Managing lupus nephritis: algorithms for conservative use of renal biopsy

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SUMMARY Despite the widespread use of renal biopsy to guide the treatment of lupus nephritis, the disease can usually be diagnosed and managed on the basis of its clinical presentation alone. We propose a conservative approach in which biopsy is used selectively and present three algorithms that allow for a simplified initial approach to managing lupus nephritis.

KEY POINTS Although the grading systems of the World Health Organization and the National Institutes of Health for renal biopsy results are commonly used to guide the treatment of lupus nephritis, there are limits to the utility of these systems. Physicians can distinguish clinically mild lupus nephritis, the nephrotic syndrome, or the nephritic syndrome on the basis of the urine sediment, urine protein excretion, serum albumin and creatinine concentrations, and creatinine clearance, and can initiate treatment on the basis of this information, rather than performing a renal biopsy. Corticosteroids are the cornerstone of therapy for lupus nephritis, but new therapies are emerging. The nephritic syndrome reflects active disease and requires more vigorous treatment. It may be prudent to reserve renal biopsy for situations that arise later in the course of lupus nephritis, such as failure to respond to therapy based on the initial clinical presentation.

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PHYSICIANS disagree about the role of renal biopsy in guiding treatment decisions and in determining renal prognosis in patients with lupus nephritis. Although renal biopsy is widely used, it is not without potential complications and may not add much information to that available from a clinical evaluation that includes a careful analysis of the urine sediment. As a result, some physicians advocate a conservative use of renal biopsy, while others favor a more liberal use, with no clear consensus for either approach. Further complicating the issue for the clinician, no prospective clinical trials have assessed the effect on outcome of a more limited vs a more universal use of renal biopsy.

In this paper we review the pathology of lupus nephritis, discuss the role of renal biopsy, review current therapies, and propose treatment algorithms based on clinical presentation, in which renal biopsy is used only selectively.

TABLE 1
SCORING SYSTEMS FOR RENAL BIOPSIES IN LUPUS NEPHRITIS*

Class	WHO system	ISKDC system
I	Normal	Normal A No changes B Normal on light microscopy but deposits on electron microscopy
II	Mesangial glomerulonephritis (GN)	Pure mesangiopathy A Mild B Moderate
III	Focal proliferative GN with fewer than 50% of glomeruli involved	Segmental and focal proliferative GN A Active necrotizing B Active and sclerosing C Sclerosing
IV	Diffuse proliferative GN with more than 50% of glomeruli involved	Diffuse proliferative GN A Without segmental necrotizing lesions B With segmental necrotizing lesions C With segmental active and sclerotic lesions D Inactive, sclerotic
V	Membranous GN	Diffuse membranous GN A Pure membranous B Associated with lesions in group IIA or IIB C Associated with lesions in group IIIA, IIIB, or IIIC D Associated with lesions in group IVA, IVB, IVC, or IVD
VI	—	Advanced sclerosing GN

*WHO, World Health Organization; ISKDC, International Study of Kidney Disease in Children; from Ponticelli, reference 43

PREVALENCE AND MORTALITY OF LUPUS NEPHRITIS

Renal disease causes considerable morbidity and mortality in patients with systemic lupus erythematosus (SLE), even though glucocorticoids and cytotoxic drugs have increased the survival rate markedly. Patients with lupus nephritis now have a 10-year survival rate of 65% to 85%,[1] most likely due to earlier diagnosis and better treatment of both the nephritis and of associated complications. In contrast, the 5-year survival rate was less than 50% before the use of corticosteroids.[1] The prevalence of clinically apparent renal disease in patients with SLE ranged from 29% to 65% in a number of series.[1] However, if histologic criteria (which are more sensitive) are used, almost all patients with SLE have renal abnormalities.

RENAL BIOPSY IN CLINICAL DECISION-MAKING

Percutaneous needle biopsy of the kidney was first described by Iverson and Brun[2] in 1951 and was used extensively by Muehrcke[3] in 1957, Pirani and Pollak[4,5] in the 1960s, and Baldwin and McCluskey[6] in the 1970s to study renal disease in SLE. In early studies, the use of renal biopsy added immensely to the understanding of this disease's etiopathogenesis,[7,8] response to treatment,[9–11] and natural history.[5,12] It also led to the recognition that distinct histologic subsets exist,[3,5] glomerulosclerosis and interstitial scarring carry a poor prognosis,[13,14] and lesions can transform from one histologic type to another.[9,12]

The World Health Organization (WHO) classification system

The World Health Organization (WHO) system for grading renal biopsy findings in SLE recognizes five distinct histologic classes (*Table 1*).[15,16] Class I is normal. Classes II through IV likely share a common etiopathogenic mechanism and may represent the spectrum of severity of the same lesion,[7,12,17] postulated to result from deposition of circulating immune complexes within renal tissue with subsequent immune-mediated renal damage. The site and degree of deposition depend partially on genetic factors and on the nature of the antibodies formed. In contrast, the membranous (class V) lesion is thought to result from deposition of antigen in the glomerular basement membrane, with later formation of antigen-antibody complexes in situ. Patients with class V lesions have less serologic abnormalities (eg, low serum complement levels, elevated levels of serum immune complexes, high anti-double-

TABLE 2
NATIONAL INSTITUTES OF HEALTH RENAL PATHOLOGY SCORING SYSTEM*

Activity index†	Chronicity index†
Glomerular abnormalities	
Cellular proliferation	Glomerular sclerosis
Fibrinoid necrosis‡ karyorrhexis	Fibrous crescents
Cellular crescents‡	
Hyaline thrombi, wire loops	
Leukocyte infiltration	
Tubulointerstitial abnormalities	
Mononuclear-cell infiltration	Interstitial fibrosis
Fibrous crescents	Tubular atrophy

*System from Austin et al, reference 20; table from Ponticelli, reference 43
†Each factor is graded on a scale of 0, 1, 2, or 3 (absent, mild, moderate, and severe, respectively); the maximum activity index is 24, the maximum chronicity index is 12
‡Fibrinoid necrosis and cellular crescents are weighted by a factor of 2

stranded DNA antibody titers), lending support to this theory.

Appel[12] subsequently divided class II lesions into "mild" and "moderate," and the Pathology Advisory Group for the International Study of Kidney Disease in Children (ISKDC)[16] further modified the WHO system to distinguish between "active" and "sclerosing" lesions, included subdivisions for mixed lesions, and added a sixth class, advanced sclerosing glomerulonephritis (*Table 1*).

Untreated, class IV lesions (diffuse proliferative glomerulonephritis) carry a particularly poor prognosis. However, classes II, III, and IV respond better to treatment than class V lesions do. Class II has the most favorable course and response to treatment.[6,12,13] These observations have led to the widespread use of renal biopsy and the WHO classification system for making treatment and management decisions. The goal was to detect diffuse proliferative glomerulonephritis by renal biopsy and treat it more aggressively.

Problems with renal biopsy and the WHO system

However, there are problems with overreliance on renal biopsy and the WHO system in making treatment decisions. Sampling error, interobserver variation in histologic classification, and transition between classes result in findings that do not always correlate with the clinical condition, limiting the utility of renal biopsy in lupus nephritis. The procedure poses some risk of complications.[18] Multivariate analysis of clinical predictors of renal outcome in large patient series suggests that the results of renal biopsy, especially the WHO classification, do not add to the predictive power of models based on clinical information.[13,19–21] In addition, even though untreated proliferative lesions have a poor outcome, such a diagnosis on an initial biopsy does not guarantee progression to renal failure, because repeat biopsy studies have indicated that many of the features of aggressive, active disease can be reversed with treatment.[9–11]

The National Institutes of Health (NIH) activity and chronicity indices

Another system for grading biopsy findings, the NIH activity and chronicity indices (*Table 2*) may be more accurate than the WHO classification in predicting long-term prognosis.[14,19] The NIH activity index reflects acute and potentially reversible renal damage; the chronicity index reflects permanent damage.[11,19,20]

These two indices assign point values (0, absent; 1, mild; 2, moderate; and 3, severe) for each of a list of different findings. The activity index assesses the findings of cellular proliferation, leukocyte infiltration, and so on, and has a maximum score of 24; the chronicity index assesses degree of glomerular sclerosis, fibrous crescents, interstitial fibrosis, and tubular atrophy and has a maximum score of 12. Some studies found that a high chronicity index (> 3) predicted a poor renal outcome, especially when it occurred in combination with a high activity index (> 10).[20,22] However, not all studies have confirmed this association.[23,24] For example, the Lupus Nephritis Collaborative Study Group found that the activity and chronicity indices were not predictive of chronic renal failure in 83 patients followed for a mean of 5.5 years.[23] Another, recent study in community hospitals has shown the association between these indices and outcome to be only moderately reproducible.[24] The investigators suggested that widespread use of the NIH indices may result in erroneous predictions of renal failure and of response to therapy and may misdirect therapy.

We feel there is a role for the NIH scoring system in the management of lupus nephritis, but interpretation of renal histology should be done by experienced renal pathologists with a special interest in lupus.

In particular, there is increasing support for the use of renal biopsy to assess for other predictors of

TABLE 3
CLINICAL CHARACTERISTICS OF DIFFERENT CLASSES OF LUPUS NEPHRITIS

Class	Clinical presentation	Transformation	Incidence
I	No renal or urine abnormality	To class II or IV: 15%–20% To class V: 2%–5%	Rare
II	Mild proteinuria (< 1 g/24 hours) and sediment Normal creatinine concentration and clearance (30% with IIB have increased creatinine concentration or decreased creatinine clearance)	To class IV: 20%–40%	10%–30%
III	Moderate proteinuria (> 1 g/24 hours) Hematuria Active sediments Decreased creatinine concentration or increased creatinine clearance Occasionally hypertension	To class V: 2%–5%	10%–25%
IV	Frequent nephrotic range proteinuria (> 3 g/24 hours) Very active, telescopic urine sediment Nephritic syndrome in 60% Increased creatinine concentration or decreased creatinine clearance in most	To class III or V: 5%–10%	40%–60%
V	Most with nephrotic range proteinuria Active sediments in < 30% May have hypertension late in course	—	10%–20%
VI	Hypertension Inactive sediments Chronic renal insufficiency or end-stage renal disease	—	—

*Modified from Ponticelli, reference 43

poor renal outcome such as fibrosis and scarring, especially in proliferative nephritis or more active disease as assessed by the activity index. A number of groups have shown that the degree of scarring or sclerosis and fibrosis adds to clinical models in predicting poor prognosis.[13,19,20]

ASSESSING LUPUS NEPHRITIS CLINICALLY

In most patients, early lupus nephritis has one of three presentations: the nephritic syndrome with acute renal insufficiency (reflecting diffuse proliferative glomerulonephritis—class IV), the nephrotic syndrome with an inactive urine sediment (suggesting membranous nephritis—class V), or a more indolent urine sediment with a normal creatinine clearance (suggestive of a mesangial lesion—class II or early class III) (*Table 3*). This is true even though the clinical manifestations and course of lupus nephritis within each class can overlap,[7] and mixed lesions can occur, especially later in the course of renal disease. The WHO classification adds little information when the clinical presentation is consistent with one of these three clinical pictures.

Therefore, in most circumstances, physicians can initiate appropriate therapy on the basis of the clinical presentation, and the response to therapy can guide further decisions.[25,26] This approach has support: in one study, four experienced clinicians were able to predict both short-term and long-term outcome (defined by the serum creatinine level at 1 year and renal insufficiency, respectively) in 87 patients with lupus nephritis. Their predictions approximated computer-generated statistical models, and improved only slightly if they were given information from renal biopsies.[27]

Table 4 lists the clinical features most helpful in the evaluation and follow-up of lupus nephritis, and the most suggestive of active renal disease, in order of clinical importance. If markers suggestive of active renal disease are absent, a persistently high serum creatinine concentration, proteinuria, or persistent hypertension despite aggressive antihypertensive therapy implies chronic disease. Again, the correlation between these histologic and clinical features is not absolute. Patients with lupus nephritis can present with a high chronicity index (implying longstanding renal disease) despite a relatively short period of clinically apparent, active nephritis before the biopsy.[22]

Diffuse proliferative glomerulonephritis without an active urinary sediment ("silent, diffuse lupus ne-

TABLE 4
CLINICAL INDICATORS OF ACTIVE LUPUS NEPHRITIS*

Active urine sediment in the absence of a urinary tract infection
Red blood cell casts, white blood cell casts, or granular casts
More than five red blood cells per high-powered field
More than five white blood cells per high-powered field
2+ or 3+ proteinuria on dipstick testing
Urine protein > 1g/24 hours
Serum creatinine concentration > 1.2 mg/dL at presentation† or a persistent increase above baseline in serum creatinine concentration†
Acute increase in blood pressure above baseline
Decrease in C3
Increase in anti-double-stranded DNA

*Indication for 24-hour urine collection for calculation of creatinine clearance
†Look for other causes of acute renal insufficiency

phritis") has been reported in one series.[28,29] There is little evidence that this entity is a true subset of diffuse proliferative glomerulonephritis or that it has any potential to cause progressive renal damage. It is unlikely that diffuse proliferative glomerulonephritis will be missed in a patient without clinically evident renal disease, further supporting the importance of following clinical parameters of active renal disease (*Table 4*).

Overreliance on any one or on a few clinical parameters can be misleading in judging the severity of the histologic lesion; therefore, the clinician must incorporate all available clinical data in making treatment decisions without a biopsy. In addition, other causes of renal failure or conditions that produce features of an active urinary sediment (such as infection) need to be considered before attributing them to lupus nephritis.

Certainly if there is an unclear clinical picture or an inadequate response to therapy based on the presumed nature of the renal disease, a biopsy is warranted. If the renal disease is chronic or previously treated, a renal biopsy can be helpful in establishing new baseline data to better determine the nature of the nephritis and direct further treatment.

TREATING LUPUS NEPHRITIS

Given the limitations of renal biopsy, we propose three algorithms for the early treatment of the three most common initial clinical presentations (*Figures 1–3*). These algorithms offer several advantages by allowing for: (a) the treatment of mild cases (WHO class II and early class III) without the risk and expense of a biopsy, (b) early, aggressive treatment of potentially severe nephritis (by generally addressing persistent indicators of active, aggressive disease within the first 2 months), (c) biopsy later in the disease (when a switch may occur or when indicators of chronic disease may have a greater impact on management), (d) multiple opportunities to change therapy, and (e) maintenance therapy with alternate-day steroids, which limits toxicity.

These algorithms are only suggested guidelines that allow for an initial, simplified approach to the management of a potentially complicated clinical problem. Patients who do not fit these algorithms, those for whom therapy based on initial clinical information fails, or those with previously treated chronic lupus nephritis may be better served by a renal biopsy earlier in the course of their renal disease. We emphasize early treatment with immunosuppressive agents for clinical scenarios suggestive of proliferative lesions, since delayed treatment is associated with a poor outcome.[30]

RECOMMENDATIONS: WHEN TO PERFORM A BIOPSY

A renal biopsy should be obtained early in the course of treatment if the result will influence treatment decisions in favor of immunosuppressive agents.

However, it is prudent to reserve renal biopsy for situations that arise later in the course of lupus nephritis, for example, after failure to respond to therapy that was based on the initial clinical picture and the most likely corresponding renal lesion. Performing a biopsy after treatment fails would allow for identification of a potentially more aggressive class IV lesion, whereas an earlier biopsy might miss the lesion because of sampling error or because the lesion had not yet switched from a class II or, more commonly, a class III lesion. In this way, biopsy material obtained later in the course of lupus nephritis could be scrutinized for features related to the NIH activity and chronicity index when the nephritis is more "established," and better, more rational

Figure 1: Treatment for clinically mild lupus nephritis

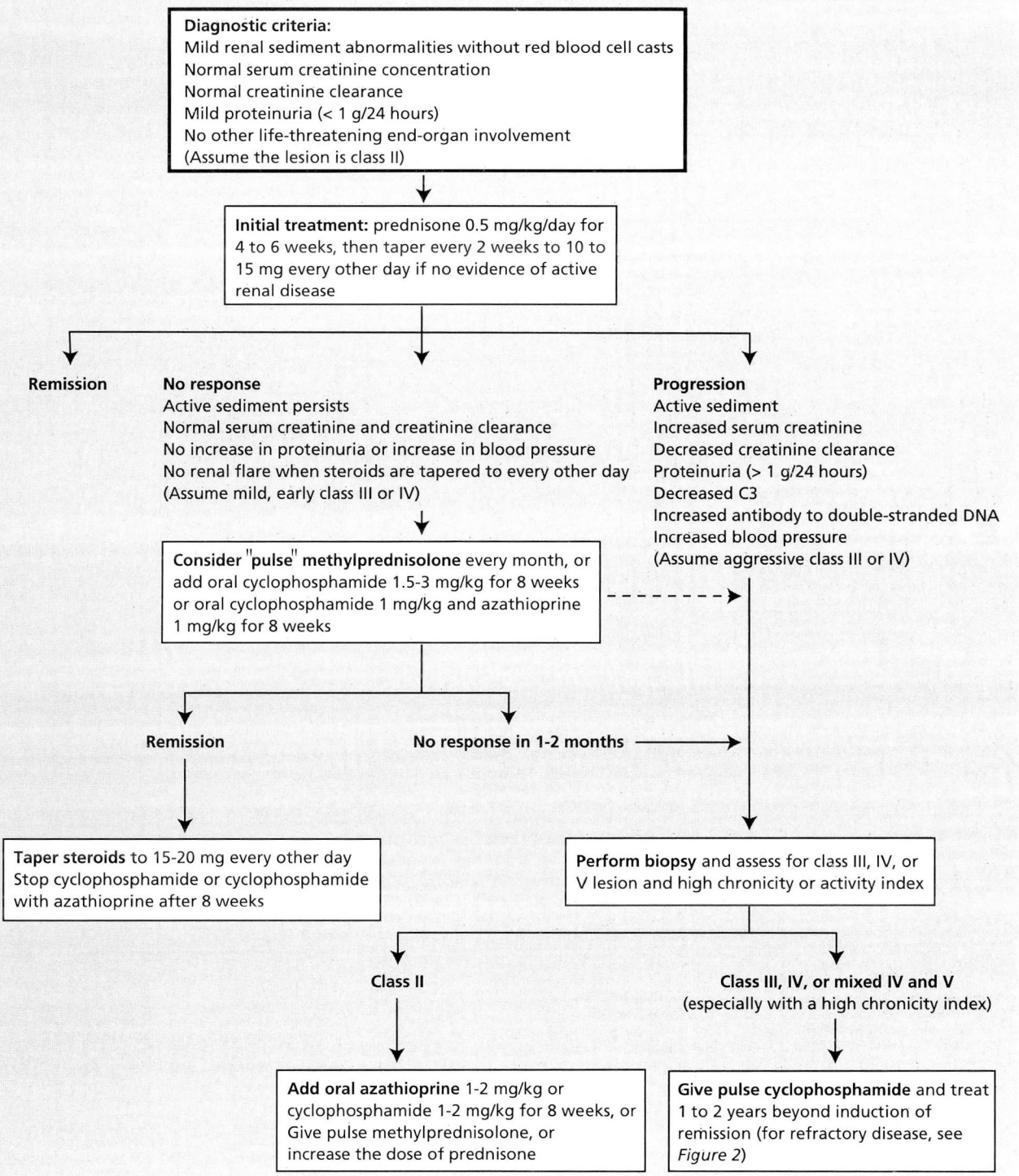


Figure 2: Treatment for lupus nephritic syndrome

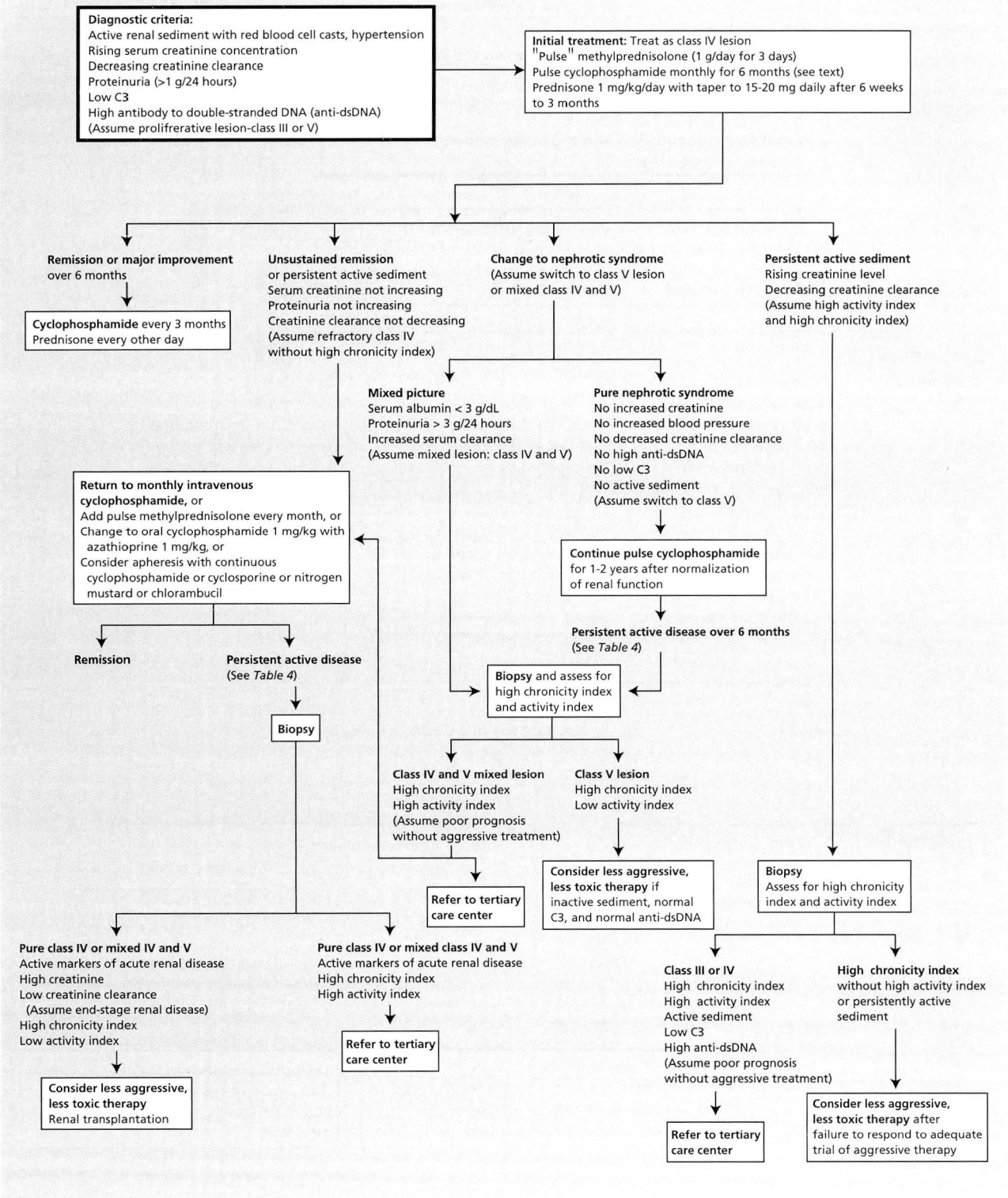
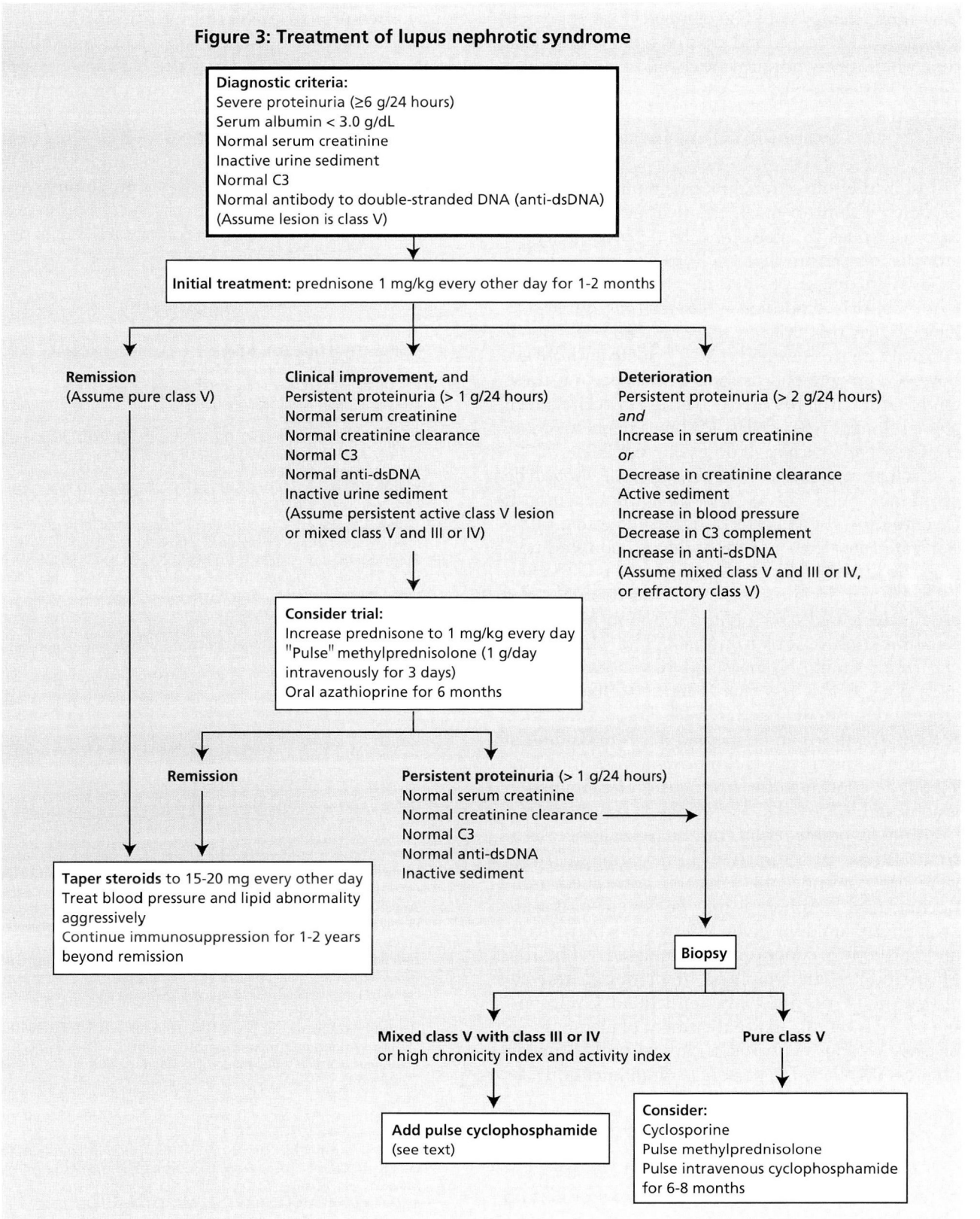


Figure 3: Treatment of lupus nephrotic syndrome



long-term therapy could be planned. This approach would avoid the risk and cost of renal biopsy at a time when it may not provide the most accurate and relevant information.

EVOLVING TREATMENTS

Just as the role of renal biopsy in managing lupus nephritis is controversial, the treatment of the disease continues to evolve and be debated. There is growing consensus that cyclophosphamide should be used in diffuse proliferative glomerulonephritis (the nephritic syndrome—class IV), as NIH trials have shown this drug to increase the 5-year renal survival rate in this condition.[31,32] Some authorities, however, recommend caution in interpreting these trials and initially treat diffuse proliferative glomerulonephritis or class IV lupus nephritis more conservatively with high doses of prednisone.[1,33]

Cyclophosphamide, when indicated, should be given in a "pulse" intravenous dosage once a month for 6 months, then quarterly. If the glomerular filtration rate is more than 33% of the age-adjusted normal, the initial cyclophosphamide dose is 0.75 g/m^2. If the glomerular filtration rate is less than this, the dose is decreased to 0.5 g/m^2 for 6 months or until renal function returns to normal. The white blood cell count should be measured 10 to 14 days after each dose; if it is less than 1500×10^9/L, the subsequent dose should be decreased, if more than 4000×10^9/L, the dose can be increased to a maximum of 1.0 g/m^2. Quarterly cyclophosphamide infusions should be continued for 1 to 2 years after remission is achieved.[21,34]

Initial favorable reports on the use of apheresis to treat diffuse proliferative glomerulonephritis[35,36] were not confirmed by a recent, controlled, multicenter trial.[37] Apheresis may be beneficial if pulse cyclophosphamide is given afterward, when B-cells and antibody production are stimulated.[38] The role of ancrod,[39] total lymphoid irradiation,[40] and cyclosporine[41–43] need to be better defined. Cyclosporine may have a role in the treatment of membranous or class V lupus nephritis; a clinical trial is now in progress (Wallace DJ, personal communication).

SUMMARY

The prognostic value of the WHO classification of renal biopsies is unclear, and the role of certain clinical features in predicting prognosis are better defined. There is evidence supporting as well as refuting the predictive value of the NIH activity and chronicity indices, and their routine use is controversial. Experienced clinicians can predict short- and long-term renal outcome as well as statistical models can, and their predictions improve only slightly with biopsy information.[27] In summary, a more limited, conservative approach to the use of a renal biopsy in the management of early lupus nephritis may be the best approach.

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