment characteristics without UTI.

The statistical analysis included central tendency measures. The bivariate analysis included difference between means measured by Student *t* test, and differences between proportions were tested using  $\chi^2$ . Association measurements were also calculated.

The protocol was reviewed and approved by the hospital ethics committee according to the Helsinki declaration of 1964, reviewed by the World Health Assembly in Tokyo 1975, Venice 1983, Hong Kong 1989, and in the XLVIII Summerset West assembly, South Africa 1996. It also complies with the rulings of the Mexican Ley General de Salud and the rulings of the Instituto Mexicano del Seguro Social, regarding research in health sciences.

## Results

### Demographic Analysis

Fifty patients with SLE and DPGN (class IV of the World Health Organization [WHO]), and confirmed using a renal biopsy were evaluated; 41 women (82%) and 9 men (18%). Mean age was 31.3±11.5 years. Mean age since disease onset was 5.9 years and since the onset of nephritis was 2.3 years (2.4 vs 2.1 years, in groups I and II, respectively). The results of renal function testing

**TABLE 1. Demographic, Biochemical, Immunologic, and Histological Baseline Data. The Results Are Homogeneous When Comparing Both Study Groups\***

Variable	Group I (Cases UTI)			Group II (Controls)			P
	Mean	Median	DE	Mean	Median	DE	
<b>Patient characteristics</b>							
Age	31.3	28	11.5	30.2	29	8.3	.97
Time since onset of SLE, y	5.9	4	4.7	7.3	5	5.7	.52
Time since onset of nephropathy	2.4			2.1			
<b>Disease characteristics</b>							
Baseline SLEDAI	29.2	30	9.8	29.3	29	8.9	.80
Baseline SLICC	0.7	0	0.9	1.4	1	1.4	.03
Activity index	8.2	8	4.3	8	7.5	3	.74
Chronicity index	3	3	1.2	3.5	3	1.5	.33
<b>Renal function</b>							
Urea	49	42	25.9	59.4	39.5	47.9	.83
BUN	23.2	19	13.7	31.3	25	19.6	.15
Creatinine	1.2	1	0.8	1.2	1	0.7	.89
Creatinine clearance	63.4	52	37.8	72.1	59	50.5	.51
Urinary creatinine	70.8	66	34.3	68.5	67	36.1	.65
Albuminuria/24 h	2.5	2.1	2.0	2.9	1.9	2.5	.74
Urine volume	1479.5	1320	606.6	1783	1500	968.7	.33
<b>Immunology testing</b>							
Antinuclear antibody titer	352	160	380.7	293.9	320	188.2	.574
Anti-DNA antibodies	40.4	20	62.3	53.0	40	60.6	.139
C3	54.3	57	26.4	62.2	50.5	33.6	.655
C4	7.3	7	5.3	8.9	8	6.0	.347
Anticardiolipin antibodies IgM	3.0	3.5	1.2	2.8	4	1.4	.784
Anticardiolipin antibodies IgG	3.1	4	1.1	3.1	4	1.1	.974

\*SD indicates standard deviation; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; SLICC, damage index for SLE.

were similar for both groups; differences observed were not statistically significant. Activity and chronic damage of SLE was similar and there was no significant difference in the immunology studies. The histopathology activity and chronicity indexes were also similar (Table 1).

The results of the urinary sediment study did not show any statistically significant difference between both groups. As would be expected, there was a larger number of patients that had bacteria and inflammatory cells in their urine in group I. Some patients of the control group had bacteria and pyuria, nonetheless these patients had a negative

culture, did not have urinary symptoms and did not require antibiotic treatment. Some patients in group I had more than one episode of UTI throughout the year of follow-up, making the number of positive cultures (34) larger than the number of patients in the group. In group I there were 34 episodes of infection due to the fact that some patients had more than one episode during follow-up: One episode of UTI was documented in 18 patients, 2 episodes in 6 patients and one patient had 4 UTI's. The pathogens most frequently isolated were *E coli* (73%), *Klebsiella* (11.8%), *Acinetobacter* (8.8%), and *Candida albicans* (5.9%).

**TABLE 2. Mean Results in the Evaluation of Kidney Function and Immunology Testing, Comparison Between Groups\***

Variable	Patients With UTI and Treatment Delay (n=19)		Patients With UTI and Therapeutic Delay (n=22)		P
	Mean	DE	Mean	SD	
Serum creatinine, mg/dL	1.04	0.66	0.8	0.32	.32
Urea, mg/dL	46.9	19.6	34.0	9.2	.12
24 h creatinine clearance, mL/min	83.9	37.1	88.2	22.07	.37
Albuminuria, g/24 h	2.2	3.9	1.5	1.7	.05
Cellular casts	1.95	0.57	1.80	0.39	.056
Hematuria	1.90	0.22	1.60	0.22	.031
C3	50.4	28.8	93.3	11.54	.079
C4	8.8	6.7	16.3	7.5	.074
Anti-DNA	45	19.4	15	7.07	.44

\*SD indicates standard deviation; UTI, urinary tract infection.

On Table 3 a tendency towards deterioration of the kidney function and systemic disease activity can be seen in the group of patients that had to temporarily interrupt the application of pulse CY due to the presence of UTI.

### Delay in Treatment in Relation to UTI

Twenty-two patients had a delay of at least 4 weeks in the start of their intravenous CYC treatment. The presence of UTI determined the temporal interruption of treatment in 19 cases (76%), while in the group without UTI only 3 patients (12%) were delayed for non-infection related motives: severe leucopenia, hypersensitivity and gastrointestinal symptoms (odds ratio [OR] =23.22; 95% confidence interval [CI], 5.26-105.2;  $P<.001$ ). In 2 patients the delay lasted for a month and in one case it was interrupted for 2 months.

For the analysis of results at the end of follow-up, in each patient the mean of the different values that related to renal function and the immunology tests done in the year of follow-up were obtained (at least 4 determinations per patient), and the mean for each group was then calculated. These results are shown in Table 2.

Among the 25 patients in group I, 19 had a delay in treatment due to UTI; an elevation of serum creatinine was observed in 8 of them (mean,  $1.04\pm 0.66$  mg/dL). In group II, 2 patients had an elevation of serum creatinine (mean,  $0.8\pm 0.32$ ;  $P=.324$ ). This tendency was observed also for urea ( $46.9\pm 19.6$  vs  $34.6\pm 9.2$  mg/dL;  $P=.126$ ), and in the 24 hour creatinine clearance ( $83.9\pm 37.1$  vs  $88.2\pm 22$  mL/min;  $P=.83$ ). There was an increase in 24 hour albuminuria in all patients in group I and in 89% of patients in group II (mean,  $2.2\pm 3.9$  vs  $1.5\pm 1.7$  g/24 h;  $P<.05$ ). The results of the urinary sediment analysis showed a larger frequency of cellular casts in patients of group I when compared to those in group II ( $1.95\pm 0.57$  vs  $1.8\pm 0.39$ ;  $P=.05$ ), as was the case for hematuria ( $1.9\pm 0.22$

vs  $1.6\pm 0.22$ ;  $P<.03$ ). The immunology tests showed the same tendency to a higher disease activity in patients that had to interrupt treatment. Complement values were lower in patients from group I compared to group II (C3 of  $50.4\pm 28.8$  vs  $93.3\pm 11.4$ , and C4 of  $8.8\pm 6.7$  vs  $16.3\pm 7.5$ ). In spite of the numerical differences, these values did not achieve statistical significance ( $P=.79$  y  $.74$ , respectively). In the same way, the titers of anti-DNA antibodies were positive in 94% of the patients of group I, in contrast to 67% of group II, with a mean  $45\pm 49.9$  versus  $15\pm 7.07$  U;  $P=.44$  (Table 3).

### Type of Response and Exacerbations in Relation to Delay of Treatment or Lack Thereof

At the end of follow-up (month 18), response (partial or complete, according to what previously was explained) was evaluated. In the group of patients with UTI, 19 had a delay in treatment—13 had a partial response and 6 had a complete response. In the group of patients without UTI, only 3 showed a delay; among the 22 that did not have a delay in treatment, 7 had a partial response and 15 had a complete response (Table 3). These findings emphasize that the response to treatment was more satisfactory while the patient was able to comply with the proposed treatment strategy and vice versa: the presence of UTI leads to interruptions in treatment with a consequential lack of adequate response.

During follow-up, 27 episodes of relapse were seen; 18 presented in patients from the group with UTI and 9 in the control group. The distribution by groups according

**TABLE 3. Response Type at the End of Patient Follow-Up in Groups With or Without UTI That Had a Delay in the Treatment Schedule\***

Type of Response to Treatment	Patients With UTI and Therapeutic Delay (n=19)		Patients With UTI and Therapeutic Delay (n=22)	
	No.	Percentage	No.	Percentage
Partial	13	68.4	7	31.8
Complete	6	31.5	15	68.1

\*UTI indicates urinary tract infection. In this table one can observe how response was partial in the majority of cases with an infection, while in patients who did not have an infection, the response was more frequently complete.

to the type of relapse was as follows: proteinuric, 5 and 7 ( $P=.32$ ); slight nephritic, 6 and 1 ( $P=.12$ ); moderate nephritic, 1 and 0 ( $P=.78$ ); and severe nephritic, 6 and 1 ( $P=.37$ ), in groups I and II, respectively.

## Discussion

SLE is the prototype of systemic autoimmune diseases. Renal involvement is one of the most common and most severe manifestations. It can present itself in up to 75% of patients during the course of disease. The ample specter of renal manifestations included from asymptomatic forms ("silent lupus") to aggressive forms such as rapidly progressive glomerulonephritis. DPGN is the severest histological class and therefore, the one with the worst prognosis, being the cause of chronic kidney failure in 50% of cases at 10 years after it started. Due to this fact, there is a need for aggressive immunosuppressive therapy. During many years, intravenous CYC has been shown to be an effective treatment of severe lupus nephritis because it helps preserve renal function in the long-term. But therapy with intravenous CYC is associated to complications such as myelosuppression, hemorrhagic cystitis, premature ovarian failure and a larger risk for infections to which SLE patients are susceptible,<sup>2,3</sup> due to the abnormal T cell mediated cytotoxicity, a reduction in the levels of cytokine levels such as tumor necrosis alpha and interferon gamma, and to defects in macrophage chemotaxis and phagocytosis as well as polymorphonuclear cells. The most frequent sites of infection are the skin, the upper respiratory airways and the lower urinary tract.<sup>13</sup> On one hand it is known that UTI are more frequent in patients with lupus nephritis that receive intravenous CYC and on the other hand, relapses of nephritis are frequent even in patients receiving this therapeutic regimen.<sup>14-16</sup> Nonetheless, not enough analysis has been done on the impact of UTI on the delay in treatment schedules and the possible

consequence or renal relapse. In the medical literature there are different studies on the factors that negatively influence the course of nephropathy, such as an elevated creatinine level at the beginning of the disease, hypoalbuminemia, hypertension, histological data that reflects severe activity or chronicity. Some of the studies indicate that the presence of anti-DNA antibodies, the consumption of complement and recently, anticardiolipin antibodies, could be a negative prognostic factor. Associated illness also has a negative impact on the prognosis of renal function. In this last group, intercurrent illness such as infections, among which, apart from UTI, upper and lower respiratory tract infections and herpes zoster can be found.

In this study we did not set the objective of describing the frequency of complications and/or infections due to treatment with CYC, but to prospectively analyze a group of patients with lupus nephritis that had received CYC treatment for at least 6 months at the moment of inclusion. We identified at least 25 patients with episodes of UTI during the year of follow-up and we compared them with 25 controls with the same clinical and therapeutic characteristics but without infection. We found that, with a greater frequency, the presence of UTI was associated to a delay in the application of CYC pulses and, in consequence, with more renal relapses.

The participation of UTI and its relation to a delay in treatment has been scarcely discussed due to the fact that the ideas of infections of any kind leading to a reactivation of lupus nephritis is considered a given. In the case of UTI, this observation refers mainly to complicated, repeated or UTI's requiring hospitalization, but cases of bacteriuria with pyuria are not analyzed, obliging the clinician to administer outpatient antibiotic treatment and, frequently, to delay immunosuppressive treatment. In our series, no patient was hospitalized due to UTI.

In the 50 patients described, the demographic data and the clinical characteristics of the disease are similar to what previously has been published.<sup>17</sup> In our lupus nephritis clinic we used the CYC therapeutic schedule recommended by the National Institutes of Health (NIH).<sup>18</sup> 25 patients who had received at least 6 monthly pulses with CYC and who presented at least one case of UTI were identified and were compared to 25 patients with similar demographic, clinical and therapeutic characteristics. As has been commented in the medical literature,<sup>4,13,19</sup> our patients had infections that could be treated in an outpatient setting and none required hospital treatment. *E coli* was the most frequently isolated microorganism, and with a much lesser frequency, the presence of *Klebsiella* (11.8%), *Acinetobacter* (8.8%) and *C albicans* (5.9%) was described. Petri and Genovese<sup>19</sup> identified *E coli* and *Klebsiella* in more than 50% of cases.<sup>13</sup> The largest frequency of

*E coli* in our cases was probably owed to a higher frequency of infection in the genital area that underwent insufficient treatment. The frequency of sexual contact and alterations in pelvic anatomy are other factors for repeated UTI.<sup>7,20</sup>

In the present study, patients with UTI were identified and they were paired with patients that presented a similar disease and treatment, but not UTI. This design did not allow us to establish the prevalence of UTI in our cases, but diverse studies<sup>21,22</sup> have attributed a significant risk to immunosuppressive drugs. It is not possible to establish with precision the frequency of uncomplicated UTI in a patient with lupus nephritis, mainly because most studies in the medical literature relating to the treatment of this affection refer, when they describe it, to serious complications<sup>23</sup> and do not mention other intercurrent illnesses that can interfere with treatment, therefore and because of this, altering the course of nephritis. In the present study we found that the delay in the administration of CYC was more frequent in patients with UTI (76%) and that such a temporal interruption was significantly evident on the clinical variables used in the evaluation of nephritis, such as 24 hour albumin excretion and hematuria. The same tendency was observed in the other nephritis parameters, including the immunology tests, but without any statistically significant differences when compared to the control group. It is likely that, by increasing the sample size, a significance level could be attained regarding these variables. Nonetheless, the difference is clear and statistically significant when comparing the therapeutic delay between the groups with and without UTI (OR=23.22; 95% CI, 5.26-105.1;  $P=.001$ ). In coincidence with this argument, several studies<sup>21,22,24-26</sup> indicate that patients that do not complete the intravenous CYC schedule, due to infection or other causes such as pregnancy or lack of compliance, have a larger risk of progressing to nephropathy and that their biochemical and immunologic parameters improve with an adequate immunosuppressive regimen.<sup>27,28</sup>

Relapses of nephropathy after treatment with intravenous CYC have been described with wide ranging numbers, from 26% to 66%.<sup>14-16,18,24</sup> This variability can be explained by different follow-up periods and by the diversity of therapeutic strategies, and it is probable that other factors, such as the presence of intercurrent illness, also favor the frequency of relapses. If we consider the total group of 50 patients that are described above, the frequency of relapses is in agreement with what has been described in the international medical literature (56%). When they are analyzed separately, in the group with no UTI that maintained a regular treatment, the percentage of relapses (32%) was much lower than in the group with a delay in treatment due to UTI (81%), which clearly exceeds the communicated range in the medical literature.

Taking into account the data described here, we think it is necessary to emphasize the search as well as a proper registration of adverse events in the clinical trials for proliferative lupus nephritis that, as is the case with UTI, can negatively influence the course of the disease.

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