The International Society of Nephrology (ISN) and the World Health Organization (WHO) systems for classifying the various forms of lupus nephritis have significantly improved our understanding of the natural history of the disease and facilitated the development of new and effective treatments. The classification of the different manifestations of lupus nephritis is based upon light, immunofluorescent and electron microscopic changes. As shown in Table 1, the WHO system of nomenclature identifies six different classes of lupus nephritis, with classes III and IV being the “proliferative” forms of the disease. WHO class III, or focal proliferative glomerulonephritis, is defined by the presence of proliferating endocapillary cells within the glomerular capillary loops. As shown in Figure 1, proliferating endocapillary cells lead to occlusion of capillary lumen, leading to a direct reduction in filterable glomerular surface area. By definition, patients with WHO class III have less than 50% of the volume of an individual glomerulus or less than 50% of the total number of glomeruli with endocapillary proliferation. While many patients with severe class III may exhibit focal necrosis (karyorrhexis) or extracapillary proliferation (crescents), these findings are not required for staging a particular biopsy as class III or class IV. The overall prevalence of class III is 25% to 30%.1 In general, class III is associated with higher titers of anti-DNA antibodies, low complement levels, and active extra-renal manifestations of SLE. Progression from class II to class III (focal proliferative disease) occurs in about 20% to 25% of patients,2 while conversion from class III to class IV occurs in over two-thirds of patients over 36 months.3 The long-term renal survival of patients with class III lupus nephritis generally has been thought to be better than for those with class IV. However, Najafi and colleagues reviewed the 10-year survival of 85 patients with biopsy-confirmed lupus nephritis and demonstrated that only 52% of patients with class III lupus nephritis had functioning kidney, compared with 75% for patients with class IV.4 The etiology for this survival difference is unknown but may represent a treatment bias, in which patients with class II receive less aggressive immunosuppression.

WHO class IV (diffuse proliferative) lupus nephritis shares many similarities with class III but generally demonstrates more extensive and aggressive histopathology. At the histologic level, class IV is defined by the presence of endocapillary proliferation in greater than 50% of glomeruli. While not required for the diagnosis, patients with class IV lupus nephritis often demonstrate extensive crescents and karyorrhexis. Figure 2 demonstrates a glomerulus from a biopsy of a patient with severe lupus flare. A solitary glomerulus with a large circumferential crescent is shown collapsing the glomerular tuft (black arrow). The large, rounded cells present in the crescent are derived from the parietal epithelial cell layer. Figure 3 demonstrates an area of endocapillary proliferation with an area of focal necrosis or karyorrhexis (white arrow). These histopathologic signs are independent predictors of patients developing progressive renal disease.5

At the clinical level, patients with class IV lupus nephritis frequently demonstrate severe extra-renal manifestations, including lupus cerebritis and lupus pneumonitis. Renal function at presentation can range from mild renal insufficiency to dialysis-dependent acute kidney injury. The nephrotic syndrome is uncommon with patients presenting a pure class IV, but often accompanies patients presenting with mixed lesions, including WHO class Vc and Vd. In the absence of significant immunosuppression, the long-term renal survival of patients with class IV is poor, with more

James A. Tumlin, M.D. is Professor of Medicine, University of Tennessee College Medicine, and Director of the Southeast Renal Research Institute, Chattanooga, Tennessee.

Correspondence: James A. Tumlin, M.D., j tumlin@emory.edu.
than 70% of patients progressing to end-stage renal disease within 5 years.\(^6\)

Membranous lupus nephritis (WHO class V) is present in between 10% to 20% of renal biopsies and is characterized by thickened capillary loops and mesangial expansion, but without significant crescent formation or endocapillary proliferation. However, the histopathology of class V is more diffuse than other forms of lupus nephritis and can be subdivided into three other forms. Patients with class Vb exhibit membranous features in conjunction with mesangial proliferation, while class Vc and Vd demonstrate focal or diffuse endocapillary proliferation.\(^7,8\) As shown in Figure 4, the glomerular capillary loops are thickened but show no evidence of crescents, focal necrosis, or endocapillary proliferation. Electron microscopy demonstrates the presence of mesangial dense deposits. Along the basement membrane, immune complex deposits can be seen in the subepithelial, intramembranous, and subendothelial distribution (Fig. 5).

<table>
<thead>
<tr>
<th>WHO Class</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
<th>Class V</th>
<th>Class VI</th>
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<td>Focal proliferative</td>
<td>Diffuse proliferative</td>
<td>Membranous</td>
<td>Sclerosing</td>
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<td>&lt; 50% Glomeruli endocapillary proliferation</td>
<td>&gt; 50% Glomeruli endocapillary proliferation</td>
<td>Thickened capillary loops</td>
<td>Interstitial fibrosis</td>
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<tr>
<td>Immuno-fluorescent microscopy</td>
<td>Immune complex deposits</td>
<td>IgG/IgM mesangial staining</td>
<td>IgG-IgM to full house</td>
<td>IgG-IgM to full house</td>
<td>IgG mesangial subepithelial</td>
<td>IgG/IgM mesangial</td>
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<tr>
<td>Electron microscopy</td>
<td>Immune complex deposits</td>
<td>Mesangial dense deposits</td>
<td>Mesangial subendothelial deposits</td>
<td>Mesangial subendothelial/ subepithelial</td>
<td>Mesangial subepithelial</td>
<td>Variable</td>
</tr>
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</table>

**Table 1** World Health Organization (WHO) Nomenclature for Classifying the Various Forms of Lupus Nephritis

*Figure 1* Proliferating endocapillary cells lead to occlusion of capillary lumen, leading to a direct reduction in filterable glomerular surface area.

*Figure 2* A glomerulus from a biopsy of a patient with severe lupus flare. A solitary glomerulus with a large circumferential crescent is shown collapsing the glomerular tuft (black arrow). The large, rounded cells present in the crescent (white arrow) are derived from the parietal epithelial cell layer.
significantly reduced 10-year survival. Despite an assortment of immunosuppressive regimens, including cyclosporin, azathioprine, and cyclophosphamide, patients with WHO class Vc and Vd were found to have 55% and 20% 10-year survival, respectively (Fig. 6).

Indications of Renal Biopsy

The indications for lupus nephritis typically center around clinical and laboratory findings that suggest severe underlying pathology with the potential for active proliferative forms of lupus nephritis. For example, patients with microscopic or gross hematuria are generally viewed as having a more severe form of lupus nephritis and thus are more likely to undergo renal biopsies. Several studies cast doubt on the ability of urinary findings to predict underlying renal pathology. For example, Eiser and associates performed renal biopsies on 13 patients with a clinical diagnosis of systemic lupus erythematosus (SLE) and active nonrenal manifestations, but without signs of chronic renal failure or abnormal urinalysis. Interestingly, 7 of the 13 patients were found on renal biopsy to have focal or diffuse proliferative lupus nephritis. These observations suggested the possibility that occult lupus nephritis could be present in the absence of typical laboratory findings that indicate the presence of renal disease. Stamenkovic and colleagues examined 56 patients with a known diagnosis of SLE and examined the correlation between serum creatinine and the level of hematuria or proteinuria using the WHO stage of lupus nephritis. While there was a general trend that patients with the more proliferative forms of lupus nephritis (i.e., WHO class III and IV) had higher levels of proteinuria and increased serum creatinine, the correlation with urine sediment was less pronounced. A total of 14 patients were found on biopsy to have WHO class I, but up to 25% of those patients had an active urine sediment and significant proteinuria. In contrast, none of the patients with class V lupus nephritis were found to have an active urine sediment. The failure of serum creatinine levels and urinary proteinuria to correlate with specific classes of lupus nephritis has been observed by other investigators. For example, Jacobsen and coworkers retrospectively reviewed the biopsies of 94 patients with active lupus but normal serum creatinines. Despite spared renal function at the time of biopsy, 55% of patients were found to have class IV diffuse proliferative lupus nephritis. Urinary protein ranged from less than 300 mg/24 hours to greater than 31 grams/24 hours. There was no correlation between the degree of proteinuria and the underlying histology except for patients with class V membranous disease, who tended to have higher levels of proteinuria.

The observation that serum creatinine, proteinuria, and urine sediment are poor predictors of renal pathology led
Robert and associates to conduct a prospective, double-blind study comparing the urinalysis findings with renal biopsy results in 15 patients with active SLE. Of the 15 patients, six (40%) had no signs of renal involvement, while nine had active renal disease. No single urinalysis parameter correlated with the underlying class of lupus nephritis or identified patients with progressive kidney disease. These observations suggest that the decision to perform a kidney biopsy is best made by examining multiple variables that indicate the presence of clinically significant renal disease. Conversely, no single clinical or laboratory finding (i.e., hematuria or proteinuria) can effectively rule out the presence of lupus nephritis. The use of real-time ultrasound has significantly reduced complication rates of renal biopsies, which in turn has allowed clinicians to use a patient’s individual histology to gauge the intensity and duration of therapy.

**Therapy of Lupus Nephritis**

The development of effective protocols for managing lupus nephritis has been slowed by an incomplete understanding of its natural history; the difficulty in organizing large, multicenter trials; and a lack of pharmacologic agents with...
hypertension, and persistent anemia (Hct less than 26%) that patients with hypocomplementemia (C3 less than 80), factors for progressive disease. Austin and colleagues studied graphic variables have been identified as independent risk long-term renal survival by reducing renal scarring. It suggests that aggressive immunosuppression can improve no aggregate increase in renal scarring. These observations demonstrated that the addition of intravenous cyclophosphamide significantly improved renal survival.

In addition to renal histology, other clinical and demographic variables have been identified as independent risk factors for progressive disease. Austin and colleagues studied 166 patients with biopsy-proven lupus nephritis and noted that patients with hypocomplementemia (C3 less than 80), hypertension, and persistent anemia (Hct less than 26%) demonstrated increased risk for progressive renal disease. Interestingly, Austin and coworkers noted that patients of African ancestry exhibited more refractory disease and were at increased risk for end-stage renal disease. In a similar study, Dooley and associates retrospectively analyzed 89 patients with biopsy-proven lupus nephritis and determined the effect of African race on renal survival. All patients received a standard NIH (National Institutes of Health) induction protocol, which included pulse solumedrol and monthly intravenous cyclophosphamide for 6 months. As shown in Figure 8, renal survival after 5 years was significantly lower among African-American patients receiving identical induction protocols. Caucasian patients demonstrated excellent response to cyclophosphamide therapy, with over 95% renal survival at 5 years. However, less than 57% of the African-American patients maintained renal function over the same period. Moreover, these differences were independent of duration of lupus, age, control of hypertension, or access to medical care.

The presence of high-risk populations with poor clinical outcomes suggests that some patient cohorts receive suboptimal therapy, while other groups may be receiving excessive immunosuppression. To address this question, Gourley and colleagues conducted a prospective randomized trial comparing monthly pulses of solumedrol, intravenous cyclophosphamide, or the combination of the two in 82 patients with lupus nephritis. As shown in Figure 9, the combination of monthly pulse solumedrol in conjunction with intravenous cyclophosphamide led to improved renal survival at 10 years. Patients randomized to a 12-month course of pulse solumedrol exhibited significantly higher rates of disease progression, with over 60% reaching the primary endpoint of doubling serum creatinine. Moreover, significant side-effect profiles, including the onset of major infections, herpes zoster, avascular necrosis, and premature ovarian failure were similar between the three groups, allowing clinicians the ability to increase the intensity of immunosuppression among high risk groups.

SLE and lupus nephritis predominate among females; therefore, there has been a drive to develop protocols that are effective but do not increase the risk for ovarian failure. Mycophenolate mofetil is a novel immunosuppressive agent developed for solid organ transplantation that prevents purine synthesis in circulating T and B cells, resulting in selective inhibition of clonal expansion. In a large multicenter trial, Ginzler and coworkers randomized 149 subjects with known lupus nephritis to oral mycophenolate or intravenous cyclophosphamide. As shown in Figure 10, there was no difference in serum creatinine, C3 complement levels, anti-dsDNA titers, or level of proteinuria. The presence of high-risk populations with poor clinical outcomes suggests that some patient cohorts receive suboptimal therapy, while other groups may be receiving excessive immunosuppression. To address this question, Gourley and colleagues conducted a prospective randomized trial comparing monthly pulses of solumedrol, intravenous cyclophosphamide, or the combination of the two in 82 patients with lupus nephritis. As shown in Figure 9, the combination of monthly pulse solumedrol in conjunction with intravenous cyclophosphamide led to improved renal survival at 10 years. Patients randomized to a 12-month course of pulse solumedrol exhibited significantly higher rates of disease progression, with over 60% reaching the primary endpoint of doubling serum creatinine. Moreover, significant side-effect profiles, including the onset of major infections, herpes zoster, avascular necrosis, and premature ovarian failure were similar between the three groups, allowing clinicians the ability to increase the intensity of immunosuppression among high risk groups.
for lupus nephritis, it is important to continue long-term (10 year) surveillance of patients to determine rates of relapse and overall renal survival.

**Relapse of Lupus Nephritis**

The rate of relapse of lupus nephritis following induction therapy is unknown due to the lack of a validated and accepted definition of a relapse. Mosca and associates attempted to address this question by defining a renal flare as a 30% rise in serum creatinine or at a 2.0 gram/day rise in proteinuria following induction therapy. A full 54% of patients experienced a renal flare with a mean follow-up of 30 months. Patients with a high activity index and the presence of karyorrhexis were more likely to experience recurrent disease.\(^5\) Ioanidis and colleagues defined recurrent disease as an active urine sediment (8 to 10 RBC/hpf) or greater than 500 mg of proteinuria per 24 hours.\(^6\) They prospectively treated 85 patients with biopsy-proven focal or diffuse proliferative lupus nephritis with an intravenous cyclophosphamide induction protocol. Only a third of the patients at the end of 6 months of therapy met the full definition of remission, whereas only 58% and 78% achieved remission at 12 and 24 months, respectively. When patients were prospectively followed for relapse, approximately 30% developed recurrent lupus nephritis within 30 months.\(^6\) Interestingly, both Mosca and coworkers and Ioanidis and associates observed a significant reduction in the rate of renal flares in patients with greater than 6 years of disease duration.\(^5,6,17\) These observations may be important for the design of clinical trials where flare rate is used as a primary endpoint. Patients with greater than 6 years of disease duration may experience lower flare rates and thus be excluded from some prospective studies.

**Utility of Serial Renal Biopsies**

There is a growing body of evidence indicating the utility of performing serial renal biopsies in the management of lupus nephritis. For example, Moroni and colleagues retrospectively studied 31 patients with biopsy-proven lupus nephritis and attempted to identify clinical and pathologic features that would predict long-term renal survival. All patients received pulse methylprednisolone for 3 days, followed by tapering doses of prednisone with additional therapy that included oral cyclophosphamide or azathioprine. All patients with rising serum creatinine or persistent proteinuria underwent repeat renal biopsies. Of the patients with persistent proteinuria, three of 12 patients (25%) were found to have worsening nephritis, while seven patients (58%) showed no response to therapy. Among patients with rising creatinine, 59% were found to have persistent or worsening lupus nephritis.\(^18\) In a recent study, Hill and coworkers demonstrated the utility of protocol surveillance biopsies in a study of 71 patients with biopsy-proven lupus nephritis. Patients received a standard NIH induction protocol, with pulse solumedrol and intravenous cyclophosphamide for 6 months. All patients received repeat renal biopsy after induction therapy, whereupon Hill and associates evaluated specific histologic features that would be predictive of long-term renal survival. The presence of residual cellular crescents, karyorrhexis, or endocapillary proliferation on the second biopsy strongly predicted patients that would experience a doubling of serum creatinine within 5 years. For example, patients with persistent karyorrhexis after 6 months of induction therapy had a 75% chance of doubling serum creatinine at 10 years, whereas only 27% of patients with no residual karyorrhexis doubled serum creatinine. A global disease activity of less than 1.73 was associated with progression (doubling of serum creatinine) at 4,000 days in only 15% of cases versus 80% in patients with a disease activity of greater than 1.73.\(^3\)

These observations demonstrate the complexity in the management of lupus nephritis. It is apparent that current biochemical markers including serum creatinine, urinalysis, and level of proteinuria are not sufficient for knowing the degree and severity of an individual patient’s histology. The use of the renal biopsy allows for more real-time and patient-specific directed therapy that will allow for both an amplification and reduction of therapy, based on the demographic, clinical, and histologic degree of severity.

**Disclosure Statement**

The author has no financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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