

# Lupus Nephritis and End-stage Kidney Disease

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**Abstract:** Systemic lupus erythematosus (SLE) is a multisystem disease affecting many organs. Varying degrees of renal involvement are seen in up to 60% of adults with SLE, and severe lupus nephritis (LN) (World Health Organization class III and above) progresses to end-stage kidney disease (ESKD) within 15 years of diagnosis in 10% to 30% of patients. In fact, renal injury is the most important predictor of mortality in patients with SLE. Identifying patients at risk of progression to ESKD and providing them with aggressive and appropriate immunosuppressive therapy are important factors that affect the morbidity and mortality of LN patients. Management of LN-related ESKD requires attention to persistent activity of SLE and need for continuous immunosuppressive treatment because a decrease in SLE activity in this population can improve their outcome.

**Key Indexing Terms:** Lupus nephritis; End-stage kidney disease; Systemic lupus erythematosus. [*Am J Med Sci* 2013;346(4):319–323.]

Systemic lupus erythematosus (SLE) is a multisystem disease affecting many organs. However, the involvement of the kidneys, or lupus nephritis (LN), is a major cause of morbidity and mortality in SLE patients. Up to 60% of adults with SLE suffer from varying degrees of renal involvement, and severe LN (World Health Organization class III and above) progresses to end-stage kidney disease (ESKD) within 15 years of diagnosis in 10% to 30% of patients. In fact, renal injury is the most important predictor of mortality in patients with SLE.<sup>1</sup> In this review, we discuss the history of lupus and kidney disease, lupus activity after ESKD development and management of these patients.

## HISTORICAL OVERVIEW OF LUPUS NEPHRITIS

Although the clinical features of lupus erythematosus were first described in the first century AD, the term lupus (Latin for “wolf”) was not used until the 12th century; the physician Rogerius was believed to have coined this term. Despite the ancient history of this disease, the renal manifestations of lupus were not described until the early 1900s.<sup>2</sup> The prevalence of renal involvement only became apparent after corticosteroids and antibiotics were introduced in medical practice in the 1950s. Paradoxically, clinicians at the time were concerned that the use of these novel therapies would actually cause renal injury. Until Muehrcke et al<sup>3</sup> described similar nephropathological features in SLE patients, both on and off these therapies, clinicians did not realize that these measures actually improved the survival of SLE patients, thereby facilitating the observation of renal involvement and progression to ESKD. Renal failure soon emerged as an important cause of death among SLE

patients, with a reported survival rate of less than 50% at 5 years for LN patients in the late 1950s.

Over the ensuing decades, with improvements in the renal biopsy technique, systematic analysis of pathological data with standardized classifications and risk recognition, the introduction of serological markers and the development of new immunosuppressive therapies, the outcome of LN patients significantly improved and mortality decreased. Development of standardized protocols for induction and maintenance therapies in the treatment of LN also universally improved the standard of care,<sup>4</sup> such that studies from the 1990s reported that more than 93% of LN patients survived for 5 years and 85% survived for 10 years.<sup>5</sup> In addition, investigators who were part of the Euro-Lupus Nephritis Trial found a survival probability of 88% at 10 years when a cohort of LN patients was followed from 1990 to 2000.<sup>6</sup>

However, the survival of LN patients with ESKD was negatively affected by the delayed utilization of available renal replacement therapies (RRTs). Despite issuing Medicare waivers for ESKD patients in 1971, patients who developed LN-associated ESKD were often deprived of these therapies (Figure 1). Hemodialysis (HD) therapy for LN was first reported only in the mid-1970s and only in the European literature. This treatment did not gain wide acceptance because initial reports indicated that the outcomes of LN patients with ESKD who underwent RRT seemed to be worse than those of the general ESKD population.<sup>7</sup> The 5-year survival rate in the early 1980s was reported to be significantly lower in HD-dependent SLE patients than in non-SLE patients (58.6% versus 88.5%). Morbidity in the SLE group was primarily associated with infection and vascular access problems, but no deaths were directly attributable to SLE activity. With advances in lupus treatment as a whole, outcomes improved dramatically. By the 1990s, the 5-year survival rate for patients on dialysis increased to 73%.<sup>7,8</sup> In fact, dialysis has provided the opportunity for renal recovery. There are a number of cases of unexpected recovery from presumed ESKD in SLE patients, and thus in this era, LN patients with ESKD are uniformly offered RRT.

A recent study demonstrated a higher rate of hospitalization and mortality among pediatric and adult patients with ESKD on maintenance HD, with cardiovascular disease being the most common cause of death.<sup>9</sup> This study should not take us back to the “dark ages” where LN-associated ESKD was denied appropriate treatment but reiterate the need for a close monitoring of these patients in the outpatient setting, with the help of a multidisciplinary team including the nephrologist and the rheumatologist, and the need for continued research to improve outcomes of patients with LN-associated ESKD.

Similar to RRT history, LN patients with ESKD were not offered renal transplantation as often as other ESKD patients. Although the first successful kidney transplantation procedures were reported in the 1960s, it was a decade before LN patients received allograft kidney transplants at a frequency equivalent to that of other ESKD patients. Perhaps the susceptibility of SLE patients to infection prevented them from being perceived as good candidates for RRT. However, survival of LN patients with ESKD has continued to improve, and SLE patients are

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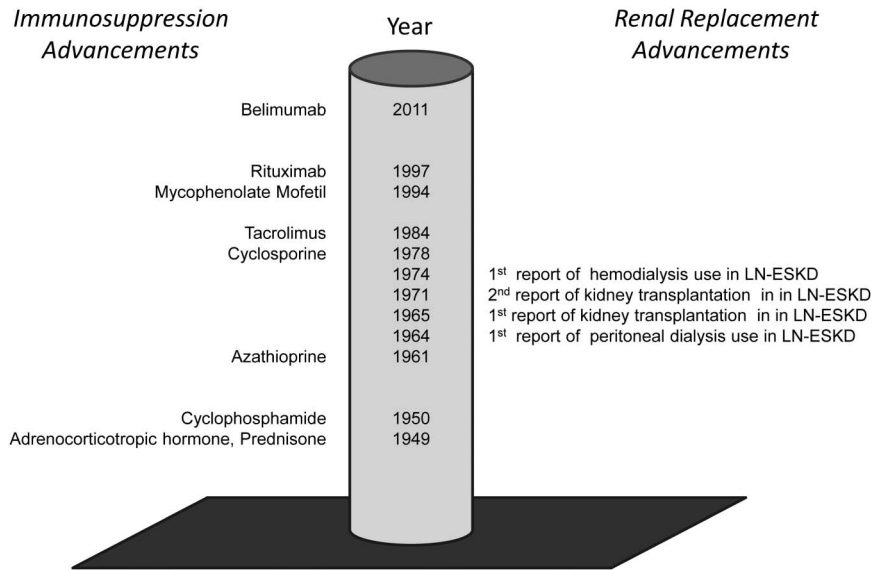


FIGURE 1. Evolution of accepted immunosuppressive therapies for treatment of lupus nephritis, history of renal replacement therapy for patients with lupus nephritis related end-stage kidney disease in the United States, 1949 to 2011.

currently offered unfettered access to life-saving therapies, including dialysis and renal transplantation.

### INCIDENCE OF ESKD AND RISK FACTORS FOR LN PROGRESSION TO ESKD

The incidence of LN-associated ESKD has increased from 1.16 cases per million in 1982 to 4.9 cases per million in 2004 in the United States (Figure 2).<sup>10,11</sup> Analysis of the U.S. Renal Data System from 1996 to 2004 showed that there were 9199 new cases of ESKD attributable to LN,<sup>11,12</sup> with most patients being of African American descent and of female sex (49% and 82% of cases, respectively).<sup>12</sup> This increase in the incidence of ESKD attributable to LN is a cause for concern. Recent epidemiological studies have pointed to several risk factors associated with the progression of LN to ESKD that could affect these numbers (Figure 3). For instance, young age is one of the primary risk factors for progression to ESKD. It was reported that up to 75% of children with SLE eventually develop nephritis and 18% to 50% show progression to ESKD.<sup>13,14</sup> The lack of standardized protocols for treating LN in pediatric populations is a challenge in managing treatment. Children with LN receive more intensive

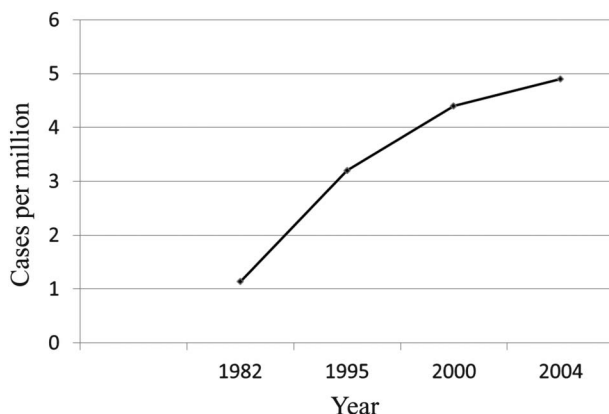


FIGURE 2. Incidence of end-stage kidney disease from lupus nephritis in the United States, 1982–2004.<sup>10,11</sup>

immunosuppressive therapy than adult LN patients, and they frequently develop therapy-related toxicity. Pediatric patients of African American descent and those with nephrotic range proteinuria (estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup>) at the time of diagnosis tend to have worse renal outcomes.<sup>15</sup>

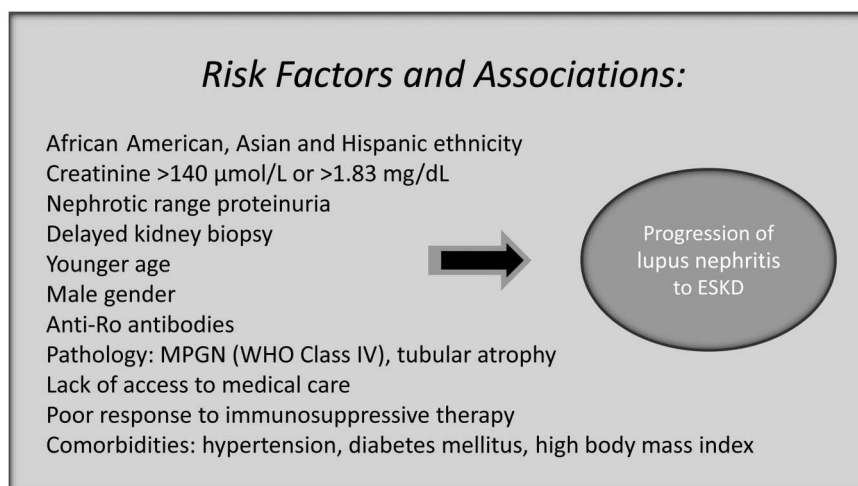
Both pediatric and adult patients showed disparities in the incidence of LN-related ESKD according to racial, ethnic, and geographical backgrounds (Figure 3). For instance, there is a greater likelihood of progression to ESKD among African American and Hispanic patients with LN than among Whites.<sup>16</sup> African American LN patients who lived in southeastern United States and had higher body mass indexes or diabetes mellitus with hypertension had the highest risk of ESKD progression (Figure 3).<sup>12</sup> Furthermore, response to treatment regimens is different for the different populations.

Whereas the incidence of SLE among the male population is low when androgen levels are high, this incidence approaches that among the female population during childhood and old age when androgen levels are low. Male gender was found to be a poor prognostic factor for the clinical course of LN, progression to ESKD and morbidity.<sup>5,17–19</sup>

Delay in treatment of LN is an important risk factor associated with poor outcomes and progression to ESKD. A significantly higher risk of progression to kidney failure has been reported among patients with delayed renal biopsy.<sup>20,21</sup> Specifically, an elapsed time of more than 6 months between urinary evidence of nephropathy and biopsy has been associated with progression to ESKD.<sup>22</sup> High serum creatinine levels (>140 μmol/L or >1.83 mg/dL), diffuse proliferative glomerulonephritis, tubular atrophy, lower complement levels, and presence of anti-Ro antibodies have also been reported to be strong independent risk factors for ESKD progression (Figure 3).<sup>22,23</sup> Not surprisingly, patients who showed a poor response to immunosuppressive therapy also had a relatively high incidence of ESKD.<sup>4</sup> These data suggest that promptness in obtaining kidney tissue for diagnosis and in initiating effective immunosuppressive therapy are modifiable factors that can affect the prognosis of LN patients.

Finally, lack of access to medical care can limit preventive treatment (Figure 3). A population-based epidemiological study of residents in California showed that patients without health insurance, with public insurance, or with high

FIGURE 3. Progression of lupus nephritis to ESKD—risk factors and associations. ESKD, end-stage kidney disease; MPGN, membranoproliferative glomerulonephritis; WHO, World Health Organization.



rates of avoidable hospitalizations had a relatively high incidence of LN-related ESKD.<sup>24</sup> Additional studies must be conducted to explain the growing incidence of LN-associated ESKD and to further define risk factors for ESKD progression.

### SLE ACTIVITY AFTER DEVELOPMENT OF ESKD AND THE NEED FOR CONTINUED IMMUNOSUPPRESSION

Despite initial reports in the 1980s and 1990s of worse outcomes for LN-associated ESKD patients compared with other ESKD patients, several investigators noted that the initiation of HD was associated with a quiescence of SLE signs and symptoms. These observations gave rise to the notion that SLE activity is tempered by HD, a dogma that persists even today.

Contrary to this dogma, several investigators retrospectively showed that the clinical activity of the disease not only failed to improve but also worsened after initiation of RRT.<sup>25–27</sup> There have also been alarming case reports of patients with long-term ESKD who unexpectedly developed clinical and serological SLE activity after as many as 14 years on RRT or Libman-Sacks endocarditis after a prolonged period on dialysis.<sup>28,29</sup> In light of this evidence, continued monitoring of disease activity in lupus patients on RRTs seems crucial.

Although desirable, the assessment of lupus activity in ESKD patients is not easy. Despite the introduction of more than 60 systems for defining disease activity, flare assessment is inevitably arbitrary. Although the Systemic Lupus Erythematosus Disease Activity Index, Systemic Lupus Activity Measure and British Isles Lupus Assessment Group have been used by many investigators to report outcomes with regard to SLE activity,<sup>27,30</sup> none of these scoring systems were developed for SLE patients with ESKD, and no system for specifically accessing SLE activity in the ESKD population is currently available.

Serological markers such as complement and anti-double-stranded DNA are routinely tested in patients with LN to assess disease activity. However, reports on the correlation of disease activity with serological markers in ESKD patients are conflicting.<sup>8,31</sup> Moreover, serological markers are not accurate measures of disease activity during the posttransplantation period. Thus, current data suggest that, in the ESKD population, serologic markers cannot reliably assess disease activity. Therefore, there is a compelling need to develop an ESKD-specific tool for accessing disease activity in the SLE population. Until then,

we recommend clinical alertness to the potential development of extrarenal manifestations of SLE in ESKD patients.

After initiation of RRT, patient care typically shifts to the nephrologist, and contact with the rheumatologist is lost. However, a recent retrospective study showed that SLE patients on dialysis who continued to have regular follow-up visits with their rheumatologist (2 or more per year) had improved longevity and were more likely to receive effective immunosuppressive therapy.<sup>32</sup> Importantly, aggressive immunosuppressive therapy was found to correlate with a better 10-year survival rate than prednisone and hydroxychloroquine, prednisone alone or no immunosuppressive medication. In addition, the combined use of prednisone and hydroxychloroquine was associated with better survival than prednisone alone.<sup>32</sup> Although immunosuppression increases the risk of infection, the overall mortality rate seems to improve with aggressive immunosuppression therapy. Nevertheless, patients who continue with immunosuppression should be carefully monitored for infection. When dosing immunosuppressive agents, it is important to keep in mind that most agents, except for azathioprine and cyclophosphamide, show no intradialytic clearance with HD (Table 1). Unfortunately, little is known about the clearance of immunosuppressive agents during peritoneal dialysis (PD). Thus, undertreatment of active SLE in ESKD patients seems to be an important and modifiable factor in patient care.

### DIALYSIS MODALITIES IN PATIENTS WITH SLE

Analysis of the U.S. Renal Data System data from 1995 to 2006 indicated LN progression to ESKD in 11,317 patients; 85% of these patients were initiated on HD, 12.2% were started on PD and 2.8% underwent preemptive kidney transplantation at the onset of ESKD.<sup>33</sup> This distribution is similar to that of RRTs in the general ESKD population.

Data regarding the modality that might be most advantageous for LN-associated ESKD indicated similar 5- and 10-year survival outcomes for HD and PD populations, with a nonsignificant trend favoring PD in a retrospective multicentered study. This was despite a lower technique-associated survival rate in the PD group than in the HD group because of a higher incidence of intra-abdominal infections over the 5 to 10 years of follow-up.<sup>34</sup> But, several single-center studies on the survival advantage of different RRTs in LN-associated ESKD have reported worse outcomes for PD (eg, cumulative survival, infectious complications and clinical and serological disease activity).<sup>30,35,36</sup>

TABLE 1. Clearance of immunosuppressive agents with high-permeability hemodialysis (HD) and peritoneal dialysis (PD)

Immunosuppressive agent	Molecular weight (dalton)	Clearance with high-permeability HD	Clearance with PD
Azathioprine	277.26	Likely	No data
Basiliximab	144,000.0	No data	No data
Cyclophosphamide	279.1	Likely	No data
Cyclosporine	1202.61	Unlikely	No
Mycophenolate mofetil	433.50	Unlikely	No
Prednisone	358.43	No data	No
Rituximab	145,000.0	Unlikely	Unlikely
Sirolimus	914.2	Unlikely	Unlikely
Tacrolimus	804.02	Unlikely	Unlikely
Thymoglobulin	669,000.0	Unlikely	No data

In the absence of large RCTs demonstrating a clear benefit of a dialysis modality in patients with LN-associated ESKD, the decision to choose a dialysis modality should be personalized for each patient. For patients on immunosuppressive medications, avoiding PD may be considered based on the higher incidence and technique failure related to peritonitis that has been reported in these patients.<sup>34</sup> Similarly, PD may be preferable in patients with a history of antiphospholipid antibodies syndrome (APLS) because of the possibility of access failure with HD.<sup>37</sup> The gratifying fact is that we now know that patients with LN-associated ESKD do well with all modalities of RRT, and if one modality does not work, there is always the option of converting them to another modality, with the ultimate goal of procuring a renal allograft considering their excellent outcomes with renal transplantation.

### OUTCOMES OF RENAL TRANSPLANTATION

The belief that lupus activity became quiescent with dialysis has led to the view that patients should be allowed to “burn out” their disease with dialysis before transplantation, even though no study has shown a benefit of pretransplantation dialysis.<sup>34</sup> In fact, a recent large analysis of the United Network for Organ Sharing data set from 1987 to 2009 revealed that LN patients who received a kidney transplant preemptively, before the need for dialysis, had better graft survival and a lower risk of recipient death.<sup>38</sup> Additionally, kidney transplantation significantly improves survival and reduces extrarenal SLE manifestations compared with dialysis.<sup>30,32,39</sup> However, these studies included confounding variables that may have contributed to the better outcomes in transplantation patients, such as the selection of healthy and compliant patients for transplantation and effective suppression of extrarenal manifestations with immunosuppressive therapy.

The practice of having lupus “burn out” on dialysis before transplantation was adopted in an effort to prevent recurrence of the disease in the transplanted kidney. Remarkably, recent data from the United Network for Organ Sharing database show that the prevalence of recurrent LN was as low as 2.44% among 6850 SLE kidney allograft recipients between 1987 and 2006. Although some surveillance biopsy studies reported recurrence rates as high as 54%, the majority of the LN cases were clinically nonrelevant World Health Organization class I to II cases, for which no specific therapy was indicated. Overall, graft survival and infection-related complications are comparable between transplantation patients with LN-associated ESKD and allograft recipients with ESKD because of other causes.<sup>13,40</sup> Nevertheless,

it is important to recognize that in an absence of universally established criteria, most transplant centers (including our institution) only accept SLE patients for kidney transplant after they have sustained clinical remission for 6 to 12 months.

Despite reports of better outcomes in LN patients with transplants from living donors in the postcyclosporine era,<sup>41</sup> the possibility of a higher recurrence of LN and risk of rejection on receiving an allograft from a living donor than on receiving a cadaveric kidney is still a cause for concern.<sup>14</sup> However, the benefits associated with receiving an allograft from a living donor are clear and pronounced in patients with ESKD because of other causes. Given the small sample sizes of the studies that reported worse outcomes for LN patients, the findings of these studies should not deprive lupus patients of the overwhelming benefit of receiving an allograft from a living donor.

Presence of antiphospholipid antibodies in patients with SLE remains a concern for kidney transplantation because of the risk of graft thrombosis. Recent studies revealed that the presence of antiphospholipid antibodies alone negatively impacts 10-year graft survival, but the impact is not as large as the impact pretransplant history of APLS. SLE patients with history of APLS have significantly lower long-term graft survival even while on anticoagulation and need to be monitored closely for thrombotic complications.<sup>42</sup>

Despite advances in the care of lupus patients and an increasing number of transplantations, long-term survival of lupus patients with transplant lags behind that of nonlupus patients with transplants, with the most frequent cause of death being cardiovascular events.<sup>43–45</sup> Thus, although renal transplantation is probably the best treatment for lupus patients with ESKD, the underlying disease still affects long-term survival.

### CONCLUSIONS

Despite advances in the treatment of LN, incidence of ESKD in this population is growing. The mortality of patients with LN-associated ESKD has not changed in recent years and is attributable primarily to cardiovascular complications. Preemptive renal transplantation should be pursued in this population to improve survival. In addition, because disease activity does not always remit with dialysis, patients with SLE should continue to visit their rheumatologist and receive appropriate immunosuppressive therapy.

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