Research Article

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Lupic Nephropathy: Our experience at the Department of Nephrology

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Introduction

Systemic lupus erythematosus (SLE) is the most common disease systemic autoimmune disorders that cause kidney damage. AT Conversely, kidney damage is the most common and the most severe visceral involvement of SLE. The most frequent renal involvement is glomerular and there are several types of glomerulonephritis (GN) Lupus now evaluated according to classification histological ISN / RPS (International Society of Nephrology/Renal Pathology Society) [1]. Other glomerular disorders such as a Nephrotic syndrome with minimal glomerular lesions are possible but rare. Vascular or interstitial lesions related to lupus may be associated with glomerular damage; they are rarely isolated. Finally, lupus nephropathy is sometimes mixed with renal diseases associated with lupus, the most common being renal antiphospholipid Syndrome.

Epidemiology

The global incidence and prevalence of SLE are between 1 and 5 per 100,000 and between 20 and 150 per 100,000, respectively. In France, they are estimated at 3.32 per 100,000 and 40.8 per 100,000. The frequency of the disease in women is 9 times higher than frequency encountered in men. Renal impairment is more common in subjects of African descent, Hispanic or Asian only in subjects of Caucasian origin [2]. African origin is probably a factor of severity. Reaching kidney is particularly common (50 to 80% of cases) and potentially more severe in pediatric cohorts. The male sex is a risk factor for early renal damage and greater severity; a low socio-economic level is a risk factor for lupus nephropathy and severity of impairment [3].

Diagnostic Approach: Clinical manifestations and indications kidney biopsy

Initialdiagnosis

Renal involvement of lupus occurs most often at the diagnosis of SLE or within 3 to 5 years. There does not seem to be any preferential association between renal impairment and other manifestations of lupus; also must we consider that all can accompany it [4]. Sometimes the damage renal is inaugural with litte or no clinical signs of lupus, the renal biopsy then being diagnosed with SLE. Triggers are those of SLE (sun exposure, stress, contraceptives including estrogen, pregnancy, etc.) and there is no factor specific to kidney damage [4,5]. The clinical manifestations have three characteristics:

- The important variability of the nephrological signs: simple silent proteinuria and/or microscopic hematuria associated renal failure, these manifestations may constitute chronic glomerulopathy syndrome, up to noisier manifestations such as glomerulonephritis syndrome quickly progressive, nephrotic syndrome or syndrome acute nephritic [6]. Aseptic leukocyturia accompanies sometimes glomerular signs [7-9].
- The clinical constant is proteinuria which must be take into account at a low flow rate (from 0.5 g / g creatinine urea to 0.3 g / g if it exists) concomitant hematuria), the other renal abnormalities being inconstant [10-12].
- There is no anatomic-clinical parallelism: it is not possible to predict the type of histological involvement and therefore the severity by the analysis semiological; so, for example, a proteinuria of 0.5 g / g can all as much to translate an Active Class III or IV GN as a Class III or IV chronic, that a class II or a class V [13, 14].

One can thus affirm the existence of a lupus GN as soon as the detection permanent proteinuria, but we cannot say how serious it is [15].

Immune abnormalities are associated with nephropathies the most severe lupus: consumption of complement by the way (C4 and C3 lowered) and the presence of anti-double DNA antibodies strand. Nevertheless, their predictive value is insufficient and only one renal biopsy can typify lupus GN and define the need treatment [16-18].

As a reminder, any patient with SLE should benefit from research renal anomaly, during diagnosis but also during follow-up. Currently, in the absence of contraindications, any patient with SLE and higher proteinuria 0.5 g per day must have a kidney biopsy because of the lack of correlation between clinical-biological presentation and lesions histological. Glomerular lesions are then graded according to the ISN-RPS classification from I to VI [19, 20].

- It is also important to quantify the activity or chronicity of the lesions because these parameters guide the clinician in

indication as well as in the choice of treatments [21-23].

Histological features of the different classes of lupus nephritis (ISN / RPS 2003 classification)

Class Histological Features

The classification of LN is based on histological features, using the International Society of Nephrology (ISN) and Renal Pathology Society (RPS) criteria developed in 2003 (Table 1). Although the classification is mainly glomerulocentric, it includes features of tubulointerstitial disease, from which features of chronicity can be determined. The relationship between the histological class of LN and clinical course of the disease is well recognised. Patients with class II and class V (pure membranous LN) disease usually have a slow decline in renal function over long periods of observation. In contrast, patients with class III and class IV (or those with mixed class V) disease mostly have a more aggressive course of disease. Various studies have shown that the proliferative forms of LN (i.e. class III, class IV and mixed class V) occur more frequently than the other histological Morphologies [24-26].

Table 1. Abbreviated International Society of Nephrology/Renal Pathology Society classification of lupus nephritis (2003)[4]

Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal lupus nephritis (<50% involvement)
Class IV	Diffuse segmental or diffuse global lupus nephritis (≥50% involvement)
Class V	Membranous lupus nephritis*
Class VI	Advanced sclerosing lupus nephritis

* Can be pure membranous lupus nephritis or mixed class V if combined with class III or class IV.

Diagnosis

One of the major challenges with regard to SLE is its early recognition and diagnosis. Many physicians assume that SLE is a rare condition in Africa - it is therefore seldom considered as a differential diagnosis, except when patients present with classic features, such as malar rash and swollen painful joints of the hands and feet [27-29]. Hence, many patients tend to remain ill for prolonged periods before the diagnosis is made. In some instances, chronic damage to organs including the kidneys would have occurred [30, 31].

Role of Urinalysis and Urine Microscopy

LN is unlikely to present alone - it often manifests with other extra renal features such as joint pain, malar rash, oral ulcers and photosensitivity. The patient with LN is likely to present with nephritic syndrome (oliguria, minimal proteinuria, haematuria hypertension and azotaemia) or with features of nephrotic syndrome (anasarca, heavy proteinuria and hypoalbuminemia) [32, 33]. Urinalysis (dipstick and microscopic examination) presents the best opportunity for early identification of LN as a dipstick is likely to show the presence of blood and protein in the urine and urine microscopy enables identification of various urinary casts (red cells, granular, hyaline) [34-36]. LN must be strongly suspected in any SLE patient with high titres of double-stranded DNA (dsDNA) and a positive dipstick for blood. Urinalysis features have been shown to be correlated with the presence of proliferative class LN. Therefore, every SLE patient should have a urinalysis performed at every clinic visit [37, 38].

Role of Lupus Auto-Antibodies (Antinuclear Antibody and dsDNA) And Complements (C3/C4)

Auto-antibodies in SLE and complements (C3/C4) are known to be elevated or lowered, respectively, in patients with increased disease activity, especially in those with proliferative LN (class III, class IV and mixed class V). One study found proliferative LN to be significantly correlated with haematuria on dipstick ($\rho<0.0001$), proteinuria on dipstick ($p=0.042$), low complement C3 ($p<0.0001$), low complement C4 ($p=0.009$) and positive dsDNA ($p=0.039$) [39-41].

Role of Renal Biopsy

The definitive diagnosis of LN requires a kidney biopsy. Renal histology also enables classification of LN and assists in the prognosis. All guidelines recommend a renal biopsy when there is a suspicion of renal involvement, as clinical and laboratory parameters, although useful, cannot accurately predict the histological class. The indication for a renal biopsy in SLE patients includes persistent decline in renal function, proteinuria (>1.0 g/24 h) or proteinuria (>0.5 g/24 h) if associated with haematuria (5 red blood cells (RBCs)/ high power field) and active urinary sediment (granular casts, white blood cell (WBC) casts, RBC casts) [42,43]. It is recommended that the biopsy be examined by light microscopy, immunofluorescence (or immunohistochemistry) and where possible by electron microscopy. Quantification of activity and chronicity indices and description of vascular and interstitial lesions are also recommended. A repeat renal biopsy is indicated if there is evidence of worsening of the disease or disease refractory to treatment, evidence of relapse (to show transformation or progression in histological class or change in activity and chronicity cores) and to demonstrate other pathologies.

Fig. 1 shows the renal histology in a patient with class IV LN.

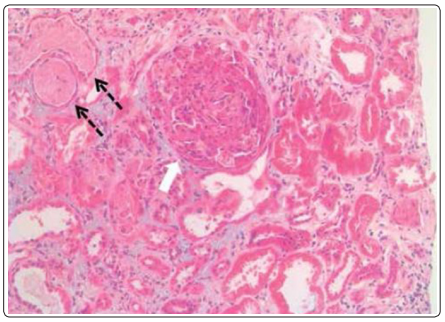


Figure 1: Renal histology of a patient with class IV lupus nephritis (white arrow shows a glomerulus with cellular crescent; black broken arrows show adjacent tubules with red cell casts)

Current Treatment

The treatment of lupus nephropathy is based on two main pillars: induction phase and the maintenance phase. The treatment of induction of NL is based on the combination of corticosteroids (CS) and cyclophosphamide (CYC) or mycophenolate mofetil (MMF). During the maintenance phase, treatment with azathioprine (AZA) or MMF can be used. The treatment of NL, however, remains imperfect. Indeed, the total re-emission rate is around 50%, generating a significant risk of evolution to the MRC, or even terminal renal failure [44,45].

The treatment of LN is dictated by the class of the disease and degree of activity and chronicity indices. All patients should receive adjuvant therapies as indicated and if tolerated. There should be a risk-benefit evaluation when deciding whether to use immunosuppression in patients with increased chronicity indices (i.e. glomerular sclerosis with tubulo-interstitial fibrosis) because of the increased risk of side-effects of treatment. The approach to treatment often involves two phases for patients with proliferative LN (class III, class IV and

mixed classV) [46, 47].

Induction Therapy

Fig. 2 summarises the common approaches used for induction for the different classes of LN. Induction therapy is not used for patients with class I, II, V (pure class V with sub-nephrotic range proteinuria) and VI LN. The approach to induction involves the use of 3 consecutive pulses of intravenous methylprednisolone (500 - 750 mg daily) together with another immunosuppressive: cyclophosphamide (CYC) (daily oral or monthly intravenous pulse therapy) or mycophenolate mofetil (MMF). The patient should continue on oral prednisone (1 mg/kg/day) after completing the pulse treatment with methylprednisolone [48, 49]. CYC is often the agent of choice for many clinicians owing to easy accessibility and cost; however, the use of MMF is increasing. Various studies have assessed the efficacy and safety of CYC with MMF or placebo for induction therapy in patients with LN (reviewed in depth by Chan). The recommended duration of induction therapy is 6 months; during this time, the dose of oral corticosteroid should be weaned.

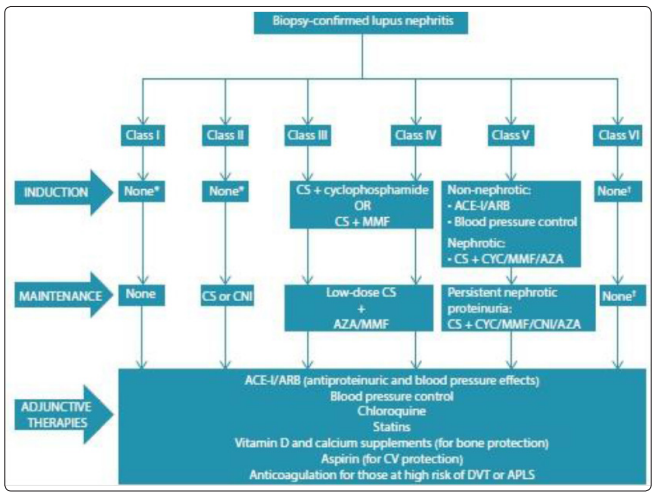


Figure 2: Treartment approach for patients with lupus nephritis (APLS = antiphospholipid syndrome; AZA = azathioprine; ACE-I=angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CNI = calcineurin inhibitor; CS = corticosteroid; CYC = cyclophosphamide; DVT = deep-vein thrombosis; MMF = mycophenolate mofetil; CV = cardiovascular).
*Immunosuppre to be dictated by extrarenal manifestations.
t Patients should be Prepared for renal replacement therapy (dialysis/ transplantation).

Maintenance Therapy

Treatment administered during the induction phase of therapy is de-escalated in the maintenance phase. The goal of the latter phase is to maintain the response (remission) gained during the induction phase and therefore to retard progression of chronic kidney disease. Immunosuppressive agents commonly used include MMF, azathioprine (AZA), and corticosteroids.

Calcineurin inhibitors may be used in special circumstances, such as in cases of intolerance to MMF or AZA or in patients with persistent heavy proteinuria (Fig.2). There is currently no consensus on the duration of maintenance therapy [50-52]. Nonetheless, the decision to withdraw maintenance immunosuppression should be guided by sustained complete clinical response over a period of at least 2 years. Withdrawal should be done gradually, starting with glucocorticoids before withdrawing immunosuppressive agents. In debilitating or life threatening complications of immunosuppression, therapy should be withdrawn [53, 54].

Adjunctive Therapies

Adjunctive therapies are usually started during the induction phase of treatment and although some need to be discontinued after completing this therapy, others will need to be continued during the maintenance phase [55-57]. Commonly recommended adjunctive therapies in LN include:

- Renin angiotensin aldosterone system (RAAS) inhibition for proteinuria and blood pressure treatment (Target<130/80 mmHg).
- Bone protection with calcium and vitamin D supplements.
- Chloroquine for all patients (unless contraindicated, e.g. visual disturbance).
- Treatment of hyperlipidaemia with statins (target low density lipoprotein <2.6 mmol/L).
- Low-dose acetylsalicylic acid in patients with antiphospholipid syndrome.
- Anticoagulant to be considered in patients with nephrotic syndrome and albumin <20 g/L.
- Avoid vaccination with live or attenuated viruses during immune suppression.
- Tuberculosis prophylaxis with isoniazid (for those in highly endemic TB regions).

Treatment of Refractory Ln

Fewer than 50% of patients are able to achieve complete remission during the 6 months of induction therapy. It may take up to 2 years to reach remission in many patients [58, 59]. Switching to an alternative agent is recommended for patients who fail to improve within 3-4 months, or do not achieve a partial response after 6-12 months or a complete response after 2 years of treatment. Treatment options include switching from MMF to CYC or from CYC to MMF; rituximab may be given as add-on treatment or monotherapy. Other options include the use of calcineurin inhibitors, intravenous immunoglobulin and plasma exchange for patients with rapidly progressive glomerulonephritis [60, 61].

Treatment of Class Vi Ln

Immunosuppression for class VI patients must be dictated by extra renal manifestations of SLE. These patients should be prepared for renal replacement therapy (haemodialysis, peritoneal dialysis or transplantation). Treatment and Prevention of cardiovascular risk factors (e.g. blood pressure control, statins for dyslipidaemia) should be continued [62, 63].

Lupica Nephropathy

Our experience at the Department of Nephrology year 2015/2016/2017/2018:

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease; lupus nephritis is usually the most serious manifestation of SLE, burdened with significant morbidity and mortality. The pathophysiological development of the systemic form and involvement of lupus has been better and better understood over the years, and various so-called targeted therapeutic approaches have recently been developed.

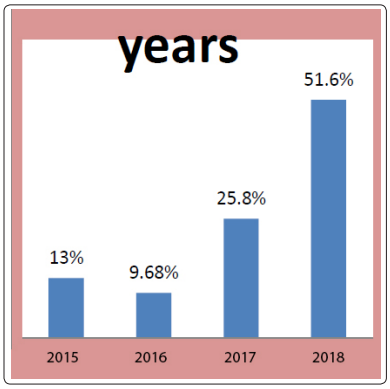
Materials and Methods

*Type of study: Our study is retrospective it concerns 31 patients

with lupic nephropathy in our department over a period of 4 years (2015-2018).
*Patients: they were selected from the hospitalization register of our department.

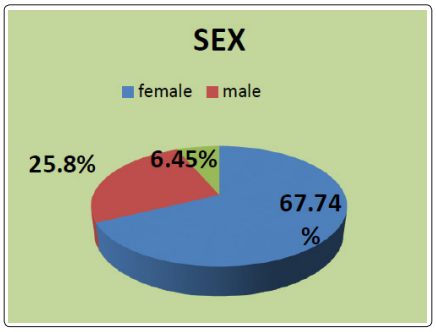
Results

The incidence of lupus Nephropathy



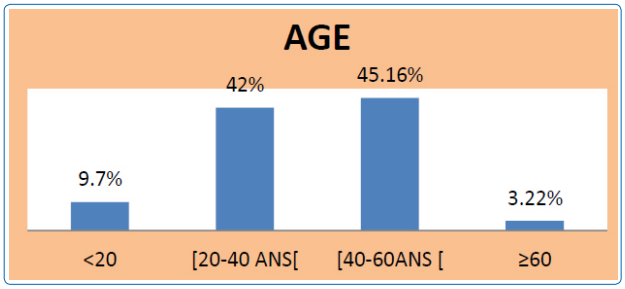
EARS	NUMBER	FREQUENCY
2015	4	13%
2016	3	9.68%
2017	8	25.8%
2018	16	51.6%
TOTAL	31	100%

SEX



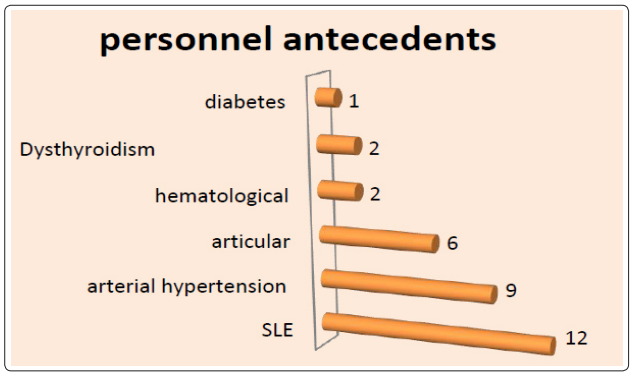
female	21	67.74%
male	8	25.8%
child	2	6.45%
total	31	100%

Age



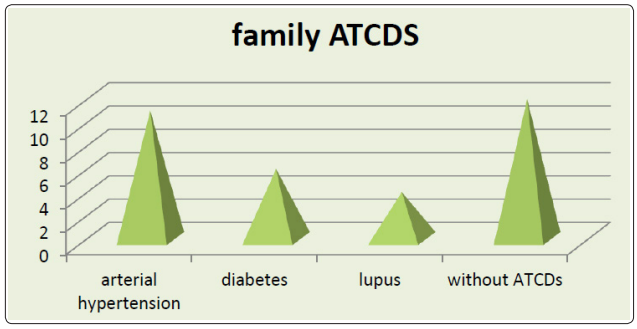
AGE	Number	Frequency
<20	3	9.7%
[20-40 ANS]	13	42%
[40-60 ANS]	14	45.16%
≥60	1	3.22%
TOTAL	31	100%

Antecedents



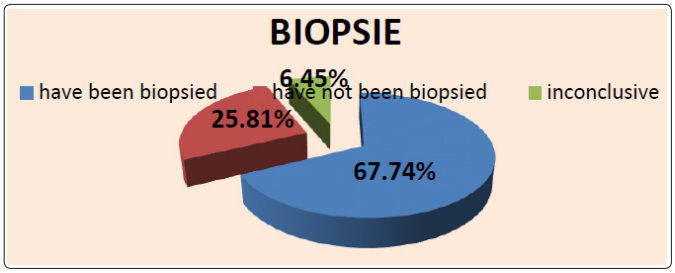
*Family antecedents(ATCDs):

ATCDs ATCDs	NUMBER
Arterial hypertension	11
Diabetes	6
SLE	4
Without antecedents	12

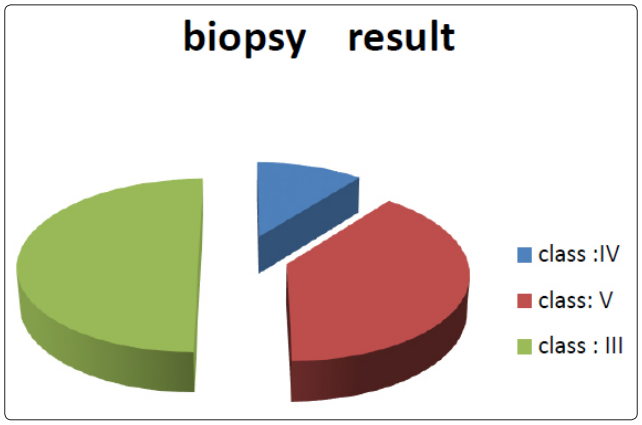


Biopsy

Have been biopsied	21	67.74%
Have not been biopsied	8	25.81%
inconclusive	2	6.45%
Total	31	100%

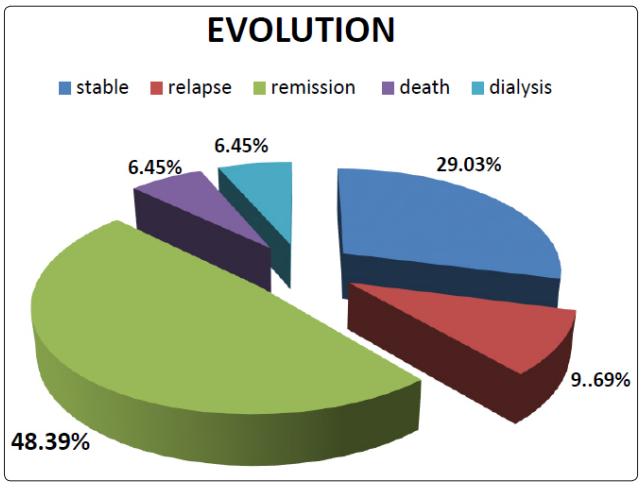


Biopsy Result

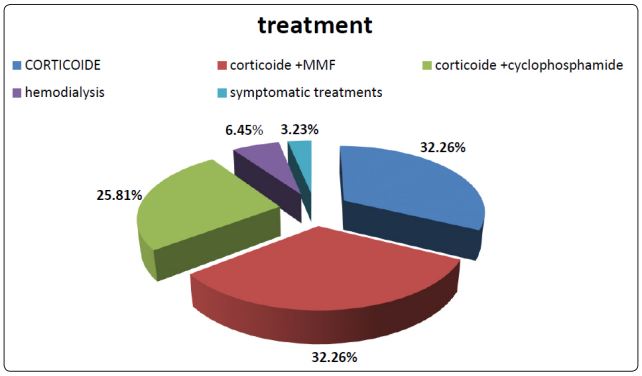


Biopsy	Number
CLASS :IV	3
CLASS :V	11
CLASS :III	7

Evolution



Treatment



Results

- The frequency of ludic nephropathy is increasing from 25.8% in 2017 to 51.6% in 2018, with a clear predominance of women at 67.74%.
- 38.7% of patients were known for lupus disease and 12.9% had familial SLE antecedents.
- Equal proportions between the age groups of 20-40 years and 40 and 60 years.
- On admission renal impairment was dominated by impure nephrotic syndrome and renal insufficiency found in more than 75% of cases
- Extra-renal signs were dominated by skin lesions and joint involvement with 62.2% of cases
- The association (anti-DNA antibodies Antinuclear antibodies (ANA)) was positive in 32% of cases, (anti-DNA antibodies+ ANA+ anti SM + anti SSA / SSB) in 25.81%.
- 23 of 31 patients were biopsied; Class V was dominant with more than 50%, elsewhere Class III and Class IV.
- 32.26% of patients received Corticoids + Cellcept (MMF), 25.81% Corticoids + Cyclophosphamides; 32.26% received Corticoids alone.
- The evolution was favourable in the majority of the cases with a percentage of remission of 48% and relapses in 9% of the cases; 6.45% required haemodialysis sessions.

Discussion

- The nature and severity of renal failure play an important role in the prognosis of SLE. in our series studied It is often a glomerular disease, but a tubulo-interstitial and vascular involvement are not negligible that can play an aggravating role and must also be evaluated.
- There is in our series a similarity in the distribution of histological classes with different series in which the non-proliferative forms predominates that's why they received corticosteroids associated with MMF.
- 25% of the patients had repetition infections, which is why they received corticoids alone
- 9.69% of patients relapsed; there is no unanimous decision regarding the criteria used for renal recurrence, which is also based on observed changes in creatinine, proteinuria and urinary sediment levels compared to baseline values. Recurrences tend to be accompanied by a reduction in complement and an increase in anti-DNA antibody titers. In case of severe recurrence, deterioration of renal function may be present.
- Regarding treatment failure (lack of response or recurrence), it is often related to non-compliance, especially in young patients who have had difficulty coping with chronic illness.

Conclusion

Lupus nephritis remains the main determinant of mortality for patients with SLE. The assessment and management of lupus nephritis has seen major advances over the past 5 years. Whose classification for lupus nephritis has been updated to allow more accurate description of renal his to pathological specimens by the International Society of Nephrology and the Renal Pathology Society (2003). The future challenge remains the design of therapeutic regimens incorporating existing and newer therapies that will rapidly induce renal remission with minimum toxicity. Patients who have SLE should be followed in dedicated clinics, and early kidney involvement should be detected by very regular assessments of proteinuria.

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