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Review article

Childhood lupus nephritis

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disease associated with significant morbidity and mortality in both adults[1] and children[2,3]. Compared to adults, paediatric SLE patients have an increased incidence (up to 82%) and severity of lupus nephritis (LN)[4,5], which determines both the renal and overall prognosis[6].

EPIDEMIOLOGY

The prevalence of SLE is 1 case in 2000 in the general population. Because of the difficulty in diagnosis and a probable underestimation of SLE cases, researchers suggest that the prevalence may be closer to 1 case in 500-1000 population[7]. Histologically, the kidneys are affected to some degree in most patients with SLE. Estimates of the prevalence of clinical renal involvement in persons with SLE range between 30 and 90% in published studies. Most patients develop nephritis early in their disease evolution[8]. Lupus nephritis is more common in females because the overall prevalence of SLE is higher in females (i.e., female-to-male ratio of 4-1 prepubertal and 9:1 postpubertal); however, males with SLE have an increased prevalence of clinical renal disease with a worse prognosis. Asians, African-Caribbeans and African-Americans may have more nephritis than other ethnic groups[9].

GENETIC FACTORS

HLA antigens have been associated with an increased risk of developing nephritis and the HLA-DR2 and HLA-B8 are more associated with the development of lupus renal disease than inheritance of the HLA-DR4 gene[10,11]. Polymorphisms of Fc receptors for IgG (FcgammaR) were recently identified as a risk factor, implicating defective handling of circulating immune complexes in the development of renal disease[12].

IMMUNOPATHOGENESIS

At least three potentially overlapping, immuno-pathogenic mechanisms are supported by experimental data. First, circulating immune complexes consisting chiefly of DNA and anti-DNA are deposited in the kidney. Resulting complement activation and chemotaxis of neutrophils leads to a local inflammatory process. Second, in situ formation of antigen and antibody complexes may similarly lead to complement activation and leucocyte mediated injury. Third, antibodies against specific cellular targets may produce renal injury. For example, antibodies, such as anti-ribosomal P, may bind to cytoplasmic antigens that have been translocated to the cell membrane with subsequent penetration and disruption of cellular function[13].

An additional mechanism is observed in SLE patients with the antiphospholipid antibody syndrome. Glomerular thrombosis can result from the hypercoagulability that accompanies antibodies directed against negatively charged phospholipid-protein complexes (e.g. biologic false positive VDRL, anticardiolipin antibodies, and lupus anticoagulant)[14].

CLINICAL PRESENTATION

Active lupus renal disease can be defined clinically or pathologically. Clinically the symptoms are generally related to hypertension, proteinuria, and renal failure. The disease is evaluated by urinalysis, 24 hour urine protein and creatinine excretion or protein/creatinine ratio in spot sample, serum creatinine, anti-DNA titers, and serum complement. Additionally, serum albumin and cholesterol can be used to help characterize the nature of lupus renal disease[15].

Unfortunately, obtaining an accurate measurement of the glomerular filtration rate is not easy. Taking inulin clearance as the 'gold standard', Shemesh et al. 1985[16] had demonstrated that creatinine clearance determinations overestimate the glomerular filtration rate during the acute phase of lupus nephritis, probably as a result of tubular secretion of creatinine. Isotopic tests (e.g. 99Tc-DTPA) appear to provide a more accurate measure of glomerular filtration rate in these patients.

The urinary sediment is useful to characterize disease activity as the presence of leukocyturia, hematuria or hyaline casts (in descending order) are typical only during periods of disease activity. A rising anti-DNA titer and hypocomplementemia, especially with low C3, are strong indicators or predictors of active lupus renal disease[17]. ESR is usually elevated during active nephritis. Clinically

relevant lupus nephritis is associated with a 30% decrease in creatinine clearance, proteinuria of greater than 1000 mg/dl[18].

Confusing clinical management is the phenomenon of fixed proteinuria. There are patients who do not have active immunologic injury who have persistent proteinuria. It is hypothesized that the prior immunologic injury and remitted inflammatory process create dysfunctional glomeruli incapable of preventing protein excretion. Therefore, patients may excrete 1-3 grams per day of protein even during periods of disease remission[19].

Hypoalbuminemia accompanied by significant proteinuria is a component of the nephrotic syndrome which may accompany active lupus renal disease. Hypercholesterolemia is another marker and clinical complication of the nephrotic syndrome that can accompany active lupus renal disease. Tubular damage, fibrosis and atrophy can be associated with hyperuricemia and renal tubular acidosis[20].

DEFINITIONS[21]

- Complete remission (CR) was defined as the presence of all of the following three criteria for at least 6 months: serum creatinine <1.2 mg/dl, absence of proteinuria (negative or trace on the urine stick and 24 h or spot urine/creatinine ratio <0.2), and inactive urinary microscopic sediments [absence of cellular casts and <10 red blood cells per high-power-field) (RBCs/HPF)].
- Partial remission (PR) was defined as improvement or stabilization of a previously elevated serum creatinine level, improvement in a previously elevated proteinuria reduced to a non-nephrotic range (24 h or spot urine protein/creatinine ratio ≤3.0) for at least 6 months, and the presence or absence of hematuria or RBC casts.
- No remission (NR) was defined as a persistent nephrotic-range of proteinuria (24 h or spot urine protein/creatinine ratio >3.0) regardless of the presence of urinary sediment, and/or no improvement in abnormal serum creatinine concentration.
- An initial response was defined as achieving a first CR or PR without the new appearance of proteinuria, hematuria, or increased serum creatinine for at least 6 months.
- Renal flares could be classified as being either proteinuric or nephritic. Proteinuric flare was characterized by the reappearance of nephrotic-range proteinuria (24 h or spot urine protein/creatinine ratio >3.0) with a stable serum creatinine level. Nephritic flare was defined as an increase in serum creatinine to 1.4 mg/dl or above (double-checked), or an increase in the last value by at least 50%, which is generally associated with active urinary sediment (RBC >10/HPF or cellular casts) and an increased quantity of proteinuria.

Lupus renal disease is also defined pathologically. Histological evidence of lupus nephritis is present in most patients with SLE, even if they do not have clinical manifestations of renal disease. Several studies have illustrated the lack of reliability of diagnoses rendered on the basis of clinical features alone[22]. Therefore, making a diagnosis on clinical grounds alone is problematic and risky, underscoring the need for kidney biopsy. With diverse renal histopathological findings possible in SLE-affected patients, biopsy determines not only the diagnosis and prognosis, but also substantially guides management of this complex disease. As the therapeutic armamentarium for lupus nephritis expands, it becomes even more imperative that the correct diagnosis be made prior to instituting therapy. In deciding whether to perform a biopsy, one must balance the risks of the biopsy procedure against the risks of limited diagnostic information, which may result in progression of potentially preventable renal disease or the unnecessary use of a possibly toxic therapy.

Material obtained by renal biopsy is evaluated by light microscopy, immunofluorescence and electron microscopy. The first World Health Organization (WHO) classification was formulated by Pirani and Pollak in Buffalo, New York in 1974 and was first used in publications in 1975[23] and 1978[24]. This classification addressed glomerular lesions only. Class I was applied to renal biopsies showing no detectable glomerular abnormalities by light, fluorescence, or electron microscopy. Class II was defined as purely mesangial immune deposition and was subdivided into two subclasses depending on whether mesangial hypercellularity was present. Class III lesions were defined as proliferative glomerulonephritis affecting fewer than 50% of the glomeruli (i.e., focal), whereas class IV was defined as proliferative glomerulonephritis affecting more than 50% of the glomeruli (i.e., diffuse). No qualitative differences between class III and class IV lesions were described. Membranous lupus nephritis was classified as class V. Tubulointerstitial and vascular lesions were not included in the classification system. In 1982, the WHO classification was modified by the International Study of Kidney Diseases in Children[25] (Table 1). It introduced subdivisions for

class III and IV based on the presence of active, chronic, or mixed types of glomerular injury. Class VI was introduced to denote advanced sclerosing glomerulonephritis.

Table 1. World Health Organization (WHO) morphologic classification of lupus nephritis (modified in 1982) Quoted from (Geoffrey et al, 2006)[25].

Class I	**Normal glomeruli**
	a. Nil (by all techniques)
	b. Normal by light microscopy, but deposits by electron or immuno-fluorescence microscopy
Class II	**Pure mesangial alterations (mesangiopathy)**
	a. Mesangial widening and/or mild hypercellularity (+)
	b. Moderate hypercellularity (++)
Class III	**Focal segmental glomerulonephritis (associated with mild or moderate mesangial alterations)**
	a. With "active" necrotizing lesions
	b. With "active" and sclerosing lesions
	c. With sclerosing lesions
Class IV	**Diffuse glomerulonephritis (severe mesangial, endocapillary or mesangio-capillary proliferation and/or extensive subendothelial deposits)**
	a. Without segmental lesions
	b. With "active" necrotizing lesions
	c. With "active" and sclerosing lesions
	d. With sclerosing lesions
Class V	**Diffuse membranous glomerulonephritis**
	a. Pure membranous glomerulonephritis
	b. Associated with lesions of class II
	c. Associated with lesions of class III
	d. Associated with lesions of class IV
Class VI	**Advanced sclerosing glomerulonephritis**

More recently the National Institutes of Health (NIH) developed activity and chronicity indices (Table 2)[26]. High chronicity scores are associated with poor outcome and a lack of response to immunosuppression. High activity indices are associated with poor outcomes, but may be reversible, especially with aggressive treatment[27]. There has been some concern regarding the reproducability of these indices in community settings[28].

Table 2. NIH renal pathology system[26].

Activity Index	Chronicity Index
Glomerular abnormalities	
1. Cellular proliferation	1. Glomerular sclerosis
2. Fibrinoid necrosis, karyorrhexis	2. Fibrous crescents
3. Cellular crescents	
4. Hyaline thrombi, wire loops	
5. Leukocyte infiltration	
Tubulointerstitial abnormalities	
1. Mononuclear cell infiltrates	1. Interstitial fibrosis
	2. Tubular atrophy

Severity of each index quantitated as 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. Fibrinoid necrosis and cellular crescents are weighted by a factor of 2. Maximum activity index is 24 and that of chronicity index 12.

In 2003, the International Society of Nephrology and Renal Pathology Society (ISN/RPS) advised a new classification of lupus nephritis (Table 3 and figures 1-12)[29]. Overall, it bears a strong similarity to the 1974 classification, but introduces several important modifications concerning quantitative and qualitative differences between class III and IV lesions. This new classification provides a clear and unequivocal description of the various lesions and classes of LN, removing the ambiguity of the WHO classification and allowing overlap cases between two classes to be documented accurately. It was strongly recommended that any significant vascular and tubulointerstitial pathology to be reported as separate entries in the diagnostic line.

Table 3. International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis[29].

Class I	**Minimal mesangial lupus nephritis**
	Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II	**Mesangial proliferative lupus nephritis**
	Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits
	May be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy
Class III	**Focal lupus nephritis** [a]
	Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits,

	with or without mesangial alterations
Class III (A)	Active lesions: focal proliferative lupus nephritis
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV	**Diffuse lupus nephritis** [b]
	Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving 50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when 50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when 50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Class IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis
Class IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis
	Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
Class V	**Membranous lupus nephritis**
	Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations
	Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed
	Class V lupus nephritis show advanced sclerosis
Class VI	**Advanced sclerosis lupus nephritis**
	90% of glomeruli globally sclerosed without residual activity

a Indicate the proportion of glomeruli with active and with sclerotic lesions.

b Indicate the proportion of glomeruli with fibrinoid necrosis and/or cellular crescents.

Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis or other vascular lesions.

The distribution and quantity of electron dense deposits, a surrogate on electron microscopy for immune complexes, are also of prognostic and therapeutic significance[30]. Class I and Class IV disease are associated with mesangial and subepithelial location of electron dense deposits, respectively. Proliferative nephritis, both Class III and IV, are both associated with subendothelial deposits.

Although clearly not without exception, there is a correlation between the pathologic type of lupus renal disease and the aforementioned clinical features. Obviously, patients with normal renal biopsies have normal diagnostic and blood tests. Mesangial lupus nephritis is accompanied by normal diagnostic findings or with a mild degree of proteinuria but typically absence of hypertension or abnormal urinary sediment. Focal and diffuse proliferative lupus glomerulonephritis are often associated with the worst prognosis for renal survival and can be accompanied by nephrotic syndrome, significant hypertension and abnormal urine sediment. Membranous lupus nephritis often presents with proteinuria, moderate to high grade, but usually normal urinary sediment in the absence of hypertension[31].

It should be mentioned that in the contra-positive there are patients with so-called silent lupus nephritis who have normal urinalyses, absence of proteinuria and normal serum creatinine but who, on renal biopsy, have anywhere from mesangial to proliferative nephritis[32]. Fortunately, it has not been demonstrated that progressive loss of renal function in these cases occurs silently, that is to say without the appearance of a perturbed urinary sediment and albuminuria.

MANAGEMENT

Goals of Therapy: Although there is no consensus on outcome definitions, such as remission and relapse of LN, most clinicians will agree on the following therapeutic goals for a patient with newly diagnosed lupus nephritis: (*1*) to achieve prompt renal remission, (*2*) to avoid renal flares, (*3*) to avoid chronic renal impairment, and (*4*) to fulfill these objectives with minimal toxicity[33].

Unmet Expectations: Although patient and renal survival rates have improved over the past decade, it should be stressed that current immunosuppressive regimens still achieve suboptimal results. First, the rate of renal remission after a first-line therapy is at best 81% in recent prospective studies[33-37]. Second, renal relapses occur in one third of LN patients[38], mostly when patients are still immunosuppressed[39]. Third, between 10 and 20% of LN patients

experience ESRD 5 to 10 yr after disease onset, although these figures are lower (between 5 and 10%) in recent studies[36,37,40]. Finally, treatment-related toxicity remains a major concern, such as metabolic and bone side effects of high-dose glucocorticoids (GC)[41-43], severe infections, or premature ovarian failure in females who receive high-dose cyclophosphamide (CYC)[44-45].

- Therapies for renal biopsy–specific pathologic lesions[46]
  - Class I lesions require no specific therapy.
  - For class II lesions, treatment of extrarenal manifestations may be the only therapy required. If proteinuria is greater than 1000 mg/d, elevated anti-dsDNA is present, and low complement levels are present, the patient could have a proliferative component not sampled in the biopsy specimen. Consider prednisone in low-to-moderate doses (i.e., 0.5-1 mg/kg/d) for 1-3 months, with subsequent taper.
  - With class III and IV lesions, patients are at high risk of progressing to end-stage renal disease and require aggressive therapy.
    - Administer prednisone 1 mg/kg/d for at least 4 weeks, depending on clinical response. Then, taper it gradually to a daily maintenance dose of 5-10 mg/d for approximately 2 years. In acutely ill patients, intravenous methylprednisolone for 3 days may be used to initiate corticosteroid therapy.
    - Use immunosuppressive drugs in addition to corticosteroids in patients who do not respond to corticosteroids alone, who have unacceptable toxicity to corticosteroids, who have worsening renal function, who have severe proliferative lesions, or who have evidence of sclerosis on renal biopsy specimens. Both cyclophosphamide (Evidence class B)[47] and azathioprine (Evidence class B)[48] are effective for proliferative lupus nephritis, although cyclophosphamide apparently is more effective in preventing progression to end-stage renal disease. Mycophenolate mofetil has been shown to be effective in treating these patients and may be used sequentially after a 6-month course of intravenous cyclophosphamide (Evidence class B)[49].
    - Administer intravenous cyclophosphamide monthly for 6 months as an induction and to control flares (Figure 13)[50] and every 2-3 months thereafter, as a maintenance therapy, depending on clinical response[51]. The usual duration of therapy is 2-2.5 years. Reduce the dose if the creatinine clearance is less than 30 mL/min. Adjust the dose depending on the hematologic response.
    - Azathioprine can also be used as a second-line agent, with dose adjustments depending on hematologic response.
    - Mycophenolate mofetil may be useful if the patient does not respond to or cannot tolerate cyclophosphamide and azathioprine.
  - For class V lesions, patients are generally treated with prednisone for 1-3 months, followed by tapering for 1-2 years if a response occurs or, if no response occurs, by discontinuation. Immunosuppressive drugs are generally not used unless worsening renal function or a proliferative component is present on renal biopsy samples. Some clinical evidence indicates that azathioprine, cyclophosphamide, chlorambucil, and cyclosporine are effective in reducing proteinuria. Mycophenolate mofetil may also be effective.
- End-stage renal disease
  - Patients with end-stage renal disease need dialysis and are good candidates for kidney transplantation[52].
  - Hemodialysis is preferred over peritoneal dialysis because several studies have documented higher anti-dsDNA levels, more thrombocytopenia, and higher steroid requirements in patients with SLE and end-stage renal disease who are on peritoneal dialysis. Hemodialysis also has anti-inflammatory effects with decreased T-helper lymphocyte levels. SLE is generally quiescent in patients on hemodialysis, although flares, including rash, arthritis, serositis, fever, and leukopenia, may occur and require specific treatment[53].

Intravenous immunoglobulins are increasingly being used in the treatment of resistant lupus, though there have been no large randomised trials. They also have a role in patients who have concomitant infection and active lupus, in whom immunosuppression is risky, and have been used in the treatment of many clinical manifestations in SLE[54].

Novel therapies

There have been major advances in the treatment of SLE, especially with biological agents. Rituximab is a chimeric human-murine monoclonal antibody directed against CD-20 on B cells and their precursors but not against plasma cells. Rituximab is widely used in the management of lymphoma and is relatively safe and well tolerated. Several open

studies have shown dramatic and long lasting remissions after only two to four infusions in patients who were previously unresponsive to conventional and even novel immunosuppressive agents such as mycophenolate mofetil[55]. The optimum combination of rituximab with methylprednisolone and cyclophosphamide remains undefined.

Specific agents that are undergoing clinical investigation include LJP397, which is known as a B cell tolerogen. This is a novel therapy consisting of four oligonucleotides attached to a triethylene glycol platform, which when infused, is bound by the Fab portion of anti-DNA antibodies in the membrane of auto-reactive B cells. Cross linking of anti-DNA antibody in the cell membrane of B cells results in a down regulation of anti-DNA immunoglobulin synthesis and apoptosis of these B cells. In animal models of lupus renal disease, this approach has not only reduced the production of anti-DNA, but mitigated renal disease. Human studies have suggested that this is a non-toxic therapy and in 1997 a multicenter randomized double blind study investigating its efficacy was initiated[56].

Additional agents that may have a role in the treatment of lupus nephritis include a monoclonal antibody to the fifth component of complement. The monoclonal anti-C5 reduces the production of C5a and C5b-9 and the inflammatory reaction which appears consequent to the generation of immune complexes in the kidney[57]. An additional agent, anti-CD40ligand monoclonal antibody, has the ability to reduce the production of auto-antibodies. Anti-CD40ligand not only inhibits production of pathogenic antibodies but can inhibit inflammatory cytokine production and T cell dependent activation of endothelial cells[58].

Clinical trials are currently assessing the potential of various peptides and biological agents such as abatacept (CTLA4 Ig)[59] and epratuzmab[60] in lupus. To date no medications of any class have ever been officially licensed for use in lupus, and these trials offer hope that several agents may be registered specifically for lupus patients.

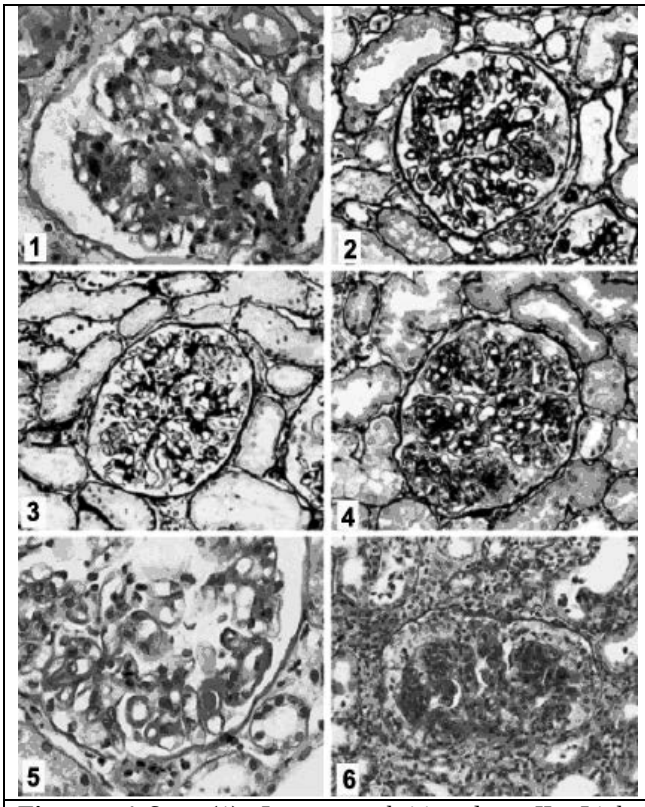
Adjuvant Management[61]

- Treatment of hypertension aggressively. To consider ACE inhibitors if the patient has significant proteinuria, unless significant renal insufficiency is present.
- Restriction of fat intake for hyperlipidemia secondary to nephrotic syndrome.
- Restriction of protein intake if renal function is significantly impaired.
- Administration of calcium supplementation to prevent osteoporosis if the patient is on long-term corticosteroid therapy, and to consider adding a bisphosphonate.
- Avoidance of drugs that affect renal function, including nonsteroidal anti-inflammatory drugs, especially in patients with elevated creatinine levels.
- Patients should avoid pregnancy if they have active lupus nephritis because it may worsen their renal disease.
- Patients with end-stage renal disease, sclerosis, and a high chronicity index based on renal biopsy findings are unlikely to respond to aggressive therapy. In these cases, focus therapy on extrarenal manifestations of SLE and on possible kidney transplantation.

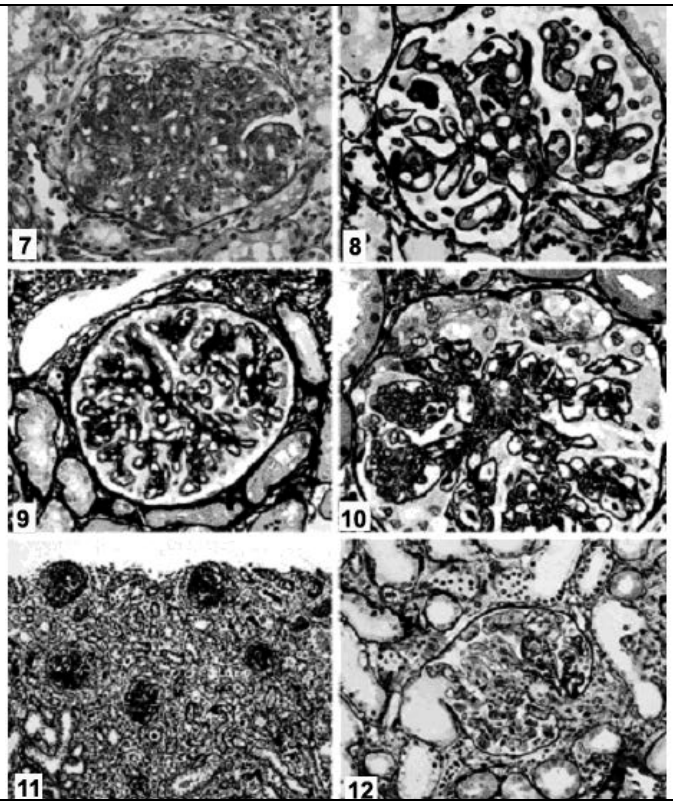
PROGNOSIS

Numerous prognostic factors have been identified[61,62]. Among others, nonwhite race (*e.g.*, black, Afro-Caribbean, Hispanic), poor socioeconomic status, uncontrolled hypertension, a high activity and chronicity index on kidney biopsy, renal impairment at baseline, poor initial response to therapy, and nephritic relapses have been associated with poor outcome. Lack of compliance to therapy, in particular to high-dose oral GC, is a trivial but underestimated (and mostly unconfessed!) cause of treatment failure. In a few cases, unrecognized association of proliferative LN with a thrombotic microangiopathy linked to the antiphospholipid clotting syndrome may further worsen the prognosis[63].

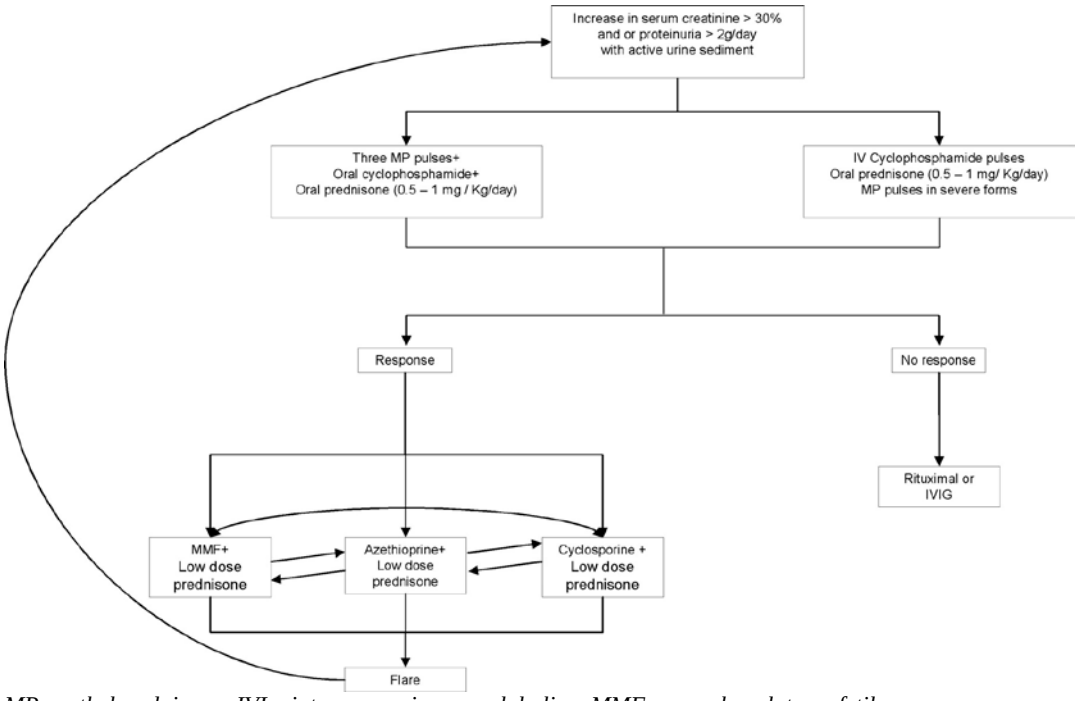
Taken together, LN still has a negative impact on lupus patients' survival as indicated by the long-term data collected between 1990 and 2000 by the investigators of the European Working Party on Systemic Lupus Erythematosus in a prospective series of 1000 European patients, whose overall survival rate at 10 yr was 88 and 94% for patients with and without renal involvement, respectively[64].



Figures 1-6. (1) Lupus nephritis class II. Light micrograph of a glomerulus with mild mesangial hypercellularity [periodic acid-Schiff (PAS)]. (2) Lupus nephritis class III (A). Light micrograph showing a glomerulus with segmental endocapillary hypercellularity, mesangial hypercellularity, capillary wall thickening, and early segmental capillary necrosis (methenamine silver). (3) Lupus nephritis class III (A). Light micrograph showing a glomerulus with segmental capillary necrosis with sparing of the remainder of the capillary tuft—a vasculitis-like lesion (methenamine silver). (4) Lupus nephritis class IV-G (A). Light micrograph showing a glomerulus with global involvement of endocapillary and mesangial hypercellularity and matrix expansion, influx of leukocytes, and occasional double contours (methenamine silver). (5) Lupus nephritis class IV-S (A). Segment of a glomerulus showing endocapillary hypercellularity, capillary wall double contours, wireloop lesions, and hyaline thrombi (PAS). (6) Lupus nephritis class IV-G (A/C). Light micrograph of a glomerulus showing global severe endo- and extracapillary proliferation, wireloop lesions, leukocyte influx, apoptotic bodies, capillary necrosis, and mesangial expansion with hypercellularity and matrix expansion; marked interstitial inflammatory infiltration (PAS) [Quoted from Weening et al, 2004][29].



Figures 7-12. (7) Lupus nephritis class IV-G (A/C). Glomerulus with global endocapillary proliferation, leukocyte influx and apoptotic bodies, double contours, crescent formation with tubular transformation, early sclerosis, and disruption of Bowman's capsule (PASd). (8) Lupus nephritis class IV-G (A). Glomerulus with widespread subendothelial immune deposits (wireloop lesions) associated with basement membrane new formation along the inner side of the capillaries but without endocapillary leukocyte infiltration or hypercellularity (methenamine silver). (9) Lupus nephritis class V. Glomerulus with advanced-stage lupus membranous nephropathy characterized by massive subepithelial accumulation of immune deposits (immunofluorescence: full house) and interdigitating spike formation (methenamine silver). (10) Lupus nephritis class IV and V (A/C). Glomerulus with lupus membranous nephropathy with subepithelial spike formation combined with global endocapillary and mesangial hypercellularity, early crescent formation, and beginning mesangial and capillary sclerosis (methenamine silver). (11) Lupus nephritis class VI. Renal cortex showing almost diffuse, global glomerular sclerosis accompanied by interstitial fibrosis, mononuclear inflammatory infiltrates, and vascular sclerosis (methenamine silver). (12) Thrombotic microangiopathy in a patient with SLE and circulating anticoagulans. A glomerulus showing severe capillary and arteriolar thrombosis, endothelial cell swelling and necrosis, neutrophil influx, and stasis of erythrocytes. No signs of immune deposits (methenamine silver) [Quoted from Weening et al, 2004][29].



MP, methylprednisone; IVIg, intravenous immunoglobulins; MMF, mycophenolate mofetil

Figure 13. Proposed therapeutic options in patients with lupus nephritis and severe renal involvement at presentation or at renal flares. In patients with normal renal function, the treatment of induction or flares may also consist of mycophenolate mofetil and oral prednisone. [Quoted from Ponticelli C, 2006][50].

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